Fronto-limbic-striatal dysfunction in pediatric and adult patients with bipolar disorder: impact of face emotion and attentional demands

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Abstract

Background—Research in bipolar disorder (BD) implicates fronto-limbic-striatal dysfunction during face emotion processing but it is unknown how such dysfunction varies by task demands, face emotion and patient age.

Method—During functional magnetic resonance imaging (fMRI), 181 participants, including 62 BD (36 children and 26 adults) and 119 healthy comparison (HC) subjects (57 children and 62 adults), engaged in constrained and unconstrained processing of emotional (angry, fearful, happy) and non-emotional (neutral) faces. During constrained processing, subjects answered questions focusing their attention on the face; this was processed either implicitly (nose width rating) or explicitly (hostility; subjective fear ratings). Unconstrained processing consisted of passive viewing.

Results—Pediatric BD rated neutral faces as more hostile than did other groups. In BD patients, family-wise error (FWE)-corrected region of interest (ROI) analyses revealed dysfunction in the amygdala, inferior frontal gyrus (IFG), anterior cingulate cortex (ACC) and putamen. Patients with BD showed amygdala hyperactivation during explicit processing (hostility ratings) of fearful faces and passive viewing of angry and neutral faces but IFG hypoactivation during implicit processing of neutral and happy faces. In the ACC and striatum, the direction of dysfunction

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varied by task demand: BD demonstrated hyperactivation during unconstrained processing of angry or neutral faces but hypoactivation during constrained processing (implicit or explicit) of angry, neutral or happy faces.

Conclusions—Findings suggest amygdala hyperactivation in BD while processing negatively valenced and neutral faces, regardless of attentional condition, and BD IFG hypoactivation during implicit processing. In the cognitive control circuit involving the ACC and putamen, BD neural dysfunction was sensitive to task demands.

Keywords

Attention; bipolar disorder; face emotion; fronto-limbic-striatal dysfunction; imaging; pediatric

Introduction

Research in bipolar disorder (BD) implicates fronto-limbic-striatal dysfunction, with meta-analyses generally suggesting prefrontal cortex (PFC) hypoactivation and limbic hyper-activation during face emotion processing paradigms (Chen *et al.* 2011; Delvecchio *et al.* 2012; Houenou *et al.* 2011; Kupferschmidt & Zakzanis, 2011; Blond *et al.* 2012; Strakowski *et al.* 2012). However, the precise nature of the dysfunction varies; differing task demands and face emotions are used across studies and may contribute to discrepancies in the literature. Moreover, there is limited research on how abnormalities differ developmentally, i.e. in pediatric *versus* adult patients (Kim *et al.* 2012). We report data from a relatively large sample [62 BD, 119 healthy comparisons (HC)] in which we compared neural activity across different attention conditions and face emotions, using a paradigm that was brief enough to be tolerated by affected children and adults.

In the current emotional face viewing task, as in other tasks, there are three types of attentional conditions: (1) implicit, (2) passive viewing and (3) explicit. During implicit paradigms, subjects focus on a stimulus feature other than the face emotion. Amygdala hyperactivity has been reported consistently in both pediatric and adult BD patients during such tasks, including gender labeling (Lawrence *et al.* 2004; Kalmar *et al.* 2009; Surguladze *et al.* 2010; Ladouceur *et al.* 2011; Garrett *et al.* 2012; Kim *et al.* 2012; Thomas *et al.* 2013), face age labeling (Pavuluri *et al.* 2009) and face image color labeling (Chen *et al.* 2006; Keener *et al.* 2012; Perlman *et al.* 2012). However, the precise direction of dysfunction in the PFC and striatum during implicit face emotion processing has been variable, with some reports indicating hyperactivation in BD (Lawrence *et al.* 2004; Wessa *et al.* 2007; Hassel *et al.* 2008, 2009; Surguladze *et al.* 2010; Ladouceur *et al.* 2011; Keener *et al.* 2012) and others reporting hypoactivation (Lawrence *et al.* 2004; Hassel *et al.* 2009; Pavuluri *et al.* 2009; Garrett *et al.* 2012).

While some researchers have included passive viewing as a form of implicit face processing, subjects' attention during passive viewing is completely unconstrained and the cognitive demands are unclear. As in implicit paradigms, amygdala hyperactivation has been reported in BD during passive viewing (Blumberg *et al.* 2005; Pavuluri *et al.* 2007; Killgore *et al.* 2008), although amygdala hypoactivation has also been observed (Blumberg *et al.* 2005). Similarly, both PFC and striatal hyperactivation (Pavuluri *et al.* 2007) and hypoactivation

(Blumberg *et al.* 2005; Pavuluri *et al.* 2007; Killgore *et al.* 2008) have been reported in passive viewing paradigms.

Explicit face emotion processing paradigms, in which the task directs attention toward the face emotion, have also elicited amygdala hyperactivity in BD (Yurgelun-Todd *et al.* 2000; Rich *et al.* 2006; Foland *et al.* 2008; Almeida *et al.* 2010; Chen *et al.* 2010; Versace *et al.* 2010; Hulvershorn *et al.* 2012), although some find hypoactivation (Lennox *et al.* 2004; Chen *et al.* 2006; Vizueta *et al.* 2012). These mixed findings in BD are consistent with meta-analyses in healthy adults (Sergerie *et al.* 2008), suggesting that explicit face emotion processing may probe the amygdala less effectively than do passive viewing paradigms, and may even be associated with decreased amygdala activation (Costafreda *et al.* 2008). In BD, as with implicit and passive viewing tasks, findings in the PFC and striatum include both hyperactivity (Rich *et al.* 2006; Foland *et al.* 2008; Robinson *et al.* 2008; Chen *et al.* 2010; Hulvershorn *et al.* 2012) and hypoactivity (Yurgelun-Todd *et al.* 2000; Lennox *et al.* 2004; Altshuler *et al.* 2008; Foland *et al.* 2008; Foland-Ross *et al.* 2012; Hulvershorn *et al.* 2012). Thus, it is difficult to determine the impact of attentional demands on BD neural dysfunction because conclusions in the literature are based on findings across studies that use different paradigms. Studies have yet to include multiple attention conditions, including constrained (implicit and explicit) and unconstrained (passive viewing) conditions within one task.

In both constrained and unconstrained attentional paradigms, a wide range of face emotions have elicited neural dysfunction in BD. These emotions include happy (Lawrence *et al.* 2004; Lennox *et al.* 2004; Blumberg *et al.* 2005; Chen *et al.* 2006; Pavuluri *et al.* 2007; Hassel *et al.* 2008, 2009; Almeida *et al.* 2009; Shah *et al.* 2009; Surguladze *et al.* 2010; Versace *et al.* 2010; Passarotti *et al.* 2011; Garrett *et al.* 2012; Keener *et al.* 2012; Mourao-Miranda *et al.* 2012; Perlman *et al.* 2012; Thomas *et al.* 2012), angry (Pavuluri *et al.* 2007; Altshuler *et al.* 2008; Passarotti *et al.* 2011; Keener *et al.* 2012; Perlman *et al.* 2012; Thomas *et al.* 2012, 2013), sad (Lawrence *et al.* 2004; Lennox *et al.* 2004; Chen *et al.* 2006; Jogia *et al.* 2008; Almeida *et al.* 2010; Versace *et al.* 2010; Garrett *et al.* 2012; Keener *et al.* 2012; Perlman *et al.* 2012), neutral (Rich *et al.* 2006; Altshuler *et al.* 2008; Hassel *et al.* 2009; Garrett *et al.* 2012; Thomas *et al.* 2012, 2013) and fearful (Yurgelun-Todd *et al.* 2000; Lawrence *et al.* 2004; Chen *et al.* 2006; Altshuler *et al.* 2008; Hassel *et al.* 2008; Killgore *et al.* 2008; Shah *et al.* 2009; Surguladze *et al.* 2010; Keener *et al.* 2012; Perlman *et al.* 2012; Thomas *et al.* 2012). However, similar to conclusions drawn about BD dysfunction across different attention conditions, it is difficult to determine the impact of specific face emotions on neural function in BD because most studies use only one face emotion or collapse analyses across face emotions. To date, no study has included multiple face emotions and attention states (including both implicit and explicit conditions, and passive viewing) in one statistical model.

We examined neural dysfunction during face emotion processing across several emotions and attention states in pediatric and adult BD patients. We used a face emotion processing paradigm because behavioral deficits in face emotion labeling have been found in BD patients irrespective of age of onset (Kohler *et al.* 2011). Face processing deficits are also present during euthymia (Schenkel *et al.* 2007; Rich *et al.* 2008), representing a potential endophenotype of the illness (Brotman *et al.* 2008; Olsavsky *et al.* 2012). However, it

remains unclear whether the neural correlates of such behavioral deficits differ in pediatric and adult BD. Meta-analyses report that decreased amygdala volume is found more consistently in youth than in adults with BD (Pfeifer *et al.* 2008; Chen *et al.* 2011), suggesting that functional amygdala abnormalities may be more prominent in BD youth than in adults (Kim *et al.* 2012).

We used a paradigm that included both implicit (nose width) and explicit (hostility, subjective fear) ratings, in addition to an unconstrained attention condition (passive viewing). The task included multiple face emotions (angry, happy, fearful, neutral). Four regions of interest (ROIs) were selected, including the amygdala, anterior cingulate cortex (ACC), inferior frontal gyrus (IFG) and putamen; these regions have been consistently implicated in BD (Chen *et al.* 2011; Delvecchio *et al.* 2012; Houenou *et al.* 2011). Our primary ROI analyses included, in one statistical model, all attention conditions, face emotion, subject age and diagnosis. We expected between-group diagnostic differences to emerge in all ROIs. We also examined main effects of diagnosis and diagnosis by age group interactions.

Specifically, given the relatively consistent literature on amygdala hyperactivation in BD across face emotions (Chen *et al.* 2011; Delvecchio *et al.* 2012; Houenou *et al.* 2011; Kupferschmidt & Zakzanis, 2011; Blond *et al.* 2012), we hypothesized that, relative to HC, both adult and pediatric BD patients would demonstrate increased amygdala activity to constrained (implicit, explicit ratings) and unconstrained (passive viewing) attention tasks across all face emotions (angry, fearful, happy, neutral). Consistent with a recent study using a gender identification paradigm (Kim *et al.* 2012), we expected amygdala dysfunction to be more pronounced in BD youth than BD adults, particularly during the implicit task. Based on meta-analyses (Chen *et al.* 2011; Delvecchio *et al.* 2012; Houenou *et al.* 2011), we also anticipated BD IFG hypoactivation. Finally, we expected that dysfunction in the cognitive control circuit composed of the ACC and striatum would be sensitive to attentional demands.

Method

Subjects

Usable functional magnetic resonance imaging (fMRI) data were obtained from 181 participants, including 36 pediatric BD (9–18 years old), 26 adult BD (24–58 years old), 57 HC children (9–18 years old) and 62 HC adults (20–53 years old). From these 181 subjects, data from 101 have been published previously, including 32 pediatric BD patients (Rich *et al.* 2006; Brotman *et al.* 2010; Olsavsky *et al.* 2012), 56 HC children (Rich *et al.* 2006; Guyer *et al.* 2008; Beesdo *et al.* 2009; Brotman *et al.* 2010; Olsavsky *et al.* 2012) and 13 HC adults (Guyer *et al.* 2008). The adult BD data (*n*=26) and data from 54 other subjects (four pediatric BD, one HC child, 49 HC adults) have not been published previously.

Pediatric BD patients were assessed using the Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime version (K-SADS-PL; Kaufman *et al.* 1997). To evaluate mood, clinicians administered the Children's Depression

Rating Scale (CDRS; Poznanski *et al.* 1984) and the Young Mania Rating Scale (YMRS; Young *et al.* 1978) to parent and child within 48 h of scanning.

Adult BD (BD-I or BD-II) was assessed using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders – Patient Edition (SCID-I/P; First *et al.* 2002) or the Diagnostic Interview for Genetic Studies (DIGS; Nurnberger *et al.* 1994). The Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders Version (SIGH-SAD; Williams, 1988) and the YMRS (Young *et al.* 1978) were used to evaluate mood state in BD adults.

Exclusion criteria included: IQ<70, history of head trauma, neurological disorder, pervasive developmental disorder, unstable medical illness, or substance abuse/dependence in the past 3 months. Medicated patients were included. For details, see online Supplementary Material.

Behavioral paradigm

For task details, see Supplementary Material and Rich *et al.* 2006; Guyer *et al.* 2008; Beesdo *et al.* 2009; Brotman *et al.* 2010; Olsavsky *et al.* 2012. In brief, subjects viewed adult faces displaying happy, fearful, angry or neutral expressions. Attention conditions included one implicit ('How wide is the nose?'), two explicit ('How hostile is the face?'; 'How afraid are you?') and one passive viewing condition.

Behavioral data analysis

We used a 2 (diagnosis: BD, HC)×2 (age group: child, adult)×4 (face emotion: angry, happy, fearful, neutral) × 3 (attention state: fear, hostility, nose width) Greenhouse–Geisser-corrected repeated-measures ANOVA, with face emotion and attention state as within-subject variables. To understand the significant interactions, separate *post-hoc* 2 (diagnosis) ×3 (attention state) and 2 (diagnosis) ×4 (face emotion) ANOVAs were used. We used *t* tests to further decompose these *post-hoc* analyses, and Pearson correlations to assess relationships between mood ratings and behavioral performance.

fMRI data

For scanning acquisition and preprocessing, see Supplementary Material.

We conducted separate left and right ROI analyses with a small volume correction (SVC), using family-wise error (FWE) correction at a statistical threshold of $p<0.05$. The primary analysis consisted of a four-way ANOVA [2 (diagnosis) ×2 (age group) ×4 (face emotion)× 4 (attention state)]. There were no supra-threshold voxels in any of the ROIs in the four-way ANOVA (see Supplementary Material for a trend).

Given our primary interest in differences between BD and HC, analyses then focused on the significant three-way interactions that included diagnosis. A 2 (diagnosis) ×4 (face emotion) × 4 (attention state) ANOVA three-way interaction yielded the highest number of significant clusters. No other significant three-way interactions (i.e. diagnosis ×age group×attention state and diagnosis×age group×face emotion) in any of the ROIs survived FWE correction. We also examined two-way interactions of diagnosis ×age group and main effects of diagnosis in each ROI.

In *post-hoc* analyses, age, behavioral ratings and reaction time were included as covariates. We performed a 2 (diagnosis) ×4 (face emotion) ×4 (attention state) repeated-measures ANCOVA, with age as a continuous covariate; a 2 (diagnosis) ×4 (face emotion) ×4 (attention state) repeated-measures ANCOVA, with ratings (hostility ratings of neutral faces) as a covariate; and a 2 (diagnosis) ×4 (face emotion) ×4 (attention state) repeated-measures ANCOVA, with reaction time as a covariate.

To test the effects of potentially confounding variables on our results (see Supplementary Material), *post-hoc t* tests compared: (1) euthymic ($n=36$) *versus* non-euthymic ($n=24$) patients, (2) patients with ($n= 34$) *versus* without a co-morbid diagnosis ($n=28$), and (3) unmedicated ($n=12$) *versus* medicated ($n=47$) patients. Finally, we used Pearson correlations to examine associations between neural activation and mood, along with neural activation and psychotropic medications.

In addition to ROI analyses, we conducted an exploratory whole-brain analysis, using a statistical threshold of $p<0.001$, uncorrected, voxel-wise extent threshold of k 20 (Lieberman & Cunningham, 2009). We obtained results consistent with the ROI analyses (see Supplementary Material and Table S4).

Results

Demographic and clinical characteristics

For demographic and clinical data, see Supplementary Material and Table 1.

Behavioral analyses

Ratings—A diagnosis ×age group×face emotion ×attention state interaction ($F_{6,1026} =2.30$, $p<0.05$) revealed that pediatric patients rated neutral faces as more hostile than did other groups (*p*'s <0.01) (see Supplementary Material and Table S1).

Reaction time—A diagnosis ×face emotion interaction ($F_{3,513} =4.41$, $p< 0.01$) revealed that patients responded slowest to fearful faces and HC responded slowest to angry faces (*p*'s <0.05) (see Supplementary Material and Table S2).

fMRI analyses

Diagnosis ×face emotion ×attention state—This three-way interaction yielded numerous significant FWE-corrected SVCs in the ROIs (Table 2).

Amygdala: Compared to HC, patients showed left amygdala hyperactivation during explicit (hostility) ratings of fearful faces ($t =2.27$, $p =0.03$) and passive viewing of angry faces ($t =2.06$, $p=0.04$) (Fig. 1). Patients also showed right amygdala hyperactivation *versus* HC during passive viewing of angry and neutral faces ($t =2.82$, $p=0.005$ and $t = 2.34$, $p=0.02$ respectively).

ACC: In response to angry faces during passive viewing, patients demonstrated hyperactivation in the right ACC ($t =2.76$, $p=0.006$). However, during explicit (subjective fear) ratings of angry faces ($t =2.46$, $p=0.02$) and during implicit (nose width) ratings of

angry, happy and neutral faces, patients demonstrated right ACC hypoactivation (*t*'s= 2.17–3.38, *p*'s =0.03–0.001) (Fig. 2).

IFG: Patients demonstrated hypoactivation in the right IFG during implicit (nose width) ratings of happy and neutral faces (*t* =1.96, *p*=0.05 and *t* =2.31, *p*=0.02 respectively) (Fig. 3).

Putamen: Patients showed left putamen hyperactivation during passive viewing of angry and neutral faces (*t* =2.38, *p*=0.02 and *t* =2.19, *p*=0.03 respectively) and left putamen hypoactivation during explicit (hostility) ratings of happy faces (*t* =2.71, *p*= 0.007).

Post-hoc analyses

Covarying age, ratings and reaction time—The three-way interactions remained significant when covarying age, hostility ratings of neutral faces and reaction time (*p*'s <0.05).

Mood state, co-morbid illnesses and medication—*Post-hoc t* tests comparing euthymic *versus* non-euthymic patients, patients with and without a co-morbid diagnosis, and unmedicated *versus* medicated patients indicated that mood state, co-morbidity and medication were unlikely to be driving the findings in most ROIs (*p*'s >0.07; see Supplementary Material). There was no association between activation in any ROI and number of medications, YMRS, CDRS or SIGH-SAD scores.

Diagnosis ×age group

This two-way interaction was significant (*p*< 0.001, uncorrected, *k*=152; *p*<0.001, FWE corrected) in the left amygdala (−16, −4, −18) ($F_{1,177}$ =5.40, *p* =0.02), with child BD demonstrating greater activation than adult BD (*p*=0.03).

Main effects of diagnosis

We found main effects of diagnosis in all ROIs (*p*'s 0.001, FWE corrected) except the left amygdala (*p*=0.26, FWE corrected) (see Supplementary Material and Table S3). Compared to HC, BD showed hyper-activation in the right amygdala (*t* =−2.20, *p*= 0.03), left putamen (*t* =−1.94, *p*=0.06) and right putamen (*t* =−1.78, *p*=0.08). Also compared to HC, BD showed hypoactivation in the left (*t* =2.39, *p*=0.02) and right (*t* =2.27, *p*=0.03) ACC and left (*t* =2.30, *p*=0.02) and right (*t* =2.79, *p*=0.006) IFG.

Discussion

To our knowledge, this is the first study to compare neural activation in response to multiple face emotions and attentional conditions in adults and children with and without BD. We found that, relative to HC, both pediatric and adult patients demonstrated amygdala hyperactivity during both explicit ratings (hostility of fearful faces) and unconstrained processing (passive viewing of angry and neutral faces). BD hypoactivation in the IFG was present during implicit processing (nose width ratings) of neutral and happy faces. ACC and putamen abnormalities were present in response to angry, happy and neutral faces; however,

the direction of dysfunction depended on attentional demands. BD patients showed ACC and putamen hyperactivation to angry and neutral faces when attention was unconstrained but ACC and putamen hypoactivation when attention was constrained, either with an implicit (nose width rating) or explicit (subjective fear or hostility rating) task. Neural dysfunction did not differ between euthymic *versus* non-euthymic, medicated *versus* unmedicated BD patients, and those with *versus* those without co-morbidities. Behaviorally, consistent with work in a partially overlapping sample (Rich *et al.* 2006; Brotman *et al.* 2010), pediatric BD patients rated neutral faces as more hostile than did other groups.

In the context of multiple face emotions and attention conditions, patients had pervasive overactivity in the amygdala in response to negatively valenced and neutral faces during both unconstrained attention and explicit face emotion processing. Main effects of diagnosis also showed BD hyperactivity in the right amygdala across the entire task (i.e. all attention conditions and face emotions). The amygdala is crucial to effective emotional appraisal and regulation (Davis & Whalen, 2001), and our results are consistent with BD patients' dysfunction in these domains (Pavuluri & Passarotti, 2008; Kohler *et al.* 2011). Our findings add to the existing literature by demonstrating amygdala hyperactivation in both pediatric and adult BD across several attentional conditions and in response to several face emotion types.

Consistent with the literature (Chen *et al.* 2011; Delvecchio *et al.* 2012; Kupferschmidt & Zakzanis, 2011; Foland-Ross *et al.* 2012), we also observed IFG hypoactivation in BD during implicit ratings of happy and neutral faces; main effects of diagnosis revealed general BD hypoactivation during the task. The IFG is also crucial in the integration of emotional information (Cabeza & Nyberg, 2000) and emotion regulation (Quirk & Beer, 2006), and plays a role in effective modulation of the amygdala. Indeed, some studies suggest that IFG dysfunction is unique to BD relative to other mood disorders (Delvecchio *et al.* 2012).

In contrast to amygdala hyperactivity and IFG hypoactivation, dysfunction in the cognitive control circuit comprising the ACC and putamen was sensitive to task demands. The relevant literature in BD is mixed, demonstrating both frontostriatal hyperactivity (Lawrence *et al.* 2004; Rich *et al.* 2006; Pavuluri *et al.* 2007; Wessa *et al.* 2007; Foland *et al.* 2008; Hassel *et al.* 2008, 2009; Robinson *et al.* 2008; Chen *et al.* 2010; Surguladze *et al.* 2010; Ladouceur *et al.* 2011; Hulvershorn *et al.* 2012; Keener *et al.* 2012) and hypoactivity (Yurgelun-Todd *et al.* 2000; Lawrence *et al.* 2004; Lennox *et al.* 2004; Blumberg *et al.* 2005; Pavuluri *et al.* 2007, 2009; Altshuler *et al.* 2008; Foland *et al.* 2008; Killgore *et al.* 2008; Pochon *et al.* 2008; Hassel *et al.* 2009; Garrett *et al.* 2012; Hulvershorn *et al.* 2012) in BD. Our work may clarify the previous findings by indicating that, compared to HC, unconstrained viewing was associated with hyperactivity in BD whereas directed attention (either explicit or implicit ratings) elicited hypoactivation in these regions.

The ACC and putamen are important components of the emotional processing and cognitive control circuits, with involvement in attention allocation, conflict detection and cognitive interference mediation (Devinsky *et al.* 1995; Bush *et al.* 2000). When attention was unconstrained during passive viewing of angry or neutral faces, BD patients demonstrated ACC, amygdala and putamen hyperactivation. It is difficult to interpret activation patterns

during passive viewing because we do not know the cognitive processes engaged. However, in the absence of attentional instructions, viewing emotional faces while continuing to comply with the demands of being in the scanning environment may require greater engagement of cognitive control regions in patients than in healthy subjects.

In contrast to hyperactivity during passive viewing of angry and neutral faces, BD patients showed hypoactivation in the ACC and putamen when asked to attend to either nose width or their subjective fear while viewing a face. Of note, the pattern of activation in these areas during constrained attention tasks was similar to that in the IFG. This suggests that, compared to healthy subjects, patients did not engage the cognitive control circuit effectively in the context of these task demands. The nose width rating task is, in essence, a cognitive interference task because subjects are asked to rate nose width while not attending to the face emotion. Healthy subjects recruited the cognitive control circuit during this task whereas BD patients showed relative hypoactivity in the circuit, consistent with prior work demonstrating executive (Fleck *et al.* 2008) and cognitive control (Strakowski *et al.* 2005; Drevets *et al.* 2008) dysfunction in BD. Similarly, when rating their subjective fear of an angry or happy face, BD patients did not engage this circuit. Despite these differences in neural activity, there were no group differences in performance, possibly because imaging measures may be more sensitive to group differences than behavioral measures. Other studies also find decreased PFC activation in BD patients without group differences in performance (Foland *et al.* 2008; Hassel *et al.* 2008; Foland-Ross *et al.* 2012).

We expected, but did not observe, three additional findings in the amygdala: (1) that the implicit task (nose width), like the explicit and passive viewing tasks, would elicit amygdala hyperactivity; (2) that during implicit processing amygdala dysfunction would be more marked in pediatric *versus* adult BD; and (3) that BD would show amygdala hyperactivity to happy faces.

While multiple reasons, including Type II error, may have contributed to not observing amygdala hyperactivity during implicit processing, one potential explanation is that our implicit task involves nose width rating rather than the more commonly used gender labeling (Lawrence *et al.* 2004; Kalmar *et al.* 2009; Surguladze *et al.* 2010; Ladouceur *et al.* 2011; Kim *et al.* 2012). We used nose width, as opposed to gender labeling (a binary option), to parallel the 1–5 ratings in the explicit rating conditions. If subjects had been allowed to process the face globally within the context of an implicit task such as gender labeling, rather than being asked to direct their attention to a specific region of the face (nose), we may have detected amygdala hyperactivity in BD. In fact, recent eye tracking work indicates dysfunctional gaze patterns in BD, whereby patients focus less on the eyes and more on the nose relative to HC subjects (Kim *et al.*, in press). In the nose width condition, subjects were instructed to focus their eye gaze to the nose. This task instruction may have obfuscated between-group differences in amygdala processing during this implicit processing condition. In addition, it has been suggested that tasks that impose fewer attentional demands (e.g. gender labeling, passive viewing) are more likely to elicit amygdala activation (Costafreda *et al.* 2008); judging nose width requires a relatively high level of effortful attention and thus may be less likely to elicit amygdala activation. Consistent with this, in the current

study we found amygdala hyperactivation during passive viewing of angry and neutral faces but not during the implicit task (nose width).

Second, we did not detect differences in amygdala function between pediatric and adult BD specifically during the implicit rating condition. However, across all attention conditions and face emotions, diagnosis by age group interactions showed that left amygdala hyperactivation was more pervasive in pediatric than in adult BD patients. The one prior study comparing pediatric *versus* adult BD used a gender labeling paradigm; across emotions, there was amygdala hyperactivity in pediatric BD *versus* adult BD and healthy subjects (Kim *et al.* 2012). Consistent with those results, our findings suggests that, relative to adult BD, pediatric patients' amygdala dysfunction may be particularly pervasive and less sensitive to attentional demands and face emotions.

Third, although angry, fearful and neutral faces elicited amygdala hyperactivity, we did not observe amygdala hyperactivation to happy faces. Others have noted amygdala hyperactivation to happy faces in both BD children and adults (Lawrence *et al.* 2004; Blumberg *et al.* 2005; Chen *et al.* 2006; Pavuluri *et al.* 2007, 2009; Surguladze *et al.* 2010). Those paradigms included varying intensities of happiness in the faces, with some studies demonstrating amygdala hyperactivity to mild, and others to intense, happiness (Lawrence *et al.* 2004; Surguladze *et al.* 2010). Here, we used only one face emotion intensity. Future studies are needed to examine the neural correlates of subtle changes in emotional expressions and corresponding patterns of neural modulation.

These findings should be considered in light of additional limitations. First, our BD patients were in a variety of mood states at the time of testing, which may influence neural activity (Foland-Ross *et al.* 2012; Liu *et al.* 2012; Townsend & Altshuler, 2012). However, findings did not differ between euthymic (*n*=36) and non-euthymic (*n*=24) BD patients, and there was no relationship between mood rating scores and activation in any ROIs, suggesting that mood state did not account for our results. Second, most BD patients had co-morbid diagnoses (*n*=34), but they did not differ from BD patients without a co-morbid diagnosis (*n*=28) in blood oxygen level-dependent (BOLD) activity in most ROIs. Of note, BD patients with comorbidities showed higher amygdala activity during passive viewing of neutral faces compared to BD without co-morbidities, suggesting that co-morbid diagnoses may be associated with more severe amygdala dysfunction. Third, most patients were medicated; although activation did not differ between medicated (*n*=47) and unmedicated (*n*=12) patients, these *post-hoc* analyses were underpowered and thus susceptible to Type II error. Studies indicate that neural dysfunction may normalize with treatment, suggesting that medication may be unlikely to be driving the between-group differences that we observed (Chang *et al.* 2008; Phillips *et al.* 2008; Passarotti *et al.* 2010, 2011; Hafeman *et al.* 2012; Pavuluri *et al.* 2012). Although our sample sizes compare favorably to those in the literature, future studies with even larger samples are needed to clarify the role of psychotropic medication, co-morbidity and mood state on the neural correlates of face emotion processing. Finally, although this face viewing paradigm enabled us to examine multiple face emotions and attention states, each is sampled relatively sparsely (eight replicates for each attentional condition). Although this design maintained short task duration and increased tolerance for youth and adults with severe psychopathology, it precluded

connectivity analyses. The task is also prone to Type II error, particularly in the context of complicated models with multiple within- and between-subject variables. Thus, the findings we observed are likely to be particularly robust.

In sum, our results demonstrate fronto-limbic-striatal dysfunction in both pediatric and adult BD. In the context of multiple face emotions and attention conditions, we observed amygdala hyperactivation during both explicit (i.e. hostility ratings of fearful faces) and unconstrained processing (i.e. passive viewing of angry and neutral faces), and IFG hypoactivation during implicit ratings of happy and neutral faces. By contrast, ACC and striatal dysfunction were most sensitive to task demands. We observed hypoactivation in BD in these regions when attention was directed during either an implicit or an explicit rating, but hyperactivation when attention was unconstrained. Future imaging studies should continue to examine stimulus valence and attentional demands in the pathophysiology of pediatric and adult BD. Moreover, work is needed to explore the functional connectivity of the frontal-limbic-striatal circuit in the development and maintenance of the illness.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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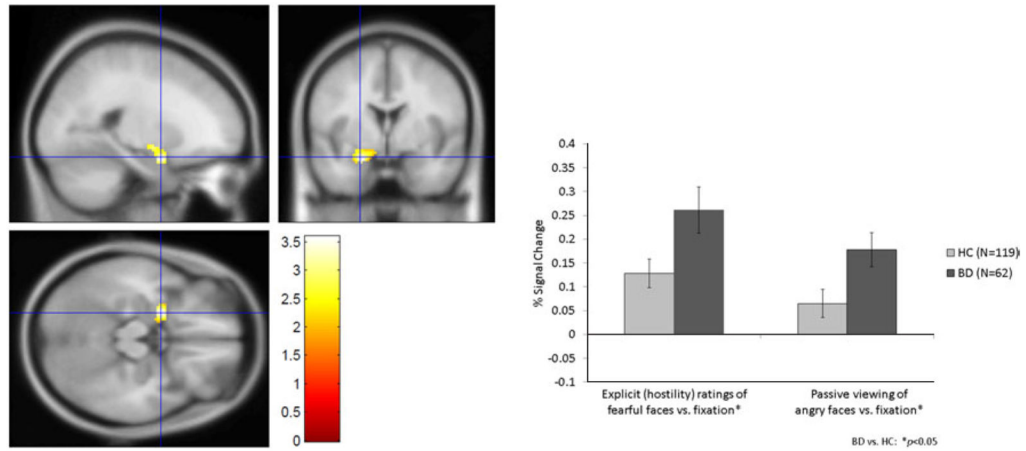
Fig. 1.
Left amygdala hyperactivity during explicit (hostility) ratings of fearful faces and passive viewing of angry faces in patients with bipolar disorder (BD) and healthy comparisons (HC).
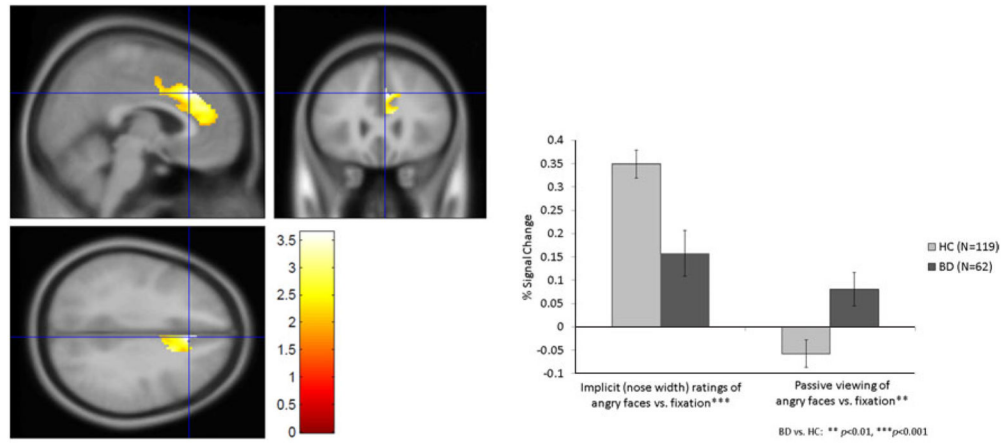
Fig. 2.
Right anterior cingulate cortex (ACC) activation during angry faces: hypoactivity during implicit (nose width) ratings but hyperactivity during passive viewing in patients with bipolar disorder (BD) and healthy comparisons (HC).
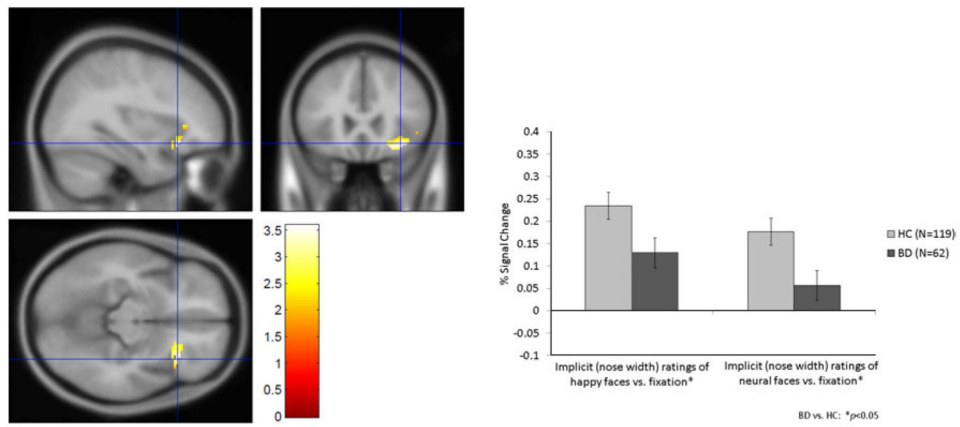
Fig. 3.
Right inferior frontal gyrus (IFG) hypoactivation during implicit (nose width) ratings of happy and neutral faces in patients with bipolar disorder (BD) and healthy comparisons (HC).

Table 1

Subject characteristics

Characteristics	Pediatric BD (*n*=36)	Adult BD (*n*=26)	Pediatric HC (*n*=57)	Adult HC (*n* =62)
Age (years)[a]	14.77±2.55	41.70±10.30	14.30±2.57	34.24±9.54
WASI full-scale IQ[b]	110.06±13.38	115.60±11.69	112.30±13.33	116.09±11.63
Age of onset (years)[c]	10.74±3.30	21.44±9.18	–	–
YMRS[d]	9.39±5.98	4.92±5.19	–	–
CDRS	27.78±8.90	–	–	–
SIGH-SAD[e]	–	16.79±10.91	–	–
No. of medications	2.21±1.50	2.11±1.55	0	0
Male	19/36 (52.8)	8/26 (30.8)	27/57 (47.4)	24/62 (38.7)
Bipolar type[f]				
BD-I	31/36 (86.1)	13/26 (50.0)	–	–
BD-II	5/36 (13.9)	13/26 (50.0)	–	–
Mood state[d,e]				
Euthymic	22/36 (61.1)	14/24 (58.3)	–	–
Depressed[g]	3/36 (8.3)	7/24 (29.2)	–	–
Hypo/manic[h]	9/36 (25.0)	1/24 (4.2)	–	–
Mixed	2/36 (5.6)	2/24 (8.3)	–	–
Co-morbid conditions[i,j]				
Any co-morbidity	25/36 (69.4)	9/15 (60.0)	–	–
Any anxiety disorder[k]	14/36 (38.9)	9/26 (34.6)	–	–
ADHD[j]	15/36 (41.7)	0/9 (0)		
ODD or CD[l]	11/36 (30.6)	0/26 (0)	–	–
Any substance abuse/dependence	0/36 (0)	1/26 (3.8)	–	–
Medication[m]				
Unmedicated	9/35 (25.7)	3/24 (12.5)	57 (100)	62 (100)
Atypical antipsychotic	16/35 (45.7)	6/24 (25.0)	–	–
Lithium	12/35 (34.3)	6/24 (25.0)	–	–
Antiepileptic[n]	18/35 (51.4)	20/24 (83.3)	–	–
Antidepressant	10/35 (28.6)	10/24 (41.7)	–	–
Stimulants[o]	8/35 (22.9)	0 (0)	–	–

[a]Adult groups were older than children groups (*p*'s<0.001). Adult BD patients were older than adult HC (*p*<0.005).

[b]Missing data from one adult BD, one child HC and seven adult HC.

[c]Missing data from one pediatric BD. Pediatric BD patients had an earlier age of onset than adult BD patients (*p*<0.001).

[d]Missing data from two adult BD patients. Higher YMRS scores in pediatric than in adult BD patients (*p*<0.005).

[e]Missing data from two adult BD patients.

[f]Pediatric BD were more likely to be type I compared to adult BD ($p<0.005$).

[g]Adult BD were more likely to be depressed compared to pediatric BD ($p<0.05$).

[h]Pediatric BD were more likely to be hypomanic compared to adult BD ($p<0.05$).

[i]Missing co-morbid diagnosis data from one pediatric BD.

[j]Missing co-morbid ADHD diagnostic data from 17 adult BD.

[k]Includes generalized anxiety disorder, separation anxiety disorder, social phobia, panic disorder, post-traumatic stress disorder and obsessive–compulsive disorder.

[l]Higher rates of ODD/CD in pediatric than in adult BD ($p<0.005$).

[m]Missing medication data from one pediatric and two adult BD patients.

[n]Adult BD patients were more likely to be taking antiepileptic medications compared to pediatric patients ($p<0.01$).

[o]Pediatric BD patients were more likely to be taking stimulant medications compared to adult patients ($p<0.01$).

Table 2

Region of interest (ROI) results of the diagnosis×face emotion×attention state analysis

Area of activation	BA	Side	Cluster size	MNI coordinates x, y, z	F	p FWE corrected	Attention condition, face emotion *versus* fixation	Between-group differences
Amygdala		L	215	−22, 0, −18	3.58	0.006	Explicit (Hostility)	BD>HC*
							Fearful	
							Passive	BD>HC*
							Anger	
Amygdala		R	147	28, 0, −12	3.43	0.009	Passive	BD>HC**
							Anger	
							Passive	BD>HC*
							Neutral	
ACC	32	R	972	4, 26, 34	3.63	0.029	Explicit (Afraid)	HC>BD*
							Anger	
							Implicit (Nose width)	HC>BD***
							Anger	
							Implicit (Nose width)	HC>BD*
							Happy	
							Implicit (Nose width)	HC>BD**
							Neutral	
							Passive	BD>HC**
							Anger	
IFG	45/47	R	159	34, 24, −12	3.59	0.021	Implicit (Nose width)	HC>BD*
							Happy	
							Implicit (Nose width)	HC>BD*
							Neutral	
Putamen		L	471	−30, −8, −8	3.72	0.009	Explicit (Hostility)	HC>BD**
							Happy	
							Passive	BD>HC*
							Anger	

Area of activation	BA	Side	Cluster size	MNI coordinates x, y, z	F	p FWE corrected	Attention condition, face emotion *versus* fixation	Between-group differences
							Passive	BD>HC[*]
							Neutral	

ACC, Anterior cingulate cortex; IFG, inferior frontal gyrus; BA, Brodmann area; BD, bipolar disorder; HC, healthy comparisons; R, right; L, left.

*
p<0.05,

**
p<0.01,

***
p<0.001.