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Deficits in Attention to Emotional Stimuli Distinguish Youth with Severe Mood Dysregulation from Youth with Bipolar Disorder

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Abstract

Studying attention in the context of emotional stimuli may aid in differentiating pediatric bipolar disorder (BD) from severe mood dysregulation (SMD). SMD is characterized by chronic irritability, arousal, and hyper-reactivity; SMD youth frequently receive a BD diagnosis although they do not meet DSM-IV criteria for BD because they lack manic episodes. We compared 57 BD (14.4± 2.9 years old, 56% male), 41 SMD (12.6±2.6 years old, 66% male), and 33 control subjects (13.7±2.5 years old, 52% male) using the Emotional Interrupt task, which examines how attention is impacted by positive, negative, or neutral distracters. We compared reaction time (RT) and accuracy and calculated attention interference scores by subtracting performance on neutral trials from emotional trials. Between-group analyses indicated that SMD subjects had significantly reduced attention interference from emotional distracters relative to BD and control subjects. Thus, attention in SMD youth was not modulated by emotional stimuli. This blunted response in SMD youth may contribute to their affective and behavioral dysregulation.

Keywords

Pediatric bipolar disorder; Mood dysregulation; Children; Attention; IAPS

Introduction

The use of neurocognitive measures to complement clinical information has the potential to improve our understanding of the etiology of mental disorders and clarify the diagnostic process. This is particularly true with pediatric bipolar disorder (BD), where the pathophysiology of the disorder is unclear and the diagnostic boundaries remain a topic of debate.

Epidemiological studies indicate low rates of BD in youth (approximately 1%) (Lewinsohn et al. 1995; Costello et al. 1996). However, results of recent studies indicate that the diagnosis is

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being assigned to young people with increasing frequency, with up to a forty-fold increase in diagnosis in outpatient settings (Moreno et al. 2007).

A possible explanation for the upsurge in rates of BD is that the boundaries for diagnosing mania in youth have expanded such that youth with mood and behavior dysregulation, but without distinct episodes of mania, are being diagnosed with BD. Youth with severe mood dysregulation (SMD) (Leibenluft et al. 2003) may exemplify these individuals in whom the appropriate diagnosis is unclear. SMD youth exhibit chronic, severe irritability and anger, along with the subset of Attention Deficit Hyperactivity Disorder (ADHD) symptoms that overlap with the DSM-IV "B" criteria of BD listed in the DSM-IV (i.e. intrusiveness, pressured speech, distractibility, psychomotor agitation) (American Psychiatric Association 1994). SMD youth also display extreme hyper-reactivity to negative emotional stimuli which, while similar to the "loses temper" criterion of Oppositional Defiant Disorder (ODD) (McMahon and Wells 1998), is operationalized more precisely in the SMD classification.

SMD youth reflect an important research sample because they are "nosological orphans" (Carlson et al. 2004). That is, while many SMD youth have ADHD and/or Oppositional Defiant Disorder (ODD), these diagnoses fail to capture the severity of their mood impairment, i.e. their extreme irritability. In addition, although SMD youth have many symptoms which overlap with BD, they fail to meet DSM-IV criteria for mania because SMD irritability is unremitting and non-episodic. Classifying and studying youth according to the SMD categorization is advantageous to relying on established diagnoses such as ADHD or ODD because the SMD criteria operationalize specifically extreme irritability, and the role of irritability in the diagnosis of pediatric BD is central to the controversy over the diagnosis.

The lack of consensus regarding the diagnostic status of SMD youth has significant clinical ramifications, including the escalation of prevalence rates of pediatric BD and the implementation of potentially ineffective treatments for SMD youth. Regarding the latter, SMD youth diagnosed with BD may be prescribed psychotropic medications (e.g. lithium, atypical anti-psychotic medications) that are not efficacious, while medications that might treat their depression, anxiety, and ADHD (e.g. anti-depressants, stimulants) may be withheld for fear of causing a manic reaction. Direct comparisons of BD and SMD youth are needed to clarify the nosological relationship of these two conditions and to ultimately inform optimal treatments.

Data from a number of domains suggest that the validity of the SMD classification is distinct from BD. For example, two longitudinal epidemiological studies have examined the developmental progression of SMD and chronic irritability. First, an examination of the Great Smoky Mountains Study found that children with SMD at a mean age of 11 were at significant risk for unipolar depressive disorders by early adulthood (Brotman et al. 2006). A separate study with the Children in the Community longitudinal dataset assessed associations between chronic irritability, such as is seen in SMD, assessed at mean age 13, and psychiatric diagnosis assessed at mean age 33. These data indicated that chronic irritability in adolescence predicts MDD, dysthymia, and generalized anxiety disorder (GAD), but not BD, in adulthood (Stringaris et al. 2009). Thus, two separate longitudinal epidemiological studies suggest that SMD-like youth in early adolescence are at risk for unipolar depressive disorders and anxiety in adulthood.

A small preliminary study indicates a lack of familial aggregation of BD in SMD youth. Specifically, we found that the rate of BD diagnosis is significantly lower in the parents of SMD youth than in the parents of youth with strictly-defined BD (3% vs. 33%) (Brotman et al. 2007a). In fact, the rate seen in SMD youth is comparable to that seen in the general population (Kessler et al. 2005).

Other studies find behavioral, cognitive, and pathophysiological differences in BD and SMD youth. For example, studies of cognitive flexibility, the ability to adapt to changing environmental contingencies, find that whereas both SMD and BD youth show deficits in cognitive flexibility, across tasks these deficits are more consistent in BD youth (Dickstein et al. 2007). In addition, although both SMD and BD youth have deficits in accurately identifying and categorizing facial emotional displays (Rich et al. 2008; Guyer et al. 2007), the neural mechanisms of this impairment may differ. Specifically, SMD youth display decreased amygdala activation, relative to both BD youth and controls, when rating their fear of neutral faces (Brotman et al. 2009). These studies provide neurocognitive data differentiating SMD and BD youth.

Finally, we have also found differences in how BD and SMD youth respond to frustration (Rich et al. 2007). In this study, we used a standard attention task with an added emotional component, the affective Posner (Perez-Edgar and Fox 2005), to induce frustration. We found that while both BD and SMD youth displayed more negative affective responses to the frustrating context than did controls, the two patient groups displayed different psychophysiological deficits, as measured by cortical event-related potentials (ERP's). Further, whereas psychophysiological perturbations in BD subjects were isolated to the emotional condition, SMD deficits were seen in both emotional and nonemotional contexts. Thus, the global attention deficit in SMD youth was relatively impervious to the emotionality of the context. In sum, similar affect in BD and SMD youth may have divergent attention-related neurocognitive deficits which are differentially impacted by emotional stimuli.

These results support the use of a paradigm which systematically manipulates emotional and attention conditions to provide information about the pathophysiological relationship between SMD and BD youth. The emotion-attention interface is important in the development of mood and behavior regulation, since a child's ability to deploy attention properly in emotional contexts is central to his/her ability to moderate mood and behavior (Mischel et al. 1989; Kopp 2002; Sethi et al. 2000; Posner and Rothbart 1998). Evidence indicates that environmental stimuli compete for limited attentional resources (Desimone and Duncan 1995). One potential consequence is that emotionally salient stimuli preferentially engage attention, which subsequently impacts information processing and the resulting cognition, affect, and behavior (Pessoa et al. 2002; Vuilleumier et al. 2001). A hallmark of many affective disorders is impaired attention to task-relevant stimuli when salient emotional stimuli are also present (Yamasaki et al. 2002).

We compared responsivity to emotional stimuli in SMD, BD, and healthy control participants. We used the Emotional Interrupt task (Mitchell et al. 2006, 2008), which examines the impact of positive and negative emotional stimuli on attention and thus allows for an examination of attentional biases and their impact on cognitive functioning. Consistent with prior work (Vuilleumier et al. 2001; Simpson et al. 2000), we predicted that controls would display attention biases to emotional stimuli; as such they would show greater interference from emotional relative to neutral distracters (Mitchell et al. 2006). Further, given the results of our prior work with the affective Posner task (Rich et al. 2007, 2005b), we predicted that BD youth would display attention biases to emotional stimuli greater than in controls (i.e., they would show greater interference by emotional distracters relative to controls). In contrast, again as seen on the affective Posner task (Rich et al. 2007), we hypothesized that in SMD youth, attention performance would not differ in the presence of emotional vs. neutral stimuli, meaning SMD youth would display diminished reactivity to emotional stimuli compared to controls. Finally, to examine a possible relationship between attention biases and the real-world clinical experience of BD and SMD youth, exploratory analyses compared performance on the Emotional Interrupt task to parent and clinician ratings of social functioning.

Method

Participants

Fifty-seven BD (14.4±2.9 years old, 56% male), 41 SMD (12.6±2.6 years old, 63% male), and 33 control (CON) (13.7±2.5 years old, 52% male) youth were enrolled in an IRB-approved study at the National Institute of Mental Health (NIMH). Subjects and a guardian provided written informed assent/consent. All subjects and a parent completed the Kiddie-Schedule for Affective Disorders-Present and Lifetime Version (K-SADS-PL) (Kaufman et al. 1997), a semi-structured diagnostic interview administered to parents and children separately by graduate level clinicians with established reliability (i.e. kappa ≥0.9, by blinded review of taped evaluations). SMD diagnoses were made using a K-SADS supplementary module. Differentiation of SMD from BD also had excellent reliability (i.e. kappa ≥0.9, by blinded review of a randomly selected sample of taped evaluations).

All BD subjects met DSM-IV criteria for BD, with the additional strict proviso that the history of at least one full duration hypomanic or manic episode—i.e. lasting ≥4 days for hypomania or ≥7 days for mania—was defined by an abnormally elevated or expansive mood and/or grandiosity (Leibenluft et al. 2003); at least three other DSM-IV criterion "B" mania symptoms were also required (Geller et al. 2002). Comorbid diagnoses, also assessed using the K-SADS, were diagnosed based on their impairing presence during euthymia and met criteria for impairment, as per the DSM-IV.

Inclusion criteria for SMD were non-episodic abnormal mood (anger or sadness), present at least half of the day most days, and of sufficient severity to be noticeable to others, over-reactivity to negative emotional stimuli (e.g. explosive tantrums) at least three times weekly, and hyper-arousal symptoms (including at least three of: insomnia, intrusiveness, pressured speech, flight of ideas/racing thoughts, distractibility, psychomotor agitation) (Leibenluft et al. 2003). Symptoms had to begin prior to age 12, and be present for at least one year without remission for longer than 2 months. Symptoms had to cause severe impairment in one setting (home, school, peers), and at least mild impairment in another. Euphoric mood or distinct episodes lasting ≥1 day were exclusionary (Leibenluft et al. 2003).

Control subjects and a parent completed the K-SADS to ensure that there was no mood disorder in the subject, and a review of family psychiatric history confirmed no psychiatric history in first-degree relatives. All controls had normal physical and neurological examinations.

Exclusion criteria included I.Q. <70 [as measured with the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler 1999)], pervasive developmental disorder, unstable medical illness, or substance abuse within 2 months.

Measures

A series of clinician- and parent-report questionnaires were administered to establish the patient samples' mood at the time of testing and overall functioning. In addition, given that differential attention to emotional stimuli may yield mood and behavior dysregulation, which would likely impair social interactions with peers and family members, we also evaluated social function in patients.

Children's Depression Rating Scale (CDRS) (Poznanski et al. 1984)—The CDRS is a 17-item, clinician-completed measure of current severity of depression, including affective, cognitive, somatic, and psychomotor symptomatology. Information is obtained based on child and parent report and the interviewer's observations. A score of 40 or above is considered indicative of clinically significant depression symptoms. Convergent validity is strong, as demonstrated by its correlation with other rating scales of depression (r's = 0.84–0.87)

(Poznanski et al. 1984; Myers and Winters 2002; Shain et al. 1990). Two week test-retest reliability is good (0.86), interrater agreement is acceptable (r=0.86), and the measure has strong discriminant validity in that it consistently distinguishes children with a depressive disorder from those without such a diagnosis (Poznanski et al. 1983).

Young Mania Rating Scale (YMRS) (Young et al. 1978)—The YMRS is an 11-item clinician interview administered to child and parents to assesses core manic symptomatology presented over the past 48 hours (e.g. elevated mood, speech problems, language-thought disorder, motor activity, sleep). Item scores range from 0 to 4, with total scores ranging from 0 to 60. Scores of 12–25 are considered indicative of hypomania, and scores of 26 and above are considered indicative of mania. Concurrent validity was demonstrated via strong correlations with DSM criteria and a structured interview (Fristad et al. 1992), and correlations with other measures of mania (r's = 0.71–0.89) (Young et al. 1978). It has adequate internal consistency (α = 0.80–0.90), divergent validity (nonsignificant correlations with ratings of hyperactivity and depression) (Fristad et al. 1995; Youngstrom et al. 2003), and interrater reliability (0.93) (Young et al. 1978). The YMRS also has strong diagnostic efficiency in that scores differentiate youth with bipolar disorder from those with MDD, ADHD, and a heterogeneous collection of disorders (Youngstrom et al. 2003).

Children's Global Assessment Scale (CGAS) (Shaffer et al. 1983)—This clinician-completed measure provides an assessment of general level of symptomatology and functional impairment during the past 1 and 6 months. It was adapted from the Global Assessment Scale, which also serves as the basis for Axis-V ratings in the DSM-IV. The rating is based on information gathered by the clinician during interactions with the child and parents (e.g. structured diagnostic interview). Ratings are made along a 100-point scale, with 1 being most impaired. Descriptors are given for each 10-point interval. Six-month test-retest reliability is strong (r=0.85), and it has strong concurrent validity based on significant correlations with the Child Behavior Checklist (CBCL) (Bird et al. 1987), the Rutter's Parental Questionnaire (Sourander et al. 1995) and the Columbia Impairment Scale (Steinhausen and Metzke 2001). The CGAS displays strong discriminant validity, in that it accurately differentiates youth presenting to inpatient and outpatient psychiatric clinics (Shaffer et al. 1983), cases and non-cases (Bird et al. 1990), and those using and not using mental health services (Steinhausen and Metzke 2001).

Longitudinal Interval Follow-up Evaluation (LIFE) (Keller et al. 1987)—The LIFE is a clinician-administered interview of parents to evaluate the child's psychosocial functioning over the previous 6 months. The semistructured interview format allows clinicians to probe for information so as to establish the child's best and worst functioning in the domains of relationships with family members and peers, as well as academic performance. Scores range from 1 to 3 on for each domain, with higher scores indicating more severe impairment. The measure's authors report very high interviewer-observer reliability, along with an ICC of 0.82 to 0.86 for social functioning items, and significant concurrent reliability using the Global Assessment Scale (r=0.58) (Keller et al. 1987).

Social Responsiveness Scale (SRS) (Constantino et al. 2004)—The SRS is a 65-item parent-completed scale that assesses trait social behaviors, in particular social reciprocity (e.g. social awareness, social information processing, and capacity for reciprocal social responses). Each item uses a 4-point Likert scale, with total scores ranging from 0 to 195, where higher scores indicate greater impairment. Although originally developed for use in youth with autism spectrum disorders, the scores have been shown to be continuously distributed in the general population (female mean score = 27.6±18.1, male mean score = 33.7±20.9) (Constantino et al. 2000; Constantino and Todd 2003; Constantino and Gruber 2005). SRS

scores are unrelated to IQ (Constantino et al. 2003; Constantino et al. 2000), ICC for test-retest reliability up to 27 months is 0.80, and interrater reliability between parents is 0.91 (Constantino and Gruber 2005). The SRS displays significant concurrent validity with the CBCL Social Problems subscale (r=0.64) (Bolte et al. 2008), and it distinguishes youth with autism spectrum disorders from youth with other psychiatric conditions and healthy controls (Constantino et al. 2000; Bolte et al. 2008)

Procedure

The Emotional Interrupt Task—The Emotional Interrupt task (Mitchell et al. 2006, 2008) assesses the impact of emotional stimuli on attention. On each trial, a fixation point appeared (800 ms), followed by a picture of varying emotional valence (200 ms): either negative, positive or neutral. After this picture, the target stimulus was presented, either a circle or a square (150 ms), then the same picture that had preceded the target shape (400 ms), and then the inter trial interval (a blank screen; 1,200 ms) (see Fig. 1). Participants were instructed to respond as quickly as possible to the circle/square stimuli (left button press to circle, right to square). Reaction time (RT) was the time required for the subject to identify the shape of the target. A trial was considered to be an error if the subject misidentified the circle/square, or failed to respond. Trials for which the participants' RTs were less than 150 ms or greater than 1,500 ms were considered outliers and excluded from analysis.

Pictorial stimuli bracketing the target consisted of images from the International Affective Picture System (IAPS) (Lang et al. 1999). Pictures were classified as neutral, positive, or negative according to standard ratings in the IAPS manual, on a 1–9 scale, based on valence (higher scores corresponding to greater pleasantness) and arousal (higher scores corresponding to greater arousal). There were a total of 192 trials, 64 each of the three picture emotion types: negative, positive and neutral. Selected images were appropriate for presentation to children. Prior to a subject's participation, parents were allowed to review a subset of the images to insure their appropriateness.

Statistical Procedures—To compare our samples on demographic and clinical variables, we used chi-square analyses to examine gender, diagnoses, and medication use, and ANOVAs to examine age, IQ, and clinician and parent report of functioning based on the CDRS, YMRS, CGAS, LIFE, and SRS.

For our primary analyses, we conducted two separate repeated measures MANCOVAs, one for RT and the other for accuracy. Group (BD, SMD, control) was the between-group variable, performance (RT, accuracy) on positive, negative, and neutral distracter trials was the independent variables, and age and IQ served as covariates due to group differences (see below).

Due to group differences in performance during the neutral trials (see below), we conducted additional analyses controlling for such differences. Specifically, we calculated attention interference scores by subtracting performance on trials with neutral pictures from performance on trials with negative and positive pictures. We conducted two repeated measures MANCOVAs, one for attention interference for RT and the other for accuracy, to compare the groups on the positive and negative attention interference scores. For all MANCOVA and ANOVA analyses we applied the Greenhouse-Geisser procedure to minimize Type I errors, and post-hoc comparisons employed the Tukey test.

Post hoc analyses examined the impact of demographic and clinical variables on attention interference scores. These were conducted to identify potential confounds and examine if particular variables (e.g. mood, medication status, diagnoses) altered the nature of our results. We used the attention interference scores for these secondary analyses because they controlled

for between-group differences in response to neutral stimuli. With the clinical variables, we conducted a series of ANCOVAs where age and IQ served as covariates, we applied the Greenhouse-Geisser procedure to minimize Type I errors, and used the Tukey test for post-hoc comparisons. Specifically, to determine if the differing mood states of our BD subjects during testing impacted our results, we divided the BD sample into those who were euthymic and noneuthymic and compared them to the euthymic SMD subjects and controls. Given that our BD and SMD subjects presented with multiple diagnoses, we divided our patient samples based on the presence of the most common disorders: anxiety, ODD, and ADHD. Specifically, we divided the BD and SMD samples into those with and without an anxiety disorder or ODD, and compared them to controls, with each diagnosis analyzed separately. We divided only the BD sample by ADHD status due to the insufficient number of SMD youth without ADHD (N=7). We examined the role of medication given the high rates of medication use in our patient samples. To do so, we conducted a 5-group ANCOVA comparing medicated and unmedicated BD and SMD subjects to controls. In addition, analyses sought to determine any relationships between demographic variables and attention interference. Bivariate Pearson correlational analyses compared task performance and IQ and age, and to examine the potential impact of gender, we compared males and females across the entire sample and within each group separately using ANOVAs. Finally, exploratory analyses sought to examine if there was a relationship between attention interferences scores and social functioning as measured by the LIFE (Keller et al. 1987) and SRS (Constantino et al. 2004) using bivariate Pearson correlational analyses. All correlational analyses used Bonferroni correction to control for multiple comparisons.

Results

Participant Demographics and Clinical Characteristics (Table 1)

ANOVA found significant group differences for age [$F(2,128) = 5.97$, p=0.003] and IQ [$F(2,128) = 7.13$, p<0.001]. SMD subjects were significantly younger than BD subjects (p= 0.002), with a trend compared to controls (p=0.07). SMD subjects (102.37±13.29) had significantly lower IQ than BD subjects (109.89±13.22) (p=0.01) and controls (113.06± 9.99) (p=0.002). Because of these results, all comparisons controlled for age and IQ. Groups did not differ on gender composition (X^2=1.11, p=0.57) (see Table 1).

Among BD youth, 82.5% (N=47) had at least one co-occurring diagnosis in addition to BD, with an average of 3.17±1.56 total diagnoses; the most common comorbid disorders were ADHD (49.1%), an anxiety disorder (40.9%), and ODD (28.1%). Among SMD youth, 78.1% (N=32) had at least two DSM-IV diagnoses, with an average of 2.7±1.4 total diagnoses; the most common DSM-IV diagnoses were ADHD (82.9%), ODD (73.3%), an anxiety disorder (43.9%), and MDD (22.0%).

ANOVA comparisons of CDRS [$F(1,96) = 0.25$, p=0.62] scores showed that BD youth (30.00 ±9.51) did not differ from SMD youth (29.07±8.53) on clinician-assessed depression symptoms. Scores showed that 64.9% (N=37) of BD subjects were euthymic at testing (CDRS ≤40 and YMRS ≤ 11). Of the 20 non-euthymic BD subjects, 10 were hypomanic (YMRS ≥12, ≤ 24), five had mixed hypomania (YMRS ≥12, ≤ 24 and CDRS ≥40), two were manic (YMRS ≥25), and three were depressed (CDRS ≥40). CDRS scores found that five SMD subjects were currently depressed. CGAS scores, comparable between patient groups, indicated severe overall impairment (BD = 48.61±12.24; SMD = 47.78±7.65). 77.2% (N=44) of BD subjects and 78.0% (N= 32) of SMD subjects were medicated. Groups did not differ on the percentage of medicated subjects, nor the rates of specific medication classes (Table 1).

Social function measures found that BD and SMD subjects were equally impaired in family [$F(1,95)=0.04$, p= 0.84] and peer [$F(1,95)=0.25$, p=0.62] relationships as measured by the

LIFE, and equally impaired in social reciprocity [F(1,82)=0.86, p=0.36], as measured by the SRS (Table 1).

Emotional Interrupt Behavioral Data

Reaction Time—The repeated measures MANCOVA revealed a significant group x picture emotion interaction [F(4,252) = 5.68, p<0.001, $\eta_{partial}^2$=0.09], with group differences for all three picture emotions: neutral [F(2,126) = 6.23, p=0.002, $\eta_{partial}^2$=0.09], negative [F(2,126) = 6.00, p=0.003, $\eta_{partial}^2$=0.09], and positive [F(2,126) = 5.43, p=0.005, $\eta_{partial}^2$=0.08]. Specifically, BD subjects were slower than controls for neutral (p= 0.001), negative (p=0.001) and positive (p=0.001) pictures, while SMD subjects were slower than controls for neutral pictures only (p=0.01). All other comparisons were nonsignificant (Fig. 2).

We conducted follow-up within-group comparisons to further clarify the nature of the interaction and explore how performance differed between the emotional and non-emotional distracters within each sample. We found that in controls, there was a significant effect of picture emotion [F(2,64) = 20.24, p<0.001, $\eta_{partial}^2$=0.26]: controls were significantly slower to both negative (p<0.001) and positive (p<0.001) pictures when compared to neutral pictures, with a nonsignificant difference for the negative vs. positive comparison (p=0.84). Similarly, in BD subjects, there was a significant effect of picture emotion [F(2,112) = 12.06, p<0.001, $\eta_{partial}^2$=0.17]: BD subjects were significantly slower to both negative (p<0.001) and positive (p< 0.001) pictures when compared to neutral pictures, with a nonsignificant difference for the negative vs. positive comparison (p=0.42). In contrast to the results in control and BD subjects, in SMD subjects there was a nonsignificant effect of picture emotion [F(2,80) = 2.05, p=0.16, $\eta_{partial}^2$=0.03]. Thus, in SMD subjects performance did not vary significantly as a function of the emotional vs. non-emotional nature of the distracting picture.

Accuracy—The repeated measures ANCOVA using response accuracy as the dependent variable found a main effect of group [F(2,126) = 8.77, p<0.001, $\eta_{partial}^2$=0.12]: both BD (p=0.006) and SMD (p<0.001) subjects had lower accuracy than did controls, while the patient samples did not differ (p=0.59). There was a nonsignificant group x picture emotion interaction [F(4, 252) = 0.38, p=0.82, $\eta_{partial}^2$=0.005].

Attention Interference Scores

Reaction Time: The repeated measures MANCOVA found a group x emotion interaction in RT attention interference scores [F(2,126) = 6.41, p<0.001, $\eta_{partial}^2$=0.09], with post hoc group differences for both positive [F(2,126) = 9.88, p< 0.0001, $\eta_{partial}^2$=0.14] and negative [F(2,126) = 8.71, p< 0.0001, $\eta_{partial}^2$=0.12] pictures. Post hoc analyses with positive pictures found that SMD subjects had lower RT interference than BD subjects (p<0.0001) and controls (p< 0.0001), but BD subjects did not differ from controls (p= 0.62). Similarly, post hoc analyses for negative pictures found that SMD subjects had significantly lower RT interference than BD subjects (p<0.0001) and controls (p= 0.001), but BD subjects did not differ from controls (p=0.86) (See Fig. 3).

Accuracy: For attention interference scores related to accuracy, the group x emotion interaction was nonsignificant [F(2,126) = 0.23, p=0.79, $\eta_{partial}^2$=0.01] as was the group effect [F(2,126) = 0.51, p=0.60, $\eta_{partial}^2$=0.01].

Secondary Analyses Using RT Attention Interference Scores

Demographic Variables—Bivariate Pearson correlations found that in each sample there was a nonsignificant correlation between IQ and RT attention interference scores, and independent sample t-tests found that females and males had comparable RT attention interference scores across the entire sample and when each group was examined separately (all

p's >0.21). With regards to age, whereas the correlation between age and RT interference was nonsignificant for both BD and control subjects, in SMD subjects there was a significant correlation between increased age and greater RT interference score to negative stimuli (r=0.55, p<0.0001).

Mood—The ANCOVA comparison of euthymic BD subjects (N=37), noneuthymic BD subjects (N=20), SMD subjects, and controls confirmed our previous results: SMD youth had significantly lower RT interference as compared to both euthymic and noneuthymic BD subjects as well as control subjects (all p values <0.01). Euthymic and noneuthymic BD subjects did not differ from control subjects (all p values >0.42).

Comorbid Diagnoses—To examine the potential impact of comorbid diagnoses, we divided our patient samples into those with and without an anxiety disorder or ODD, and compared them to controls, with each comorbidity analyzed separately. We divided only the BD sample by ADHD status due to the insufficient number of SMD youth without ADHD (N=7). For all three ANCOVA comparisons, SMD subjects, regardless of their diagnostic status, had significantly lower RT attention interference as compared to controls and all BD subjects, regardless of their comorbid diagnoses (all p values <0.001). Further, controls and BD subjects did not significantly differ on any of the comparisons.

Medication—To examine the impact of medication, we conducted a 5-group ANCOVA comparing SMD subjects who were medicated (N=32) and unmedicated (N=9), BD subjects who were medicated (N=44) and unmedicated (N= 13), and controls (N=33). We found that both medicated and unmedicated SMD samples had lower RT attention interference scores compared to controls and both medicated and unmedicated BD subjects (all p values <0.02), and all other effects were nonsignificant.

Correlations with Measures of Social Functioning—Our final set of secondary analyses used Pearson correlations to explore possible associations between RT attention interference and social functioning. While there were no significant correlations in BD subjects, in SMD subjects we found a relationship between RT interference score for negative pictures and clinician-report of impaired peer relationships, as measured by the LIFE (r=−0.35, p= 0.03), and between RT interference score for positive pictures and parental-report of impaired social reciprocity, as measured by the SRS (r=−0.47, p=0.005). Thus, the blunted response to emotional stimuli was associated with poorer social functioning in SMD youth.

Discussion

This study examined how emotional visual stimuli impact attention in youth with bipolar disorder (BD, i.e. those who meet strict DSM-IV diagnostic criteria, including a history of at least one episode of euphoric mania), those with severe mood dysregulation (SMD, i.e. those with persistent irritability, hyperarousal, and hyper-reactivity to negative emotional stimuli), and healthy controls. SMD youth are a population in need of diagnostic clarification: they have been referred to as "nosological orphans" (Carlson et al. 2004). Assigning ADHD and/or ODD diagnoses to SMD youth fails to acknowledge their prominent mood disturbances, and youth with SMD do not meet DSM-IV criteria for mania because their irritability is chronic rather than episodic. SMD youth are those in whom the BD diagnosis is most debated, and the soaring prevalence rates of pediatric BD may reflect the assignment of the BD diagnosis to SMD youth. Studies of the pathophysiology of SMD address the unclear nosological status of this population and begin to address the diagnostic controversy surrounding pediatric BD. Our goal was to determine if attention to emotional and nonemotional stimuli might differentiate neurocognitive functioning in BD and SMD youth.

To this end, we used the Emotional Interrupt task in which IAPS pictures, neutral, negative, and positive in emotional valence, served as distracters during a basic task of attention. We found that while distracting emotional pictures impacted the RT performance of BD and control subjects, SMD performance did not differ when we compared emotional and non-emotional trials. In addition, when we calculated an attention interference score to account for group differences in RT on the non-emotional trials, we found that SMD youth had significantly lower RT attention interference scores for positive and negative stimuli compared to BD and control subjects, who themselves had comparable performance.

Thus, controls and BD subjects were distracted by emotional stimuli when these competed with non-emotional stimuli for attention, consistent with prior studies of control subjects (Vuilleumier et al. 2001; Simpson et al. 2000). In contrast, in SMD subjects, attention was not modulated by the positive or negative pictures, suggesting a blunted response to emotional stimuli in SMD youth. These results suggest that emotional stimuli were less salient to SMD youth than BD and control subjects. Further, we found that SMD youth with a greater blunted response to emotional stimuli had greater social dysfunction based on parent report of social reciprocity deficits and clinician-assessed peer relationship deficits.

These results may begin to identify potential sources of the affective and behavioral dysregulation that characterizes SMD. A child's ability to properly deploy attention to emotional stimuli has been linked to multiple socio-behavioral skills, including self-control (Mischel et al. 1989), reduction of negative reactions to interpersonal rejection (Ayduk et al. 2002), and the effective enactment of coping mechanisms (Sethi et al. 2000). In sum, effective deployment of attention to emotional stimuli is central to normative mood and behavior regulation (Kopp 2002; Posner and Rothbart 1998; Newman and Lorenz 2003; Rueda et al. 2005). Given this, the failure by SMD youth to properly attend to emotional stimuli may be related to deficient self-control and an impaired ability to cope with adverse conditions. In this way, the absence of attention modulation by emotional stimuli may be one cognitive deficit that contributes to the affective and behavioral dysregulation characteristic of SMD. In sum, our results support a somewhat counter-intuitive theory regarding SMD that merits further examination: that the clinically observed hyper-reactivity to negative emotional stimuli in SMD youth may reflect a failure to properly attend to emotional stimuli (i.e. an under-sensitivity to emotional stimuli), rather than heightened attention or sensitivity to emotional stimuli.

The lack of an emotion-influenced cognitive response by SMD youth is consistent with a prior study in which the attention performance of SMD youth was not modulated by emotional and nonemotional conditions (Rich et al. 2007). This absence of performance modulation by emotional stimuli has been previously documented in individuals with disruptive behavior disorders, specifically conduct disorder (CD), as well as those with antisocial traits, such as aggression and callousness. For example, research using the Emotional Interrupt task found that adults with psychopathy showed no increase in their response latencies to target stimuli when the distracter was emotional (Mitchell et al. 2006). Similar patterns of behavioral, autonomic, and neural hypo-responsivity to emotional stimuli have been demonstrated in youth with disruptive behavior disorders (van Goozen et al. 2004; Herpertz et al. 2005; Jones et al. 2008; Sterzer et al. 2005). Thus, the blunted response to emotional stimuli displayed by SMD youth in the current study is consistent with that seen in youth with CD and anti-social traits. Although none of the SMD youth in this particular sample met CD diagnostic criteria, 73% had ODD, and all had marked hyper-reactivity to negative contexts characterized by extreme behavioral and/or verbal aggression, as is also commonly seen in subjects with CD.

Counter to our anticipated results, the performance of BD subjects was equivalent to that of controls: BD youth and controls displayed similar attention biases to both positive and negative stimuli. These results are consistent with prior work with pediatric BD samples that failed to

document differences between BD youth and controls in attention to positive and/or rewarding stimuli (Ernst et al. 2004; Rich et al. 2005a). While one study did find in BD youth a bias to positive stimuli as measured by response accuracy, no biases were evident when measured using RT, nor did this study find neural deficits in BD youth when processing positive stimuli (Pavuluri et al. 2008). Regarding negative stimuli, while BD youth have been found to negatively misinterpret neutral facial expressions (Rich et al. 2006), and improperly deploy their attention when in frustrating contexts (Rich et al. 2007, 2005b), other studies find neither attentional biases (Pavuluri et al. 2008; Brotman et al. 2007b) nor heightened psychophysiological responsivity (Rich et al. 2005c, 2005a) to negative emotional stimuli in BD youth.

There are important limitations to this work. First, most of the BD and SMD patients were medicated, and we could not discontinue medication purely for research purposes. However, we found a blunted response to emotional stimuli in both medicated and unmedicated SMD subjects, and an absence of attention bias deficits in medicated and unmedicated BD subjects; these results suggest that medication status did not alter our findings. Similarly, many of the patients were not euthymic at the time of testing. Nonetheless, dividing the BD sample into those who were euthymic and noneuthymic did not alter our results. Finally, co-occurring disorders is a possible confound because the rate of comorbidity in BD subjects is high, and most SMD youth meet criteria for multiple DSM-IV diagnoses. However, the absence of attention interference in SMD youth remained when we divided the SMD and BD samples into those with or without ODD, an anxiety disorder, or, in the case of BD, ADHD. Overall, our post-hoc analyses suggest that our results are not due to the presence of the above noted clinical confounders. However, in interpreting our results, it is important to note that broader attention deficits and/or impulsivity in our SMD subjects may also explain the performance deficits in this sample. Finally, although some data suggest that clinician report may be a more accurate assessment of symptomatology in bipolar youth than that provided by child- and parent-report rating scales (Youngstrom et al. 2003), ideally our study would have included information obtained using a child self-report rating scale.

In conclusion, this study documents a blunted response to emotional stimuli in SMD, but not BD, youth. The current data add to an expanding literature that differentiates these disorders. By identifying a lack of attention modulation to emotional stimuli in SMD youth, and linking this deficit to SMD social impairments, we hope this this study represents an initial step toward identifying disease-specific biomarkers eventually capable of complementing clinical data to improve diagnostic accuracy of BD in children and adolescents, and clarifying the nosological status of SMD youth.

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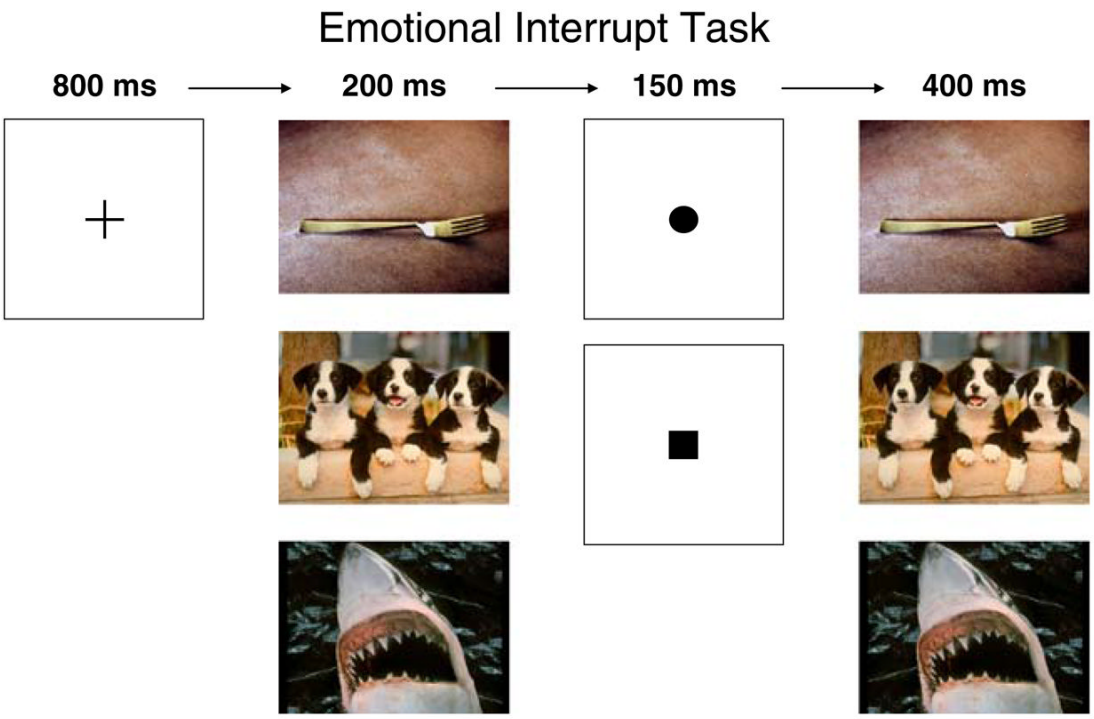

Fig. 1.
The Emotional Interrupt Task. Figure depicts the stimuli (distracter pictures: neutral, positive, or negative; targets: circle or square) and their presentation timecourse. Subject must press a button that corresponds to the circle/square target while ignoring the distracter pictures

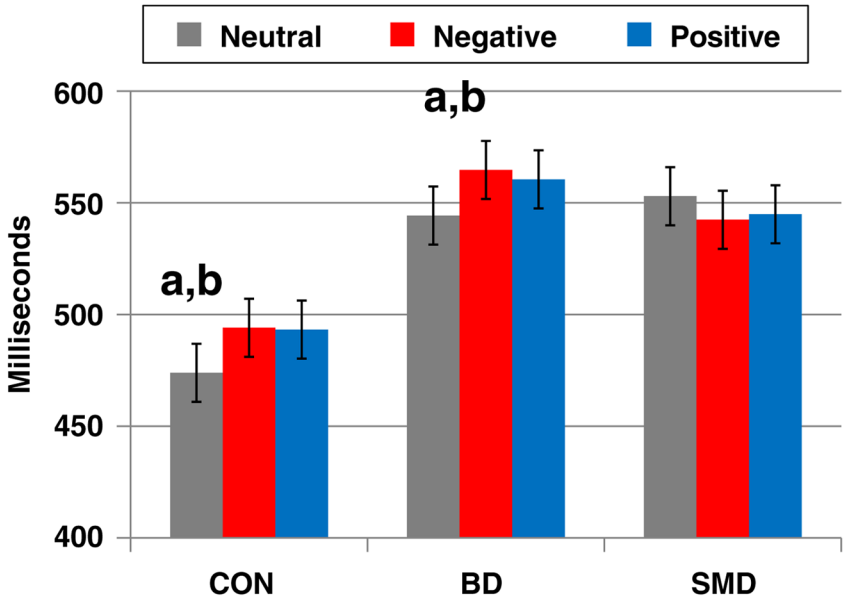

Fig. 2.

Group Differences in Reaction Time. Figure depicts group differences in reaction time (RT) on trials involving neutral, negative, and positive distracting pictures. Within-group found significant effects of picture emotion in both controls [$F(2,64)=20.24$, $p<0.001$] and BD subjects [$F(2,112)=12.06$, $p<0.001$]; both samples were significantly slower on the negative **a** and positive **b** picture trials when compared to neutral trials ($p<0.001$). However, the effect of emotion was nonsignificant in SMD subjects [$F(2,80)=2.05$, $p=0.16$], suggesting that their performance did not vary as a function of the emotional nature of the distracting picture. *CON* control subjects; *BD* bipolar disorder; *SMD* severe mood dysregulation

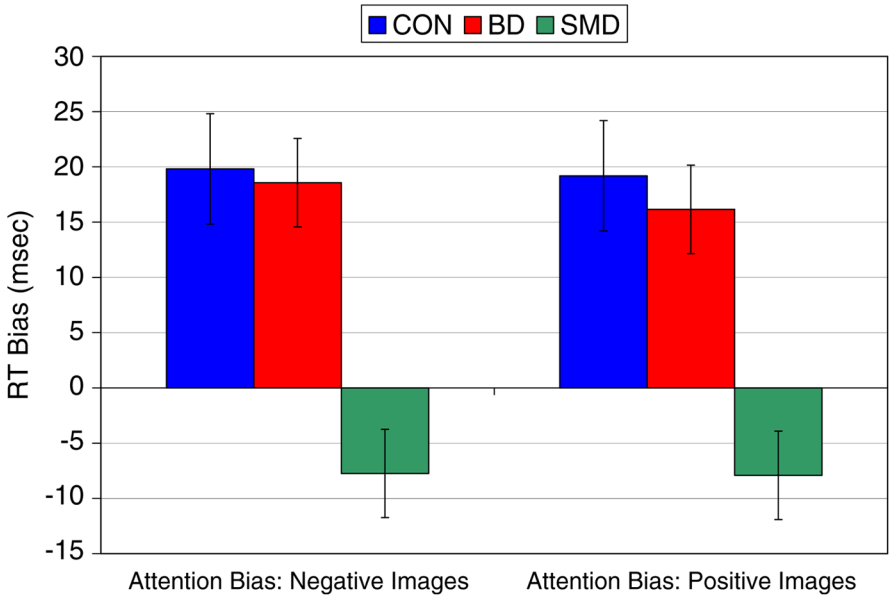

Fig. 3.

Group Differences in Reaction Time Attention Interference Scores. Figure depicts group differences in the reaction time (RT) attention interference score. Attention interference score = RT on trials with an emotional distracter—RT on trials with a neutral distracter. Scores are adjusted after controlling for age and IQ. On negative pictures, SMD subjects displayed a significantly lower attention interference compared to controls ($p<0.0001$) and BD subjects ($p< 0.0001$). Similarly, on positive pictures, SMD subjects displayed a significantly lower attention interference compared to controls ($p< 0.001$) and BD subjects ($p<0.0001$). Results indicate a blunted response to emotional stimuli in SMD subjects. *BD* bipolar disorder; *SMD* severe mood dysregulation; *CON* control subjects

Table 1

Demographic and Clinical Data

	BD	SMD	Control	p value
N	57	41	33	
Age, years	14.43±2.87	12.55±2.55	13.72±2.51	0.003**
Sex (male): % (N)	56.10 (32)	63.40 (26)	51.52 (17)	0.57
IQ	109.89±13.22	102.37±13.29	113.06±9.99	0.001**
Number of diagnoses	3.17±1.56	2.68±1.39	–	0.12
Diagnoses: % (N)				
ADHD	49.1 (28)	82.9 (34)	–	0.001**
ODD	28.1 (16)	73.2 (30)	–	0.001**
Any anxiety	40.9 (29)	43.9 (18)	–	0.63
GAD	28.1 (16)	19.5 (8)	–	0.46
Separation anxiety	26.3 (15)	24.4 (10)	–	0.99
Social phobia	21.1 (12)	7.3 (3)	–	0.11
MDD	–	22.0 (9)	–	–
Number of medications when medicated	2.44±1.82	2.05±1.45		0.26
Medicated	77.2 (44)	78.0 (32)	–	0.99
Atypical antipsychotics	54.4 (31)	43.9 (18)	–	0.41
Anti-epileptics	49.1 (28)	36.6 (15)	–	0.30
Lithium	35.1 (20)	24.4 (10)	–	0.36
Antidepressants	29.8 (17)	17.1 (7)	–	0.23
Stimulants	28.1 (16)	46.3 (19)	–	0.10
Mood Rating Scores				
CGAS	48.61±12.24	47.78±7.65	–	0.70
CDRS	30.00±9.51	29.07±8.53	–	0.62
YMRS	11.14±8.60	13.32±5.07	–	0.15
Social Functioning				
LIFE: family	2.66±0.81	2.63±0.70	–	0.84
LIFE: friends	2.81±0.96	2.71±0.87	–	0.62
SRS	73.14±22.91	77.56±19.15	–	0.36

BD Bipolar Disorder; *SMD* Severe Mood Dysregulation; *ADHD* Attention Deficit Hyper-activity Disorder; *ODD* Oppositional Defiant Disorder; *GAD* Generalized Anxiety Disorder; *MDD* Major Depressive Disorder; *CGAS* Children's Global Assessment Scale; *CDRS* Children's Depression Rating Scale; *YMRS* Young Mania Rating Scale; *CBCL* Child Behavior Checklist; *CPRS* Conners Parent Rating Scale; *LIFE* Longitudinal Interval Follow-up Evaluation; *SRS* Social Responsiveness Scale. All diagnoses are current