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Different neural pathways to negative affect in youth with pediatric bipolar disorder and severe mood dysregulation

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Abstract

Questions persist regarding the presentation of bipolar disorder (BD) in youth and the nosological significance of irritability. Of particular interest is whether severe mood dysregulation (SMD), characterized by severe non-episodic irritability, hyperarousal, and hyper-reactivity to negative emotional stimuli, is a developmental presentation of pediatric BD and, therefore, whether the two conditions are pathophysiologically similar. We administered the affective Posner paradigm, an attentional task with a condition involving blocked goal attainment via rigged feedback. The sample included 60 youth (20 BD, 20 SMD, and 20 controls) ages 8–17.

Magnetoencephalography (MEG) examined neuronal activity (4–50 Hz) following negative versus positive feedback. We also examined reaction time (RT), response accuracy, and self-reported affect. Both BD and SMD youth reported being less happy than controls during the rigged condition. Also, SMD youth reported greater arousal following negative feedback than both BD and controls, and they responded to negative feedback with significantly greater activation of the anterior cingulate cortex (ACC) and medial frontal gyrus (MFG) than controls. Compared to SMD and controls, BD youth displayed greater superior frontal gyrus (SFG) activation and decreased insula activation following negative feedback. Data suggest a greater negative affective response to blocked goal attainment in SMD versus BD and control youth. This occurs in tandem with hyperactivation of medial frontal regions in SMD youth, while BD youth show dysfunction in the

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CONTRIBUTORS

Dr. Rich assisted in designing the study, and directed the data collection, data analysis, and manuscript preparation. Drs. Carver, Holroyd, and Cornwell assisted in data collection, analysis, and manuscript preparation. Ms. Rosen and Mendoza assisted with data analysis and manuscript preparation. Drs. Fox, Pine, Coppola, and Leibenluft assisted with designing the study, data analysis, and manuscript preparation. All authors have approved the final manuscript.

CONFLICT OF INTEREST

The authors report no conflict of interests.

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SFG and insula. Data add to a growing empirical base that differentiates pediatric BD and SMD and begin to elucidate potential neural mechanisms of irritability.

Keywords

bipolar disorder; pediatric; mood dysregulation; irritability; frustration; magnetoencephalography

OBJECTIVES

The past decade has witnessed a significant rise in the rate at which the diagnosis of bipolar disorder (BD) is assigned to youth. Studies of diagnoses from outpatient visits (Moreno et al., 2007) and at discharge from psychiatric hospitals (Blader & Carlson, 2007) document dramatic increases in the rate at which the diagnosis of BD is being assigned to youth. Although empirical data are lacking, researchers have hypothesized that one possible cause for this increase may be the assignment of the BD diagnosis to youth who have severe affective and behavioral dysregulation but lack the distinct manic episodes required to meet DSM-IV criteria for BD (Donovan et al., 2003; Harris, 2005; Moreno et al., 2007; Zimmerman, Ruggero, Chelminski, & Young, 2008). This phenotype has been operationalized in the syndrome of severe mood dysregulation (SMD) (Leibenluft, Charney, Towbin, Bhangoo, & Pine, 2003). SMD is defined as 1) non-episodic, severe irritability and anger; 2) hyperarousal symptoms common to both BD and Attention Deficit Hyperactivity Disorder (ADHD); and, 3) extreme hyper-reactivity to negative emotional stimuli which, while similar to the “loses temper” criterion of Oppositional Defiant Disorder (ODD) (McMahon & Wells, 1998), is operationalized more precisely and requires greater severity in the SMD classification. SMD youth are an important research sample because while most SMD youth meet criteria for ADHD and/or ODD, neither of these diagnoses requires extreme irritability, which is operationalized clearly in SMD. 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 non-episodic. Further, SMD youth lack a history of episodic euphoric/grandiose mood lasting more than one day (Leibenluft et al., 2003).

Irritability is a mood state characterized by a low threshold for frustration, where frustration is the affective response to blocked goal attainment. This typically results from the failure to receive an expected reward or outcome, often in conjunction with rigged feedback (Moadab, Gilbert, Dishion, & Tucker, 2010; Siegrist et al., 2005; Abler, Walter, & Erk, 2005; Yu, Mobbs, Seymour, & Calder, 2010). Irritability is, in many ways, ubiquitous in childhood psychopathology. It is a diagnostic criterion for major depressive disorder (MDD) and generalized anxiety disorder (GAD), and is often seen in children with other anxiety disorders, ADHD, ODD, and pervasive developmental disorders (PDD).

Clarifying the role of irritability in the diagnosis and pathophysiology of pediatric BD, and in the differentiation of pediatric BD and SMD, has garnered significant interest. Irritability is prevalent in BD (Geller et al., 1998) and, by definition, in SMD as well. Although irritability is impairing in BD (Carlson et al., 2003), data suggest that SMD youth are significantly more irritable than BD youth (Stringaris et al., 2010). Further, the presentation of irritability differs between the syndromes. The irritability of SMD is non-episodic. In contrast, to be diagnostic of mania seen in BD, irritability must present in a distinct episode. Specifically, if irritability is to be the “index” affect for a manic episode, it has to either have the same onset as the “B” criteria of mania or, if it pre-dates the onset of the “B” criteria, it has to worsen significantly at the time that the “B” criteria occur. Thus, irritability that is chronically present would not be diagnostic of a manic episode because it would not satisfy the DSM-IV requirement that the affect present during the episode represent a “distinct”

period of abnormal mood. Results of two longitudinal epidemiological studies speak to the potential importance of this difference in presentation: youth with non-episodic irritability are at risk for unipolar depression and anxiety, rather than BD, by adulthood (Brotman et al., 2006; Stringaris, Cohen, Pine, & Leibenluft, 2009).

Additional comparisons of SMD and BD youth suggest divergent neurophysiological mechanisms mediating the response to blocked goal attainment in these two populations. We have compared the neural mechanisms mediating response to blocked goal attainment in BD and SMD youth using the affective Posner task, which uses rigged feedback that informs the subject of lost monetary reward, to a standard task of orienting attention. In our first comparison of BD and SMD youth using the affective Posner task (Rich et al., 2007) we found that in the rigged feedback context, both BD and SMD youth had slower reaction times than controls (BD also were slower than SMD), and both patient samples had more negative affective responses than controls. However, the patient samples differed in their psychophysiological deficits, as measured by ERP's, in response to the attention-cuing stimuli. Whereas BD subjects displayed lower parietal P3 amplitude than SMD or controls in the emotional rigged feedback condition only, SMD youth had lower frontal, temporal, and central N1 and central P1 amplitude than BD and controls in both emotional and nonemotional contexts. These results suggest that in BD youth, deficits in executive attention are seen specifically in the rigged feedback context, whereas SMD youth display deficits in the initial stages of attention, regardless of the emotional nature of the context. Overall, these results indicate that the affective and behavioral deficits in BD and SMD youth may have divergent attention- and emotion-driven neural perturbations.

The current study extends our prior ERP research by using magnetoencephalography (MEG) to compare SMD, BD, and controls to attain a more spatially-detailed comparison of the neural mechanisms engaged during blocked goal attainment. We previously used MEG and the affective Posner paradigm to compare BD and control subjects on theta band (4–8 Hz) power, given its role in attention to emotional stimuli (Aftanas, Varlamov, Reva, & Pavlov, 2003; Aftanas, Varlamov, Pavlov, Makhnev, & Reva, 2001). We found that, in the rigged feedback context, BD youth displayed greater theta power than controls in the anterior cingulate cortex (ACC) and parietal lobe in response to negative feedback (Rich et al., 2010b).

Here we compare SMD subjects to the previously studied BD and control subjects. We examined a broad band of MEG power (4–50 Hz), which is comparable to the approach used in our prior ERP study. Also, we examined neuronal activity in response to the emotional stimuli (i.e. negative and positive feedback) rather than to the attentional target, in order to better understand the neural correlates of processing rewarding and punishing affective stimuli. We predicted attenuated ACC activation in SMD youth compared to BD and control youth because our prior MEG study found heightened ACC activation in BD youth compared to controls (Rich et al., 2010b), while our prior ERP study found N1 amplitude deficits in SMD youth (Rich et al., 2007), and studies implicate the ACC in generating N1 (Esposito, Mulert, & Goebel, 2009; Mulert et al., 2008).

MATERIALS AND METHODS

PARTICIPANTS

Sixty youth (20 BD, 20 SMD, 20 control) ages 8–17 years enrolled in an IRB-approved study at the National Institute of Mental Health (NIMH). Subjects were recruited from across the United States through newspaper and internet advertisements, flyers distributed at professional conferences, and letters sent to child psychiatrists nationwide. Subjects and a

guardian provided written informed assent/consent. While BD and control data are published (Rich et al., 2010b), the data on SMD youth have not been presented previously.

To identify SMD and BD, we used 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).

All BD subjects met DSM-IV criteria for BD, with the requirement of at least one full duration hypomanic (≥ 4 days) or manic (≥ 7 days) episode, defined by an abnormally elevated or expansive mood and/or grandiosity (Leibenluft et al., 2003). Comorbid diagnoses, also assessed using the K-SADS, required impairment during euthymia.

SMD classification inclusion criteria 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 the following: 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 two 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).

A K-SADS supplementary module assessed the presence and severity of eight symptoms to determine if children met criteria for the SMD classification: irritable mood, insomnia, racing thoughts, distractibility, physical restlessness, intrusiveness, pressured speech, and markedly excessive reactivity in response to a negative or frustrating emotional stimulus. For all, in addition to assessing the intensity of and impairment associated with these symptoms, questions pertaining to frequency and course allowed clinicians to determine if the symptoms presented in a chronic, non-episodic manner, consistent with the SMD classification. Differentiation of SMD from BD had excellent reliability (i.e. kappa ≥ 0.9 , by blinded review of randomly selected taped evaluations).

Control subjects had no psychiatric history in themselves or first-degree relatives, determined using the K-SADS and a review of family psychiatric history. All participants had normal physical and neurological history. Exclusion criteria included I.Q. < 70 [as measured by the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999)], pervasive developmental disorder, unstable medical illness, or substance abuse within two months.

Clinicians administered the Children's Depression Rating Scale (CDRS) (Poznanski et al., 1984) to assess patients' depressive symptomatology, and the Young Mania Rating Scale (YMRS) (Young, Biggs, Ziegler, & Meyer, 1978) to assess mania symptomatology in BD subjects. The clinician-completed Children's Global Assessment Scale (CGAS) (Shaffer et al., 1983) assessed the general level of functional impairment during the past month.

PROCEDURE

Affective Posner Task—To obtain an objective measure of the affective, behavioral, and psychophysiological responses to blocked goal attainment, we used the affective Posner task (Perez-Edgar & Fox, 2005; Rich et al., 2010b; Rich et al., 2007; Rich et al., 2005) (Figure 1). The affective Posner task consists of three conditions of 100 trials each with identical stimuli and instructions, but different feedback. A fixation cross appeared in the center of

the screen (750 msec), followed by two boxes (300 msec). The cue consisted of one box illuminating blue (200 msec). Then a target square appeared inside one of the boxes (maximum 1260 msec, depending on response). Subjects were instructed to press the button (i.e. left, right) matching the target location. Feedback was presented (2000 msec) following each response.

Condition 1 was the non-emotional baseline: feedback told subjects of their response accuracy (“Good job!” or “Incorrect!”). Condition 2 introduced contingencies: subjects won (“Great Job! Win 25 Cents”) or lost (“Wrong! Lose 25 Cents”) money on each trial, based on performance. Condition 3 had the same contingencies as condition 2, but rigged negative feedback was added to measure response to blocked goal attainment. On 56% of correct responses, rigged feedback informed the subject that he/she was too slow and lost money (“Too Slow! Lose 25 Cents”); this feedback occurred independent of response time. Accurate feedback and reward (“You’re Quick! Win 25 Cents”) occurred after 44% of correct responses. Incorrect responses always resulted in punishment feedback (“Wrong! Lose 25 Cents”). The affective response elicited by the task did not exceed minimal risk standards of pediatric research, and no participant displayed affect or behavior necessitating the cessation of the task.

Behavioral data consisted of reaction time (RT) and response accuracy (i.e. percentage of responses matching target location). Self-reported mood was collected after each condition, with subjects rating (on a 1–9 scale) two aspects of their affective response (valence: happy/sad; arousal: calm/agitated) using Self-Assessment Manikin (McManis, Bradley, Berg, Cuthbert, & Lang, 2001) line-drawings.

MEG RECORDING

Neuromagnetic data were collected with a whole-head 275-sensor MEG system (CTF Systems Inc., Vancouver, Canada), located in a magnetically shielded room (Vacuumschmelze, Germany). MEG signal was recorded with a sampling rate of 600 Hz (bandwidth: 0–150 Hz). Each sensor was configured as a first-order axial gradiometer with 18 mm coils and 50 mm baseline, with an average spacing of 22 mm. Head positioning was measured continuously to monitor movement. Subjects included in the analyses did not have movement exceeding 6 mm.

ANATOMICAL MRI RECORDING AND COREGISTRATION

Each participant received a high resolution T-1 weighted structural magnetic resonance image (sMRI) with a 3-Tesla or 1.5-Tesla scanner (GE Signa, Milwaukee, WI.) We used a standardized magnetization prepared gradient echo sequence (180 1.2 mm sagittal slices; FOV = 24; NEX = 1; TR = 11.4 ms; TE = 4.4 ms, matrix = 256×256×256; TI= 300 ms; bandwidth = 130 Hz/pixel, 33 kHz/256 pixels). Anatomical scans were transformed into Talairach space using AFNI (Cox, 1996).

MRIs were converted into AFNI format and co-registered with MEG data by aligning fiducial points. MEG source localizations were calculated using multi-sphere head models derived from individual participants’ MRIs. Group 3D-maps of event-related activity were calculated with Talairach-aligned volumes (Cox, 1996). We employed 6 mm voxel spacing.

DATA ANALYSIS

Behavioral and Affective Data—Analyses focused on the rigged-feedback condition 3 because of our interest in the frustrating context. Further, high performance accuracy in conditions 1 and 2 provided an insufficient number of negative feedback trials to analyze behavioral or neural responses. We used a series of 3 (group: BD, SMD, CON) × 2

(feedback: positive vs. negative) repeated measures ANOVAs to compare mood and behavioral performance.

MEG Data—MEG raw data was filtered in 3rd gradient mode for noise reduction using reference coils with fixed weights along with DC offset removal, minimal highpass filter (0.61 Hz), and powerline (60 Hz) filtering.

To determine the optimal time-frequency windows for analysis, we conducted Stockwell Transformations (ST) (Drabycz, Stockwell, & Mitchell, 2009; Stockwell, Mansinha, & Lowe, 1996). ST produces a time-frequency (TF) representation of a real signal with absolute phase information, performed on raw MEG signals. The complex ST was then squared, yielding power for each channel. The resulting TF arrays of power were then averaged across channels and trials. We performed this operation in the active (post feedback) and control (fixation) time windows beginning 200 msec before the onset of feedback and extending to 900 msec after feedback. Visual inspection of this window indicated it was of sufficient length to capture neuronal oscillations evoked by feedback (Luu, Tucker, & Makeig, 2004; Aftanas et al., 2003; Salminen & Ravaja, 2008; Hanslmayr et al., 2008). We used a non-parametric Wilcoxon test (Cox, 1996) to identify TF regions showing significant differences between active and control arrays between groups. Results supported the use of a 500 msec window following feedback presentation as the basis for analysis. Further, results indicated an analysis of 4–50 Hz would best allow us to replicate our prior ERP analyses. As an example, Figure 2A–C displays the TF arrays for BD, SMD, and CON samples in response to negative feedback.

To investigate condition-related cortical activation, an event-related Synthetic Aperture Magnetometry beamformer technique (SAMerf) was used to calculate the electromagnetic source images of event-related responses for individual voxels (Vrba & Robinson, 2001; Ishii et al., 1999; Taniguchi et al., 2000). SAMerf produces a 3D representation of brain activity by using the recorded magnetic field across the 275 sensors and computes a set of beamformer weights to estimate activation. At each voxel an optimal spatial filter (beamformer) is determined through a minimum variance procedure that reduces extraneous power sources but preserves signal from the voxel to limit potential artifacts. The orientation of the source dipole is estimated by the vector based approach of Sekihara et al. (Sekihara, Nagarajan, Poeppel, Marantz, & Miyashita, 2001). SAMerf attenuates non-phase locked activity by averaging virtual channels at each voxel location and creating a source image based on the average for the specified active and control windows.

For each subject the SAM procedure calculated log ratios of power between the active state (500 msec following feedback presentation) and control state (500 msec of fixation cross). At the individual-subject level, SAM volumes were normalized to Z-scores and were then averaged and transformed into common Talairach coordinate space. Then, at the between-subjects level, the normalized log ratios were compared between the samples.

To correct for multiple comparisons, a false discovery rate (FDR) threshold (Ossadtchi et al., 2004; Lapalme, Lina, & Mattout, 2006) of 0.05 is consistently used in recent fMRI (Nichols & Hayasaka, 2003; Genovese, Lazar, & Nichols, 2002; Logan & Rowe, 2004) and MEG studies (Hirata et al., 2007; Kahkonen et al., 2007; Henson et al., 2007; Brunetti et al., 2007; Onoda et al., 2007). To balance the possibility of Type I and Type II errors in fMRI studies, Lieberman and Cunningham (2009) recommend a $p < .005$ intensity threshold and 20 voxel cluster cut-off to approximate an FDR equal to .05 (Lieberman & Cunningham, 2009). The recommended cluster threshold of 20 voxels is based on an FMRI voxel size of $3.5\text{mm} \times 3.5\text{mm} \times 5\text{mm}$. Given the larger voxel size (6mm^3) in our MEG data, we set our cluster threshold at 6 voxels. Therefore, we report those regions that survived a $p < 0.005$

uncorrected threshold with a minimum of 6 voxels for the ANOVA interaction. All results are reported in Left, Posterior, Inferior (LPI) coordinates and reflect the peak activation voxel of that region.

Secondary analyses examined the impact of demographic and clinical variables on MEG results. We used Pearson bivariate correlations within each group to examine associations between MEG data and behavioral performance, self-reported mood, clinician-assessed mood (CDRS, YMRS), number of diagnoses, and number of psychotropic medications. We also sought to clarify the impact of anxiety, ADHD, and ODD diagnoses on MEG power. ANOVAs compared controls to BD and SMD subjects with vs. without an anxiety disorder (both patient samples), ADHD (BD only), and ODD (SMD only). Comparisons based on certain diagnoses and medication status (i.e. medicated vs. unmedicated) were limited to due small sample size.

RESULTS

PARTICIPANT DEMOGRAPHICS AND CLINICAL DATA

BD (14.92 ± 2.03 years; 45% male; $IQ = 108.95 \pm 17.62$), SMD (14.15 ± 2.14 years; 75% male; $IQ = 104.70 \pm 13.48$) and control (14.72 ± 1.69 years; 45% male; $IQ = 111.45 \pm 9.24$) subjects did not differ in age [$F(2,57) = .82$, $p = .44$], IQ [$F(2,57) = 1.21$, $p = .31$], or gender ($X^2_{60} = 4.85$, $p = .09$). Controlling for gender did not alter the results reported below.

Within the BD sample, 80.0% ($N = 16$) had BD type I (BDI). Among BD youth, there was an average of 2.85 ± 1.53 diagnoses; the most common comorbid disorders were ADHD (60.0%), an anxiety disorder (40.0%), and ODD (20%). Among SMD youth, there was an average of 1.90 ± 1.48 total diagnoses; the most common current DSM-IV diagnoses were ADHD (70.0%), ODD (50.0%), an anxiety disorder (35.0%), and MDD (20%). Groups did not differ on total number of diagnoses.

CDRS (mean = 24.55 ± 5.50) and YMRS (mean = 5.55 ± 3.49) scores indicated that 100% ($N = 20$) of our BD subjects were euthymic (i.e. CDRS ≤ 40 and YMRS ≤ 12). CDRS scores found that two SMD subjects were currently depressed. ANOVA comparisons of CDRS [$F(1,38) = 2.86$, $p = .10$] scores showed that BD (24.55 ± 5.50) did not differ from SMD (28.45 ± 8.72) on depressive symptoms. CGAS scores, comparable between patient groups, indicated severe overall impairment (BD = 51.50 ± 11.37 ; SMD = 48.00 ± 9.50). 90.0% ($N = 18$) of BD subjects and 70.0% ($N = 14$) of SMD subjects were medicated. Groups did not differ on the percentage of medicated subjects, nor the rates of specific medication classes (Table 1).

AFFECTIVE DATA

For arousal, there was a significant group x feedback type interaction [$F(2,57) = 3.16$, $p < .04$]. Specifically, on trials involving negative feedback [$F(2,57) = 4.14$, $p = .02$], SMD reported feeling more aroused (i.e. agitated) than BD ($p = .03$) and controls ($p = .04$) (Figure 3). The main effects of group and feedback type were nonsignificant.

For valence, the group x feedback interaction was nonsignificant [$F(2,57) = 2.02$, $p = .14$]. The group main effect was significant [$F(2,57) = 7.05$, $p = .002$], indicating that both BD ($p = .04$) and SMD ($p < .001$) subjects were more unhappy than controls across feedback type, with a nonsignificant difference between SMD vs. BD youth ($p = .09$) (Figure 4). The significant main effect of feedback type [$F(1,57) = 126.77$, $p < .0001$] found that subjects were more unhappy following negative vs. positive feedback ($p < .0001$).

BEHAVIORAL DATA

For RT, we found a nonsignificant group $\times$ feedback interaction [$F(2,57)=.53$, $p=.58$], and nonsignificant group [$F(2,57)=2.48$, $p=.09$] and feedback main effects [$F(1,57)=.47$, $p=.49$] (Table 2).

For accuracy, we found a nonsignificant group $\times$ feedback interaction [$F(2,57)=.55$, $p=.58$] and group main effect [$F(2,57)=.19$, $p=.83$]. The feedback main effect was significant [$F(1,57)=9.96$, $p=.003$], with poorer accuracy across subjects following negative vs. positive feedback ($p=.003$) (Table 2).

MEG DATA

Whole-brain analyses revealed a significant group $\times$ feedback interaction in five regions: 1) left anterior cingulate cortex (ACC; BA 32) ($x=-17$, $y=42$, $z=3$) [$F(2,57)=-4.81$, $p=.009$]; 2) right medial frontal gyrus (MFG; BA 10) ($x=1$, $y=54$, $z=-8$) [$F(2,57)=4.91$, $p=.009$]; 3) right superior frontal gyrus (SFG; BA 6) ($x=1$, $y=47$, $z=33$) [$F(2,57)=4.98$, $p=.008$]; 4) left insula ($x=-29$, $y=16$, $z=16$) [$F(2,57)=5.35$, $p=.006$]; 5) right supplementary motor area (SMA) ($x=1$, $y=-18$, $z=58$) [$F(2,57)=5.00$, $p=.008$] (Table 3).

ACC—Between-group post hoc analyses found that following negative feedback, SMD had greater activation than controls ($t=-2.23$, $p=.02$) with a nonsignificant difference vs. BD ($t=-1.79$, $p=.07$). Following positive feedback, controls had greater activation than SMD ($t=2.96$, $p=.008$) (Figure 5).

MFG—Between-group post hoc analyses found that following negative feedback, SMD had greater activation than controls ($t=-1.98$, $p=.05$). Following positive feedback, controls had significantly greater activation than SMD ($t=2.39$, $p=.01$) (Figure 6).

SFG—Between-group post hoc analyses found that following negative feedback, BD had significantly greater activation than both SMD ($t=2.88$, $p=.009$) and controls ($t=3.28$, $p=.002$). There were no group differences following positive feedback (Figure 7).

Insula—Between-group post hoc analyses found that following negative feedback, both SMD ($t=-2.39$, $p=.006$) and controls ($t=-2.17$, $p=.01$) had greater activation than BD. Following positive feedback, BD had greater activation than SMD ($t=2.43$, $p=.005$) (Figure 8).

SMA—Between-group post hoc analyses found that following negative feedback, controls had significantly greater activation than SMD ($t=2.95$, $p=.008$). Following positive feedback, BD subjects had significantly greater activation than both SMD ($t=2.29$, $p=.02$) and controls ($t=3.01$, $p=.003$).

Secondary Analyses: MEG Associations with Performance and Clinical Variables—Secondary analyses focused on the five regions where subjects differed in MEG power. Pearson bivariate correlations, Bonferroni corrected for multiple comparisons and conducted for each group separately, examined associations between MEG power and behavior, self-reported affect, and clinical variables (see Methods). In SMD, greater activation of the insula to negative feedback was associated with slower RT ($r=.54$, $p=.01$) and a more negative self-reported affect ($r=.51$, $p=.01$). All other correlations were nonsignificant. Dividing the patient samples based on co-occurring disorders and comparing these subsamples to controls found that the above described MEG perturbations were evident in patients independent of the presence/absence of ADHD, ODD, and anxiety.

Further, restricting our analyses to youth with BDI, and removing the two SMD subjects who were currently depressed, did not alter the nature of our results.

DISCUSSION

SMD youth reflect one important clinical population in whom the BD diagnosis is debated. To help clarify the nosological boundaries and etiologies of these childhood mood disorders, we examined the neural responses to blocked goal attainment in BD, SMD, and control youth using magnetoencephalography (MEG) and the affective Posner task, an attention task modified to induce frustration by rigging feedback.

Affective data found that both BD and SMD youth reported being less happy in the rigged feedback context than did controls, but SMD youth also reported greater agitation following negative feedback than both BD and controls. Given that SMD youth report heightened sadness and arousal during blocked goal attainment, and this presentation is consistent with frustration, this might suggest that SMD youth experience heightened frustration in this emotional context. These results are consistent with recent data that find SMD youth to be significantly more irritable than BD youth (Stringaris et al., 2010). The groups did not differ on behavioral performance.

We found that, in response to positive and negative feedback in the rigged feedback context, the groups differed in neural activation, including in regions implicated in frustration (e.g. ACC, PFC, and insula) (Yu et al., 2010; Abler et al., 2005; Siegrist et al., 2005; Moadab et al., 2010). Specifically, in the anterior cingulate cortex (ACC) and medial frontal gyrus (MFG), SMD youth responded with greater activation than controls following negative feedback (with a nonsignificant difference vs. BD in the ACC), whereas controls responded with greater activation in these regions than SMD youth following positive feedback. Compared to both controls and SMD, BD youth displayed greater superior frontal gyrus (SFG) activation and decreased insula activation following negative feedback. Overall, our results indicate that although both SMD and BD youth report being sadder than controls in the rigged feedback context, SMD youth are more agitated by negative feedback than are BD youth and controls, and the neural mechanisms of their negative affective responses differ between patient samples.

How may these findings relate to SMD symptomatology? The ACC and MFG have strong anatomical connections, and their concomitant activation is thought to broadly reflect evaluation and regulation of emotional conflict (Etkin, Egner, & Kalisch, 2011), including automatic self-evaluation (Gusnard, Akbudak, Shulman, & Raichle, 2001), self-monitoring of emotional state (Amodio & Frith, 2006), and facilitation of response selection (Paus, 2001). Further, a recent report suggests that activation of the rostral ACC (i.e. BA 32) reflects adaptive cognitive control, i.e. formulating a course of action in response to negative affective stimuli (Shackman et al., 2011). Thus, our results suggest that, compared to controls, SMD youth's affective status and response selection are more strongly dictated by negative information and less influenced by positive information. It is possible that this pattern of neural activation in response to blocked goal attainment contributes to the emotional and behavioral dysregulation that characterizes SMD youth.

Compared to both SMD and control youth, BD youth exhibited hyperactivation of the SFG (BA 6) and hypoactivation of the insula to negative feedback. Therefore, although both BD and SMD youth displayed heightened frontal activation to negative feedback, the precise frontal regions differed. Prior fMRI (Chang et al., 2004; Pavuluri, Passarotti, Harral, & Sweeney, 2009a) and fractional anisotropy (Frazier et al., 2007; Adler et al., 2006) studies have implicated the SFG in the pathophysiology of pediatric BD. The SFG is thought to

regulate executive attention (Nagahama et al., 1999). Further, BA 6, though classically implicated in motoric functions, also regulates nonmotoric cognitive activity (Hanakawa et al., 2002; Tanaka, Honda, & Sadato, 2005), including attentional control (Hopfinger, Buonocore, & Mangun, 2000; Boussaoud, 2001), and perhaps, at a higher cognitive level, the integration of information in preparation for behavioral responses (Hanakawa et al., 2002). Thus, our MEG results suggest that heightened attention to negative emotional information, though evident in both BD and SMD youth, is mediated by different frontal regions.

Regarding the finding of insula dysfunction in BD youth, the insula is implicated in the processing of both negative and positive affect, especially when associated with visceral sensations (Craig, 2009; Jabbi, Swart, & Keysers, 2007). Two fMRI studies in BD youth report increased insula activation: one as compared to controls when viewing negative pictures (Chang et al., 2004) and the other in a within-subject comparison of incidental vs. directed emotion processing (Pavuluri, Passarotti, Harral, & Sweeney, 2009b). These studies, in combination with our current results, suggest that the pathologic responses to emotional stimuli characteristic of BD may be associated with aberrant visceral responses. However, much as with BD adults (Ellison-Wright & Bullmore, 2010; Kim et al., 2009; Wessa et al., 2007; Wessa & Linke, 2009; Lennox, Jacob, Calder, Lupson, & Bullmore, 2004; Malhi et al., 2008; Hosokawa, Momose, & Kasai, 2009; Brooks, III et al., 2009), the nature of this insula perturbation in BD youth requires clarification.

While the current results expand upon our prior use of the affective Posner with ERP's, inconsistencies between the studies are noted. Given that SMD youth displayed attenuated N1 ERP amplitude (Rich et al., 2007), thought to be generated by the ACC (Esposito et al., 2009; Mulert et al., 2008), we predicted lower ACC activation in SMD youth. Instead, we found greater ACC activation in SMD youth than controls (with no difference vs. BD youth). This result may reflect the superior localization of MEG or the fact that N1 may be generated by regions besides the ACC, including the temporal, parietal, and occipital lobes (Brem et al., 2009; Maurer, Brem, Bucher, & Brandeis, 2005; Proverbio & Adorni, 2008). Also, methodological alterations may have contributed to differing results, including our examination of neuronal response to emotional feedback rather than attentional cue. Different results across studies may also reflect differences in patients' mood state, medication status, and co-occurring diagnoses.

Given that 70% of SMD youth were diagnosed with ADHD, it is important to consider how our MEG data may inform the differentiation of the SMD classification from the ADHD diagnosis. It is challenging to compare our data with the two prior MEG studies with children with ADHD given that one involved a non-emotional task [i.e. a modified version of the Wisconsin Card Sorting Task (WCST)] and the other examined resting state neuronal activity (Fernandez et al., 2009). Both of these studies found frontal hypoactivity in ADHD youth as compared to controls, including in the ACC during the cognitively demanding shifting condition of the WCST. The authors suggested their results indicated perturbations in the allocation of attentional resources in ADHD youth (Fernandez et al., 2009; Mulas et al., 2006). We similarly found aberrations of frontal regions in SMD youth, including the ACC, but the nature of these altered activation patterns depended upon the emotionality of the context (i.e. negative vs. positive feedback). Further, activation of regions implicated in emotional processing, e.g. the insula, were also aberrant in SMD youth. To some extent, comparison of our MEG data to prior MEG studies with ADHD youth speak to the differences in the clinical presentation of SMD and ADHD youth, namely the prominent irritability and over-reactivity to negative emotional contexts that defines the SMD classification. Of note, the lone neuroimaging comparison of SMD and ADHD youth, using fMRI, found significantly lower amygdala activation in SMD vs. ADHD youth when rating

their fear of neutral faces (Brotman et al., 2010). Similar comparisons, using MEG and tasks with emotionally salient stimuli, may expand upon our current study to compare the neural correlates of SMD and ADHD youth.

As with our prior studies exploring the pathophysiology of BD and SMD using the affective Posner (Rich et al., 2005; Rich et al., 2007; Rich et al., 2010b), there was discordance between our behavioral, affective, and MEG data. Our results are comparable to numerous prior neuroimaging studies that have identified neural differences in the absence of behavioral differences (Holmes & Pizzagalli, 2008b; Tucker, Luu, Frishkoff, Quiring, & Poulsen, 2003; Chiu & Deldin, 2007; Holmes & Pizzagalli, 2008a; Santesso et al., 2008b; Santesso et al., 2008a). Some contend that this absence of group differences in behavioral data is preferred so that group differences in neural activation are less likely to indicate subject performance deficits (Callicott & Weinberger, 2000; Callicott et al., 2003). Conversely, others claim that behavioral differences aid in interpreting neural differences (Wilkinson & Halligan, 2004). It is also possible that differences reflect heightened sensitivity of neurally-based measures compared to behavioral data, such that behavior is a broader index of functioning, whereas neural data allow for a more precise differentiation of populations. Our results speak to the continued challenges of integrating varied subjective and objective measures of functioning in psychiatric populations.

A study strength is that all BD participants were euthymic. However, this may in part reflect the fact that most BD subjects (and SMD subjects) were medicated, a clear study limitation. We were unable to limit the sample to unmedicated patients due to the high rates of medication use in BD and SMD youth; indeed, it would be unethical to require medication cessation for research. Although exploratory analyses found no correlation between number of medications and MEG data, limited sample size and the unavailability of unmedicated patients prevented a thorough investigation of this variable. We note that prior neuroimaging studies with BD subjects suggest that inclusion of medicated subjects does not typically cause Type I error (Phillips, Travis, Fagiolini, & Kupfer, 2008) and may instead hinder the ability to identify between-group differences (Caligiuri et al., 2003; Leibenluft et al., 2007; Nelson et al., 2007; Blumberg et al., 2005a; Wienbruch, Paul, Bauer, & Kivelitz, 2005).

An additional limitation is the high rate of comorbid diagnoses in BD youth. Although consistent with other neuroimaging studies of BD youth (Frazier et al., 2005a; Adler et al., 2005; Blumberg et al., 2005b; Chang et al., 2005; Sanches et al., 2005; Chen et al., 2004; Kaur et al., 2005; Delbello, Zimmerman, Mills, Getz, & Strakowski, 2004; Frazier et al., 2005b), it hampers data interpretation. Secondary analyses, although limited by small sample size, suggested that MEG differences between patients (both BD and SMD) and controls were not due to the presence of ADHD, ODD, or anxiety.

Finally, this study is limited by the fact that frustration and irritability were not measured directly. The Self-Assessment Manikin provided indices of affect specific to sadness and arousal. Further, the manipulation of feedback was designed to induce frustration by blocking goal attainment. However, given our lack of direct measurement of the specific emotion of frustration, we are forced to infer its occurrence. Ideally, we would have measured this affective construct explicitly. Ongoing studies using the affective Posner and fMRI address this limitation.

In sum, during blocked goal attainment, SMD and BD youth were more unhappy than controls, and SMD youth were more agitated by negative feedback than BD and control youth. SMD youth displayed ACC and MFG hyperactivation (vs. controls) in response to negative feedback in the rigged feedback context. Data suggest that medial frontal hyperactivation in adverse contexts may mediate the mood and behavior dysregulation that

characterizes SMD. In contrast, compared to SMD and controls, BD youth displayed SFG and insula dysfunction following negative feedback. Thus, while both SMD and BD had more extreme emotional responses to blocked goal attainment than did controls, the associated neural activity differed between patient groups. The data add to a growing empirical base (Brotman et al., 2010; Rich et al., 2010a; Rich et al., 2007; Dickstein et al., 2007; Brotman et al., 2006; Stringaris et al., 2010; Brotman et al., 2007) that differentiates SMD from strictly-defined BD in youth. However, while clinical data are longitudinal in nature, pathophysiological studies are solely cross-sectional. Additional research is needed to compare other samples of SMD and BD youth and explore the developmental progression of the neurological indices of blocked goal attainment in childhood psychopathology.

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Reference List

- Abler B, Walter H, Erk S. Neural correlates of frustration. *Neuroreport*. 2005; 16:669–672. [PubMed: 15858403]
- Adler CM, Adams J, DelBello MP, Holland SK, Schmithorst V, Levine A, et al. Evidence of white matter pathology in bipolar disorder adolescents experiencing their first episode of mania: a diffusion tensor imaging study. *Am J Psychiatry*. 2006; 163:322–324. [PubMed: 16449490]
- Adler CM, Delbello MP, Mills NP, Schmithorst V, Holland S, Strakowski SM. Comorbid ADHD is associated with altered patterns of neuronal activation in adolescents with bipolar disorder performing a simple attention task. *Bipolar Disord*. 2005; 7:577–588. [PubMed: 16403183]
- Aftanas LI, Varlamov AA, Pavlov SV, Makhnev VP, Reva NV. Affective picture processing: event-related synchronization within individually defined human theta band is modulated by valence dimension. *Neurosci Lett*. 2001; 303:115–118. [PubMed: 11311506]
- Aftanas LI, Varlamov AA, Reva NV, Pavlov SV. Disruption of early event-related theta synchronization of human EEG in alexithymics viewing affective pictures. *Neurosci Lett*. 2003; 340:57–60. [PubMed: 12648758]
- Amodio DM, Frith CD. Meeting of minds: the medial frontal cortex and social cognition. *Nat Rev Neurosci*. 2006; 7:268–277. [PubMed: 16552413]
- Blader JC, Carlson GA. Increased Rates of Bipolar Disorder Diagnoses Among U.S. Child, Adolescent, and Adult Inpatients, 1996–2004. *Biol Psychiatry*. 2007
- Blumberg HP, Donegan NH, Sanislow CA, Collins S, Lacadie C, Skudlarski P, et al. Preliminary evidence for medication effects on functional abnormalities in the amygdala and anterior cingulate in bipolar disorder. *Psychopharmacology (Berl)*. 2005a; 183:308–313. [PubMed: 16249909]
- Blumberg HP, Fredericks C, Wang F, Kalmar JH, Spencer L, Papademetris X, et al. Preliminary evidence for persistent abnormalities in amygdala volumes in adolescents and young adults with bipolar disorder. *Bipolar Disord*. 2005b; 7:570–576. [PubMed: 16403182]
- Boussaoud D. Attention versus intention in the primate premotor cortex. *Neuroimage*. 2001; 14:S40–S45. [PubMed: 11373131]
- Brem S, Halder P, Bucher K, Summers P, Martin E, Brandeis D. Tuning of the visual word processing system: distinct developmental ERP and fMRI effects. *Hum Brain Mapp*. 2009; 30:1833–1844. [PubMed: 19288464]
- Brooks JO III, Wang PW, Bonner JC, Rosen AC, Hoblyn JC, Hill SJ, et al. Decreased prefrontal, anterior cingulate, insula, and ventral striatal metabolism in medication-free depressed outpatients with bipolar disorder. *J Psychiatr Res*. 2009; 43:181–188. [PubMed: 18582900]
- Brotman MA, Kassem L, Reising MM, Guyer AE, Dickstein DP, Rich BA, et al. Parental diagnoses in youth with narrow phenotype bipolar disorder or severe mood dysregulation. *Am J Psychiatry*. 2007; 164:1238–1241. [PubMed: 17671287]

- Brotman MA, Rich BA, Guyer AE, Lunsford JR, Horsey SE, Reising MM, et al. Amygdala activation during emotion processing of neutral faces in children with severe mood dysregulation versus ADHD or bipolar disorder. *Am J Psychiatry*. 2010; 167:61–69. [PubMed: 19917597]
- Brotman MA, Schmajuk M, Rich BA, Dickstein DP, Guyer AE, Costello EJ, et al. Prevalence, clinical correlates, and longitudinal course of severe mood dysregulation in children. *Biol Psychiatry*. 2006; 60:991–997. [PubMed: 17056393]
- Brunetti M, Della PS, Ferretti A, Del Gratta C, Cianflone F, Belardinelli P, et al. A Frontoparietal Network for Spatial Attention Reorienting in the Auditory Domain: A Human fMRI/MEG Study of Functional and Temporal Dynamics. *Cereb Cortex*. 2007
- Caligiuri MP, Brown GG, Meloy MJ, Eberson SC, Kindermann SS, Frank LR, et al. An fMRI study of affective state and medication on cortical and subcortical brain regions during motor performance in bipolar disorder. *Psychiatry Res*. 2003; 123:171–182. [PubMed: 12928105]
- Callicott JH, Mattay VS, Verchinski BA, Marenco S, Egan MF, Weinberger DR. Complexity of prefrontal cortical dysfunction in schizophrenia: more than up or down. *Am J Psychiatry*. 2003; 160:2209–2215. [PubMed: 14638592]
- Callicott JH, Weinberger DR. Neuropsychiatric dynamics: The study of mental illness using functional magnetic resonance imaging. *European Journal of Radiology*. 2000; 30:95–104. [PubMed: 10401590]
- Carlson GA, Jensen PS, Findling RL, Meyer RE, Calabrese J, Delbello MP, et al. Methodological issues and controversies in clinical trials with child and adolescent patients with bipolar disorder: report of a consensus conference. *J Child Adolesc Psychopharmacol*. 2003; 13:13–27. [PubMed: 12804123]
- Chang K, Adelman NE, Dienes K, Simeonova DI, Menon V, Reiss A. Anomalous prefrontal-subcortical activation in familial pediatric bipolar disorder: a functional magnetic resonance imaging investigation. *Arch Gen Psychiatry*. 2004; 61:781–792. [PubMed: 15289277]
- Chang K, Karchemskiy A, Barnea-Goraly N, Garrett A, Simeonova DI, Reiss A. Reduced amygdalar gray matter volume in familial pediatric bipolar disorder. *J Am Acad Child Adolesc Psychiatry*. 2005; 44:565–573. [PubMed: 15908839]
- Chen BK, Sassi R, Axelson D, Hatch JP, Sanches M, Nicoletti M, et al. Cross-sectional study of abnormal amygdala development in adolescents and young adults with bipolar disorder. *Biol Psychiatry*. 2004; 56:399–405. [PubMed: 15364037]
- Chiu PH, Deldin PJ. Neural evidence for enhanced error detection in major depressive disorder. *Am J Psychiatry*. 2007; 164:608–616. [PubMed: 17403974]
- Cox RW. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Comput Biomed Res*. 1996; 29:162–173. [PubMed: 8812068]
- Craig AD. How do you feel--now? The anterior insula and human awareness. *Nat Rev Neurosci*. 2009; 10:59–70. [PubMed: 19096369]
- Delbello MP, Zimmerman ME, Mills NP, Getz GE, Strakowski SM. Magnetic resonance imaging analysis of amygdala and other subcortical brain regions in adolescents with bipolar disorder. *Bipolar Disord*. 2004; 6:43–52. [PubMed: 14996140]
- Dickstein DP, Nelson EE, McClure EB, Grimley ME, Knopf L, Brotman MA, et al. Cognitive flexibility in phenotypes of pediatric bipolar disorder. *J Am Acad Child Adolesc Psychiatry*. 2007; 46:341–355. [PubMed: 17314720]
- Donovan SJ, Nunes EV, Stewart JW, Ross D, Quitkin FM, Jensen PS, et al. “Outer-directed irritability”: a distinct mood syndrome in explosive youth with a disruptive behavior disorder? *J Clin Psychiatry*. 2003; 64:698–701. [PubMed: 12823085]
- Drabycz S, Stockwell RG, Mitchell JR. Image texture characterization using the discrete orthonormal S-transform. *J Digit Imaging*. 2009; 22:696–708. [PubMed: 18677534]
- Ellison-Wright I, Bullmore E. Anatomy of bipolar disorder and schizophrenia: a meta-analysis. *Schizophr Res*. 2010; 117:1–12. [PubMed: 20071149]
- Esposito F, Mulert C, Goebel R. Combined distributed source and single-trial EEG-fMRI modeling: application to effortful decision making processes. *Neuroimage*. 2009; 47:112–121. [PubMed: 19361566]

- Etkin A, Egner T, Kalisch R. Emotional processing in anterior cingulate and medial prefrontal cortex. *Trends Cogn Sci.* 2011; 15:85–93. [PubMed: 21167765]
- Fernandez A, Quintero J, Hornero R, Zuluaga P, Navas M, Gomez C, et al. Complexity analysis of spontaneous brain activity in attention-deficit/hyperactivity disorder: diagnostic implications. *Biol Psychiatry.* 2009; 65:571–577. [PubMed: 19103438]
- Frazier JA, Breeze JL, Makris N, Giuliano AS, Herbert MR, Seidman L, et al. Cortical gray matter differences identified by structural magnetic resonance imaging in pediatric bipolar disorder. *Bipolar Disord.* 2005a; 7:555–569. [PubMed: 16403181]
- Frazier JA, Breeze JL, Papadimitriou G, Kennedy DN, Hodge SM, Moore CM, et al. White matter abnormalities in children with and at risk for bipolar disorder. *Bipolar Disord.* 2007; 9:799–809. [PubMed: 18076529]
- Frazier JA, Chiu S, Breeze JL, Makris N, Lange N, Kennedy DN, et al. Structural brain magnetic resonance imaging of limbic and thalamic volumes in pediatric bipolar disorder. *Am J Psychiatry.* 2005b; 162:1256–1265. [PubMed: 15994707]
- Geller B, Williams M, Zimerman B, Frazier J, Beringer L, Warner KL. Prepubertal and early adolescent bipolarity differentiate from ADHD by manic symptoms, grandiose delusions, ultra-rapid or ultradian cycling. *J Affect Disord.* 1998; 51:81–91. [PubMed: 10743841]
- Genovese CR, Lazar NA, Nichols T. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. *Neuroimage.* 2002; 15:870–878. [PubMed: 11906227]
- Gusnard DA, Akbudak E, Shulman GL, Raichle ME. Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. *Proc Natl Acad Sci USA.* 2001; 98:4259–4264. [PubMed: 11259662]
- Hanakawa T, Honda M, Sawamoto N, Okada T, Yonekura Y, Fukuyama H, et al. The role of rostral Brodmann area 6 in mental-operation tasks: an integrative neuroimaging approach. *Cereb Cortex.* 2002; 12:1157–1170. [PubMed: 12379604]
- Hanslmayr S, Pastotter B, Bauml KH, Gruber S, Wimber M, Klimesch W. The electrophysiological dynamics of interference during the Stroop task. *J Cogn Neurosci.* 2008; 20:215–225. [PubMed: 18275330]
- Harris J. The increased diagnosis of “juvenile bipolar disorder”: what are we treating? *Psychiatr Serv.* 2005; 56:529–531. [PubMed: 15876571]
- Henson RN, Mattout J, Singh KD, Barnes GR, Hillebrand A, Friston K. Population-level inferences for distributed MEG source localization under multiple constraints: Application to face-evoked fields. *Neuroimage.* 2007; 38:422–438. [PubMed: 17888687]
- Hirata M, Koreeda S, Sakihara K, Kato A, Yoshimine T, Yorifuji S. Effects of the emotional connotations in words on the frontal areas—a spatially filtered MEG study. *Neuroimage.* 2007; 35:420–429. [PubMed: 17188899]
- Holmes AJ, Pizzagalli DA. Response conflict and frontocingulate dysfunction in unmedicated participants with major depression. *Neuropsychologia.* 2008a; 46:2904–2913. [PubMed: 18577391]
- Holmes AJ, Pizzagalli DA. Spatiotemporal dynamics of error processing dysfunctions in major depressive disorder. *Arch Gen Psychiatry.* 2008b; 65:179–188. [PubMed: 18250256]
- Hopfinger JB, Buonocore MH, Mangun GR. The neural mechanisms of top-down attentional control. *Nat Neurosci.* 2000; 3:284–291. [PubMed: 10700262]
- Hosokawa T, Momose T, Kasai K. Brain glucose metabolism difference between bipolar and unipolar mood disorders in depressed and euthymic states. *Prog Neuropsychopharmacol Biol Psychiatry.* 2009; 33:243–250. [PubMed: 19100808]
- Ishii R, Shinosaki K, Ukai S, Inouye T, Ishihara T, Yoshimine T, et al. Medial prefrontal cortex generates frontal midline theta rhythm. *Neuroreport.* 1999; 10:675–679. [PubMed: 10208529]
- Jabbi M, Swart M, Keysers C. Empathy for positive and negative emotions in the gustatory cortex. *Neuroimage.* 2007; 34:1744–1753. [PubMed: 17175173]
- Kahkonen S, Yamashita H, Rytala H, Suominen K, Ahveninen J, Isometsa E. Dysfunction in early auditory processing in major depressive disorder revealed by combined MEG and EEG. *J Psychiatry Neurosci.* 2007; 32:316–322. [PubMed: 17823647]

- Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry*. 1997; 36:980–988. [PubMed: 9204677]
- Kaur S, Sassi RB, Axelson D, Nicoletti M, Brambilla P, Monkul ES, et al. Cingulate cortex anatomical abnormalities in children and adolescents with bipolar disorder. *Am J Psychiatry*. 2005; 162:1637–1643. [PubMed: 16135622]
- Kim E, Jung YC, Ku J, Kim JJ, Lee H, Kim SY, et al. Reduced activation in the mirror neuron system during a virtual social cognition task in euthymic bipolar disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2009; 33:1409–1416. [PubMed: 19632283]
- Lapalme E, Lina JM, Mattout J. Data-driven parcelling and entropic inference in MEG. *Neuroimage*. 2006; 30:160–171. [PubMed: 16426867]
- Leibenluft E, Charney DS, Towbin KE, Bhangoo RK, Pine DS. Defining clinical phenotypes of juvenile mania. *Am J Psychiatry*. 2003; 160:430–437. [PubMed: 12611821]
- Leibenluft E, Rich BA, Vinton DT, Nelson EE, Fromm SJ, Berghorst LH, et al. Neural circuitry engaged during unsuccessful motor inhibition in pediatric bipolar disorder. *Am J Psychiatry*. 2007; 164:52–60. [PubMed: 17202544]
- Lennox BR, Jacob R, Calder AJ, Lupson V, Bullmore ET. Behavioural and neurocognitive responses to sad facial affect are attenuated in patients with mania. *Psychol Med*. 2004; 34:795–802. [PubMed: 15500300]
- Lieberman MD, Cunningham WA. Type I and Type II error concerns in fMRI research: re-balancing the scale. *Soc Cogn Affect Neurosci*. 2009; 4:423–428. [PubMed: 20035017]
- Logan BR, Rowe DB. An evaluation of thresholding techniques in fMRI analysis. *Neuroimage*. 2004; 22:95–108. [PubMed: 15110000]
- Luu P, Tucker DM, Makeig S. Frontal midline theta and the error-related negativity: neurophysiological mechanisms of action regulation. *Clin Neurophysiol*. 2004; 115:1821–1835. [PubMed: 15261861]
- Malhi GS, Lagopoulos J, Das P, Moss K, Berk M, Coulston CM. A functional MRI study of Theory of Mind in euthymic bipolar disorder patients. *Bipolar Disord*. 2008; 10:943–956. [PubMed: 19594509]
- Maurer U, Brem S, Bucher K, Brandeis D. Emerging neurophysiological specialization for letter strings. *J Cogn Neurosci*. 2005; 17:1532–1552. [PubMed: 16269095]
- McMahon, RJ.; Wells, KC. Conduct Problems. In: Mash, EJ.; Barkley, RA., editors. *Treatment of Childhood Disorders*. New York: Guilford Press; 1998. p. 111-207.
- McManis MH, Bradley MM, Berg WK, Cuthbert BN, Lang PJ. Emotional reactions in children: verbal, physiological, and behavioral responses to affective pictures. *Psychophysiology*. 2001; 38:222–231. [PubMed: 11347868]
- Moadab I, Gilbert T, Dishion TJ, Tucker DM. Frontolimbic activity in a frustrating task: covariation between patterns of coping and individual differences in externalizing and internalizing symptoms. *Dev Psychopathol*. 2010; 22:391–404. [PubMed: 20423549]
- Moreno C, Laje G, Blanco C, Jiang H, Schmidt AB, Olfson M. National trends in the outpatient diagnosis and treatment of bipolar disorder in youth. *Arch Gen Psychiatry*. 2007; 64:1032–1039. [PubMed: 17768268]
- Mulas F, Capilla A, Fernandez S, Etchepareborda MC, Campo P, Maestu F, et al. Shifting-related brain magnetic activity in attention-deficit/hyperactivity disorder. *Biol Psychiatry*. 2006; 59:373–379. [PubMed: 16154541]
- Mulert C, Seifert C, Leicht G, Kirsch V, Ertl M, Karch S, et al. Single-trial coupling of EEG and fMRI reveals the involvement of early anterior cingulate cortex activation in effortful decision making. *Neuroimage*. 2008; 42:158–168. [PubMed: 18547820]
- Nagahama Y, Okada T, Katsumi Y, Hayashi T, Yamauchi H, Sawamoto N, et al. Transient neural activity in the medial superior frontal gyrus and precuneus time locked with attention shift between object features. *Neuroimage*. 1999; 10:193–199. [PubMed: 10417251]

- Nelson EE, Vinton DT, Berghorst L, Towbin KE, Hommer RE, Dickstein DP, et al. Brain systems underlying response flexibility in healthy and bipolar adolescents: an event-related fMRI study. *Bipolar Disord.* 2007; 9:810–819. [PubMed: 18076530]
- Nichols T, Hayasaka S. Controlling the familywise error rate in functional neuroimaging: a comparative review. *Stat Methods Med Res.* 2003; 12:419–446. [PubMed: 14599004]
- Onoda K, Okamoto Y, Shishida K, Hashizume A, Ueda K, Yamashita H, et al. Anticipation of affective images and event-related desynchronization (ERD) of alpha activity: an MEG study. *Brain Res.* 2007; 1151:134–141. [PubMed: 17408598]
- Ossadtchi A, Baillet S, Mosher JC, Thyerlei D, Sutherling W, Leahy RM. Automated interictal spike detection and source localization in magnetoencephalography using independent components analysis and spatio-temporal clustering. *Clin Neurophysiol.* 2004; 115:508–522. [PubMed: 15036046]
- Paus T. Primate anterior cingulate cortex: where motor control, drive and cognition interface. *Nat Rev Neurosci.* 2001; 2:417–424. [PubMed: 11389475]
- Pavuluri MN, Passarotti AM, Harral EM, Sweeney JA. An fMRI study of the neural correlates of incidental versus directed emotion processing in pediatric bipolar disorder. *J Am Acad Child Adolesc Psychiatry.* 2009a; 48:308–319. [PubMed: 19242292]
- Pavuluri MN, Passarotti AM, Harral EM, Sweeney JA. An fMRI study of the neural correlates of incidental versus directed emotion processing in pediatric bipolar disorder. *J Am Acad Child Adolesc Psychiatry.* 2009b; 48:308–319. [PubMed: 19242292]
- Perez-Edgar K, Fox N. A behavioral and electrophysiological study of children's selective attention under neutral and affective conditions. *Journal of Cognition and Development.* 2005; 6:89–116.
- Phillips ML, Travis MJ, Fagiolini A, Kupfer DJ. Medication Effects in Neuroimaging Studies of Bipolar Disorder. *Am J Psychiatry.* 2008
- Poznanski EO, Grossman JA, Buchsbaum Y, Banegas M, Freeman L, Gibbons R. Preliminary studies of the reliability and validity of the Children's Depression Rating Scale. *J Am Acad Child Psychiatry.* 1984; 23:191–197. [PubMed: 6715741]
- Proverbio AM, Adorni R. Orthographic familiarity, phonological legality and number of orthographic neighbours affect the onset of ERP lexical effects. *Behav Brain Funct.* 2008; 4:27. [PubMed: 18601726]
- Rich BA, Brotman MA, Dickstein DP, Mitchell DG, Blair RJ, Leibenluft E. Deficits in Attention to Emotional Stimuli Distinguish Youth with Severe Mood Dysregulation from Youth with Bipolar Disorder. *J Abnorm Child Psychol.* 2010a; 38:695–706. [PubMed: 20180010]
- Rich BA, Holroyd T, Carver FW, Onelio LM, Mendoza JK, Cornwell BR, et al. A preliminary study of the neural mechanisms of frustration in pediatric bipolar disorder using magnetoencephalography. *Depress Anxiety.* 2010b; 27:276–286. [PubMed: 20037920]
- Rich BA, Schmajuk M, Perez-Edgar KE, Fox NA, Pine DS, Leibenluft E. Different psychophysiological and behavioral responses elicited by frustration in pediatric bipolar disorder and severe mood dysregulation. *Am J Psychiatry.* 2007; 164:309–317. [PubMed: 17267795]
- Rich BA, Schmajuk M, Perez-Edgar KE, Pine DS, Fox NA, Leibenluft E. The impact of reward, punishment, and frustration on attention in pediatric bipolar disorder. *Biol Psychiatry.* 2005; 58:532–539. [PubMed: 15953589]
- Salminen M, Ravaja N. Increased oscillatory theta activation evoked by violent digital game events. *Neurosci Lett.* 2008; 435:69–72. [PubMed: 18325669]
- Sanches M, Sassi RB, Axelson D, Nicoletti M, Brambilla P, Hatch JP, et al. Subgenual prefrontal cortex of child and adolescent bipolar patients: a morphometric magnetic resonance imaging study. *Psychiatry Res.* 2005; 138:43–49. [PubMed: 15708300]
- Santesso DL, Dillon DG, Birk JL, Holmes AJ, Goetz E, Bogdan R, et al. Individual differences in reinforcement learning: behavioral, electrophysiological, and neuroimaging correlates. *Neuroimage.* 2008a; 42:807–816. [PubMed: 18595740]
- Santesso DL, Steele KT, Bogdan R, Holmes AJ, Deveney CM, Meites TM, et al. Enhanced negative feedback responses in remitted depression. *Neuroreport.* 2008b; 19:1045–1048. [PubMed: 18580576]

- Sekihara K, Nagarajan SS, Poeppel D, Marantz A, Miyashita Y. Reconstructing spatio-temporal activities of neural sources using an MEG vector beamformer technique. *IEEE Trans Biomed Eng.* 2001; 48:760–771. [PubMed: 11442288]
- Shackman AJ, Salomons TV, Slagter HA, Fox AS, Winter JJ, Davidson RJ. The integration of negative affect, pain and cognitive control in the cingulate cortex. *Nat Rev Neurosci.* 2011; 12:154–167. [PubMed: 21331082]
- Shaffer D, Gould MS, Brasic J, Ambrosini P, Fisher P, Bird H, et al. A Children's Global Assessment Scale (CGAS). *Arch Gen Psychiatry.* 1983; 40:1228–1231. [PubMed: 6639293]
- Siegrist J, Menrath I, Stocker T, Klein M, Kellermann T, Shah NJ, et al. Differential brain activation according to chronic social reward frustration. *Neuroreport.* 2005; 16:1899–1903. [PubMed: 16272875]
- Stockwell RG, Mansinha L, Lowe RP. Localization of the complex spectrum: The S transform. *IEEE Trans Sign Proc.* 1996; 44:998–1000.
- Stringaris A, Baroni A, Haimm C, Brotman M, Lowe CH, Myers F, et al. Pediatric bipolar disorder versus severe mood dysregulation: risk for manic episodes on follow-up. *J Am Acad Child Adolesc Psychiatry.* 2010; 49:397–405. [PubMed: 20410732]
- Stringaris A, Cohen P, Pine DS, Leibenluft E. Adult outcomes of youth irritability: A 20-year prospective community based study. *American Journal of Psychiatry.* (in press).
- Tanaka S, Honda M, Sadato N. Modality-specific cognitive function of medial and lateral human Brodmann area 6. *J Neurosci.* 2005; 25:496–501. [PubMed: 15647494]
- Taniguchi M, Kato A, Fujita N, Hirata M, Tanaka H, Kihara T, et al. Movement-related desynchronization of the cerebral cortex studied with spatially filtered magnetoencephalography. *Neuroimage.* 2000; 12:298–306. [PubMed: 10944412]
- Tucker DM, Luu P, Frishkoff G, Quiring J, Poulsen C. Frontolimbic response to negative feedback in clinical depression. *J Abnorm Psychol.* 2003; 112:667–678. [PubMed: 14674878]
- Vrba J, Robinson SE. Signal processing in magnetoencephalography. *Methods.* 2001; 25:249–271. [PubMed: 11812209]
- Wechsler, D. Wechsler Abbreviated Scale of Intelligence. San Antonio: The Psychological Corporation; 1999.
- Wessa M, Houenou J, Paillere-Martinot ML, Berthoz S, Artiges E, Leboyer M, et al. Fronto-striatal overactivation in euthymic bipolar patients during an emotional go/nogo task. *Am J Psychiatry.* 2007; 164:638–646. [PubMed: 17403978]
- Wessa M, Linke J. Emotional processing in bipolar disorder: behavioural and neuroimaging findings. *Int Rev Psychiatry.* 2009; 21:357–367. [PubMed: 20374149]
- Wienbruch C, Paul I, Bauer S, Kivelitz H. The influence of methylphenidate on the power spectrum of ADHD children - an MEG study. *BMC Psychiatry.* 2005; 5:29. [PubMed: 16042816]
- Wilkinson D, Halligan P. The relevance of behavioural measures for functional-imaging studies of cognition. *Nat Rev Neurosci.* 2004; 5:67–73. [PubMed: 14708005]
- Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry.* 1978; 133:429–435. [PubMed: 728692]
- Yu R, Mobbs D, Seymour B, Calder AJ. Insula and striatum mediate the default bias. *J Neurosci.* 2010; 30:14702–14707. [PubMed: 21048128]
- Zimmerman M, Ruggero CJ, Chelminski I, Young D. Is Bipolar Disorder Overdiagnosed? *J Clin Psychiatry.* 2008:e1–e6. [PubMed: 18312028]

Figure 1.

Affective Posner Task

Figure displays visual stimuli that comprise Condition 3 of the Affective Posner Task. Rigged feedback ("Too Slow! Lose 25 Cents") is introduced to elicit frustration.

Figure 2.

A–C. Stockwell transformation of raw MEG power in BD, SMD, and CON subjects. Note: BD = bipolar disorder; SMD = severe mood dysregulation; CON = controls. Figure displays the time-frequency representation of the averaged raw MEG power in response to the presentation of negative feedback as compared to presentation of the fixation cross. 2A = BD; 2B = SMD; 2C = CON. Y axis = frequency (Hz); X axis = time (sec), where 0.0 reflects the onset of feedback.

Figure 3.

Group differences in self-reported arousal following negative feedback.

Note: BD = bipolar disorder; SMD = severe mood dysregulation; CON = control. Figure displays the average arousal ratings in response to negative feedback. SMD youth reported feeling more agitated than BD ($p=.03$) and control ($p=.04$) youth.

Figure 4.

Group differences in self-reported valence during the rigged feedback condition.

Note: BD = bipolar disorder; SMD = severe mood dysregulation; CON = control. Figure displays the average valence ratings in response to negative feedback. Both SMD ($p < .001$) and BD youth ($p = .04$) reported feeling more unhappy than controls.

Figure 5.

MEG power differences between BD, SMD and CON youth in the left anterior cingulate cortex (ACC).

Note: BD = bipolar disorder; SMD = severe mood dysregulation; CON = control. Figure displays the group averages in MEG power and the cluster in the left ACC (-17, 42, 3) where SMD subjects had significantly greater activation than controls, with a nonsignificant difference compared to BD subjects, following negative feedback. In this same cluster, controls had significantly greater activation than SMD subjects following positive feedback.

Figure 6.

MEG power differences between BD, SMD and CON youth in the right medial frontal gyrus (MFG).

Note: BD = bipolar disorder; SMD = severe mood dysregulation; CON = control. Figure displays the group averages in MEG power and the cluster in the right MFG (1, 54, -8) where SMD subjects had greater activation than controls following negative feedback, and controls had greater activation than SMD subjects following positive feedback.

Figure 7.

MEG power differences between BD, SMD and CON youth in the right superior frontal gyrus (SFG).

Note: BD = bipolar disorder; SMD = severe mood dysregulation; CON = control. Figure displays the group averages in MEG power and the cluster in the right SFG (1, 47, 33) where BD subjects had greater activation than SMD and control subjects following negative feedback.

Figure 8.

MEG power differences between BD, SMD and CON youth in the left insula

Note: BD = bipolar disorder; SMD = severe mood dysregulation; CON = control. Figure displays the group averages in MEG power and the cluster in the left insula (−29, 16, 16) where both SMD and control subjects had greater activation than BD subjects following negative feedback, and where BD subjects had greater activation than SMD subjects following positive feedback.

Table 1

Demographic Data

	BD	SMD	CON	p value
Age, years	14.92±2.03	14.15±2.14	14.72±1.69	.44
Sex (male): % (N)	45 (9)	75 (15)	45 (9)	.09
IQ	108.95±17.62	104.70±13.48	111.45±9.24	.31
CGAS	51.3 ± 11.1	48.00±9.50	—	.31
Euthymic Mood State: % (N)	100 (20)	90% (18)	—	.47
Current diagnoses: % (N)				
BD I	80 (16)	—	—	—
BD II	20 (4)	—	—	—
ADHD	60 (12)	70 (14)	—	.74
GAD	20 (4)	25 (5)	—	.71
Separation anxiety	25 (5)	25 (5)	—	1.00
Social phobia	10 (2)	15 (3)	—	.63
Any anxiety	40 (8)	35 (7)	—	.74
ODD	20 (4)	50 (10)	—	.09
MDD	—	20 (4)	—	—
Average Number of Diagnoses	2.85±1.53	1.90±1.48	—	.17
Medicated: % (N)				
antiepileptics	55 (11)	35 (7)	—	.34
antipsychotics	60 (12)	45 (9)	—	.53
lithium	40 (8)	15 (3)	—	.16
stimulants	25 (5)	45 (9)	—	.32
antidepressants	40 (8)	20 (4)	—	.30
Average Number of Medications	2.40±1.39	1.55±1.32	—	.12

Note. BD = bipolar disorder; SMD = severe mood dysregulation; CON = control; CGAS = Children's Global Assessment Scale; ADHD = Attention Deficit Hyperactivity Disorder; GAD = Generalized Anxiety Disorder; ODD = Oppositional Defiant Disorder; MDD = Major Depressive Disorder; All diagnoses are current.

Table 2

Behavioral Data

	BD	SMD	CON
Reaction Time: Negative Feedback	297.17 ± 64.91	269.25 ± 83.72	253.18 ± 62.93
Reaction Time: Positive Feedback	303.83 ± 63.23	269.15 ± 77.63	252.93 ± 61.67
Accuracy: Negative Feedback	82.69 ± 11.63	80.24 ± 14.06	79.99 ± 12.21
Accuracy: Positive Feedback	85.04 ± 10.54	83.53 ± 10.94	85.25 ± 7.09

Note. BD = bipolar disorder; SMD = severe mood dysregulation; CON = control. Reaction Time = msec; Accuracy = Percent Correct.

Table 3

Regions in which MEG power differed between BD, SMD, and control subjects following presentation of negative and positive feedback

Region	BA	X,Y,Z	Between-group comparison of neural activation	t value	p value
Anterior Cingulate Cortex (ACC): L	32	-17, 42, 3	Neg. fdbk.: SMD > CON	-2.23	.02
			Neg. fdbk.: SMD > BD	-1.79	.07
			Pos. fdbk.: CON > SMD	2.96	.008
Medial Frontal Gyrus (MFG): R	10	1, 54, -8	Neg. fdbk.: SMD > CON	-1.98	.05
			Pos. fdbk.: CON > SMD	2.39	.01
Superior Frontal Gyrus (SFG): R	6	1, 47, 33	Neg. fdbk.: BD > SMD	2.88	.009
			Neg. fdbk.: BD > CON	3.28	.002
			Neg. fdbk.: SMD > BD	-2.39	.006
Insula: L		-29, 16, 16	Neg. fdbk.: CON > BD	-2.17	.01
			Pos. fdbk.: BD > SMD	2.43	.005
			Neg. fdbk.: CON > SMD	2.95	.008
Supplementary Motor Area (SMA): R		1, -18, 58	Pos. fdbk.: BD > SMD	2.29	.02
			Pos. fdbk.: BD > CON	3.01	.003

Note. BD = bipolar disorder; SMD = severe mood dysregulation; CON = control.

BA = Brodmann Area; X,Y,Z = Talairach space coordinates reflecting the peak voxel of that region; L = left; R = right; Pos. fdbk. = after positive feedback; Neg. fdbk. = after negative feedback. Regions identified based on significant group (BD, SMD, CON) x feedback type (negative vs. positive) ANOVA interaction.