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Neural recruitment during failed motor inhibition differentiates youths with Bipolar Disorder and Severe Mood Dysregulation

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Abstract

Controversy exists about whether non-episodic irritability (operationalized as severe mood dysregulation, SMD) should be considered a developmental presentation of pediatric bipolar disorder (BD). While assessments of brain function may address this controversy, only one fMRI study has compared BD versus SMD. We compared neural activation in BD, SMD, and controls during a motor inhibition task, since motor disinhibition is an important clinical feature in both BD and SMD. During failed inhibition, BD youths exhibited less activation in the right anterior cingulate cortex (ACC) and right nucleus accumbens relative to both SMD and healthy youths. Exploratory analyses indicate that, in BD youths, reduced activation in the right ACC may be independent of comorbid ADHD. These findings highlight neural distinctions between the phenotypically related BD and SMD populations.

Introduction

Considerable controversy surrounds nosologic approaches to pediatric bipolar disorder (BD), specifically with respect to the diagnostic status of children who exhibit non-episodic severe irritability coupled with symptoms of hyperarousal similar to those seen in attention deficit hyperactivity disorder (ADHD). If non-episodic severe irritability is a developmental presentation of BD (Biederman, Klein, Pine, and Klein, 1998), then children with these symptoms should resemble those with classic episodic BD on behavioral and neuroimaging tasks (Leibenluft, Charney, Towbin, Bhangoo, and Pine, 2003). Alternatively, differences between these groups on such measures, coupled with between-group differences in longitudinal course and family history, would suggest that non-episodic severe irritability is not a developmental presentation of BD, a conclusion which has important prognostic and therapeutic implications. The only published functional magnetic neuroimaging study comparing youths with classic episodic BD to those with chronic irritability (operationalized as severe mood dysregulation [SMD]; Leibenluft, Charney et al., 2003) used a face-viewing task (Brotman et al., 2010). The present neuroimaging study compared these two patient

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Disclosures

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groups and healthy subjects on a motor inhibition task because symptoms of both illnesses involve inhibition deficits (American Psychiatric Association, 2000; Leibenluft, Charney et al., 2003). Different neural activation patterns in BD and SMD youths during motor inhibition would suggest that the neural correlates of non-episodic irritability differ from those of BD, while similarities would support the argument that chronic irritability is a developmental presentation of BD.

One relatively direct way to index inhibitory processes involves the use of paradigms that require subjects to inhibit a motor response (Rubia, Russell, Overmeyer et al., 2001). Behavioral evidence suggests that youths with BD perform more poorly on motor response inhibition tasks than do healthy children (Peluso et al., 2007; Swann, Anderson, Dougherty, and Moeller, 2001; Swann, Dougherty, Pazzaglia, Pham, and Moeller, 2004; Swann, Pazzaglia, Nicholls, Dougherty, and Moeller, 2003; c.f., McClure et al., 2005). Research using the stop signal task demonstrates that, during the successful inhibition of motor responses, healthy participants typically recruit the right ventrolateral prefrontal cortex (VLPFC), dorsomedial prefrontal cortex (including the anterior cingulate cortex [ACC] and supplementary motor area [SMA]), pre-SMA, subthalamic nucleus, and striatum (for review Aron, 2011; Aron et al., 2007; Chambers, Garavan, and Bellgrove, 2009). Several of these regions (VLPFC, ACC, pre-SMA, and subthalamic nucleus) are also recruited in other motor inhibition paradigms (e.g., go/no-go). Given the high rate of failed inhibitions on the stop signal task, the task is uniquely suited to identify regions activated during unsuccessful inhibition. Among healthy participants, failure to inhibit a motor response is associated with increased ACC, prefrontal cortex, posterior parietal, and caudate activation (e.g., Padmala and Pessoa, 2010; Rubia, Smith, Brammer, and Taylor, 2003).

Imaging studies suggest that impaired recruitment of many of these regions, including the VLPFC, striatum, and ACC, may contribute to motor inhibition deficits in youths with BD and/or ADHD (Blumberg et al., 2003; Leibenluft et al., 2007; Passarotti, Sweeney, and Pavuluri, 2010c). For example, during failed inhibition, Leibenluft et al. (2007) observed reduced VLPFC, striatum, and ACC activation among BD youths versus controls. Similarly, using a block design, Passarotti et al. (2010c) reported VLPFC hypoactivation in BD youths, a deficit that normalized following lamotrigine treatment (Pavuluri et al., 2010). Abnormal striatal and ACC activation has also been observed among youths with BD during inhibitory tasks (Blumberg et al., 2003; Leibenluft et al., 2007; Passarotti et al., 2010c). The current study extends prior research by examining the performance of BD youths on a motor inhibition task relative to both SMD and ADHD, conditions with some overlapping clinical characteristics.

Motor inhibition in youths with SMD has not been assessed behaviorally or with neuroimaging techniques. However, there are reasons to believe that this population would exhibit impairments on motor inhibition tasks. First, the symptoms of SMD overlap significantly with other conditions displaying abnormal motor inhibition, including both BD and ADHD (Rubia, Oosterlaan, Sergeant, Brandeis, and v. Leeuwen, 1998; Rubia, Smith, Brammer, Toone, and Taylor, 2005; Schachar, Mota, Logan, Tannock, and Klim, 2000). Second, motor inhibition deficits have been associated with irritability (Hoeksma, Oosterlaan, and Schipper, 2004; Swann et al., 2004) - the hallmark of the SMD presentation (Leibenluft, Charney et al., 2003). Therefore, we hypothesized that youths with SMD would exhibit impairments in motor inhibition relative to healthy children, similar to what has been documented in youths with BD (Peluso et al., 2007; Swann et al., 2001; Swann et al., 2004; Swann et al., 2003; c.f., McClure et al., 2005). However, while we expected both BD and SMD to have such behavioral deficits, we hypothesized that the neural circuitry mediating such deficits would differentiate between groups. This hypothesis is based on longitudinal and family history research suggesting that BD and SMD are distinct clinical phenotypes

(Brotman et al., 2007; Stringaris et al., 2010; Stringaris, Cohen, Pine, and Leibenluft, 2009). Further, our hypothesis that SMD and BD would exhibit similar behavioral deficits with different mediating neural circuitry is consistent with the pattern that we observed in fMRI and ERP studies using face emotion processing and frustration paradigms, respectively (Brotman et al., 2010; Rich et al., 2007). Thus, we hypothesized that the neural circuitry patterns of SMD youths would differ from those with BD on this motor inhibition task, despite overlapping clinical symptoms of disinhibition.

The primary goal of the current study was to compare the neural correlates of response inhibition in BD, SMD, and healthy children (HC). To do so, we compared BOLD signal responses during the stop signal motor inhibition task in these three groups. We selected the striatum (including putamen, caudate, and nucleus accumbens), ACC, and VLPFC as regions of interest (ROIs) because an extensive literature highlights the role of these regions in successful and unsuccessful motor inhibition (Aron, 2011; Aron et al., 2007; Chambers et al., 2009; Rubia, Russell, Bullmore et al., 2001; Rubia, Russell, Overmeyer et al., 2001; Rubia et al., 2003; Rubia, Smith, Taylor, and Brammer, 2007), both youths with BD and those with ADHD (a related phenotype) show dysfunction in these areas (Blumberg et al., 2003; Leibenluft et al., 2007; Passarotti et al., 2010c; Rubia et al., 2005), and because we wanted to be consistent with prior studies in our lab (Leibenluft et al., 2007). For the reasons noted above, we predicted that SMD youths would exhibit distinct patterns of activation relative to youths with BD, although we did not advance specific hypotheses because of the paucity of neuroimaging literature in SMD.

The secondary goal of this study was to obtain preliminary data regarding the degree to which comorbid ADHD impacts on neural activity in BD. Motor inhibition deficits have been documented extensively in ADHD (Lipszyc and Schachar, 2010) and appear to be mediated by decreased VLPFC and ACC activation in ADHD patients versus controls (Aron et al., 2007; Rubia et al., 2010; Rubia et al., 2005). Comorbid ADHD is quite common in youths with BD (Geller and Luby, 1997). Therefore, in studies using the stop signal task in youths with BD, it is important to differentiate aberrant activation due to comorbid ADHD versus that due to BD itself. While limited research addresses this issue, three recent studies suggest that, in youths with BD, aberrant neural activation on motor inhibition tasks may not be entirely attributable to comorbid ADHD (Cerullo et al., 2009; Leibenluft et al., 2007; Passarotti et al., 2010c). In our prior study (Leibenluft et al., 2007), post-hoc analyses stratified the BD sample based on the presence of comorbid ADHD. Compared to HC, youths with BD, with or without comorbid ADHD, had reduced striatal and ACC activation during failed inhibition trials. Abnormally reduced activation in the VLPFC during failed inhibition was only present in BD youths with comorbid ADHD.

However, to disambiguate the impact of BD versus ADHD on neural activation during motor inhibition, it is important to directly compare BD youths (with and without ADHD) to youths with ADHD only. Two studies have done so. In one study employing a continuous performance task that included motor inhibition, youths with ADHD, compared to BD youths without ADHD, had hyperactivation in the superior temporal gyrus, posterior cingulate, cuneus, and middle occipital gyrus more during successful inhibition (Cerullo et al., 2009). Secondly, Passarotti and colleagues (2010c) compared manic/hypomanic BD, ADHD, and healthy youths, using a stop signal task with a block design. Both patient groups exhibited reduced recruitment of inferior frontal cortices relative to healthy controls; additionally, activation in this region was reduced among ADHD relative to BD youths (Passarotti et al., 2010c). Whether similar findings would exist in an event-related version of the stop-signal task is unknown. In addition, comparing BD and ADHD groups in the specific regions where BD youths differ from HC youths may provide a better estimate of the contribution of ADHD to the motor inhibition deficits exhibited by BD youths.

Therefore, we recruited an independent sample of youths with ADHD but no mood problems and conducted secondary analyses comparing these youths to those with BD in the specific regions where BD and HC youths differed.

Methods and Materials

Subjects

Participants (8–18 years of age) were part of an ongoing IRB approved study on BD at the National Institute of Mental Health. Parents and participants provided informed consent/ assent. Children received \$100 for participation.

Diagnoses were determined using the Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime (Kaufmann et al., 1997), including a supplementary SMD assessment module, conducted by clinicians with masters level or above training ($\kappa \geq 0.9$). The Young Mania Rating Scale (YMRS; Young, Biggs, Ziegler, and Meyer, 1978) and Children's Depression Rating Scale (CDRS; Poznanski, Cook, and Carroll, 1979) were completed with the BD youths, and the CDRS with the SMD youths, within 48 hours of scanning to assess mood state. Exclusions for all subjects included: IQ < 80, substance abuse (within the past three months for BD, SMD, and ADHD, lifetime for HC), neurological damage/disorder, or pervasive developmental disorder. ADHD youths were excluded if they were currently taking any psychotropic medications except for short-acting stimulants.

BD participants ($n = 32$) met criteria for “narrow phenotype” BD indicating that they satisfied DSM-IV criteria for bipolar disorder (including duration criteria) with the additional requirement that at least one of the episodes was characterized by elated or euphoric mood (Leibenluft, Charney et al., 2003). SMD participants ($n = 26$) were characterized by chronic irritability and hyperarousal symptoms and met criteria as in (Leibenluft, Charney et al., 2003). HC ($n = 21$) had no current or past psychiatric illness and no first-degree relatives with a mood disorder, however, we did not conduct diagnostic interviews with each relative. A research assistant and a clinician trained on research diagnostic interviews each asked the parent a series of structured questions about whether any first degree relative had received a diagnosis of or treatment for any psychiatric illness. Mood and psychotic disorders were specifically queried. Clinicians followed up on any positive responses to these questions using semi-structured diagnostic questions The participant was excluded if there was any suspicion of a mood or psychotic disorder in his/her first degree relative. In addition, to explore whether differences between clinical and HC youths reflected the role of comorbid ADHD, we recruited a secondary control sample of participants ($n=17$) who met criteria for ADHD but not for any mood disorder (including SMD). See Table 1.

Of the 174 individuals scanned for this study, data from 11.5% ($n = 6$ BD, 6 SMD, 7 ADHD, 1 HC) were excluded due to poor task performance (i.e., < 55% accuracy on go trials); 1.7% ($n = 2$ SMD, 1 ADHD) for failure to complete the task; 17.2% ($n = 11$ BD, 5 SMD, 6 ADHD, 8 HC) for excessive movement (defined as > 3mm or 2.5° in any direction); 5.2 % ($n = 1$ BD, 4 SMD, 2 ADHD, 2 HC) for poor scan quality; 6.9% ($n = 2$ BD, 4 SMD, 2 ADHD, 4 HC) for equipment failure; and 1.7% ($n = 2$ BD, 1 SMD) for abnormal brain findings. The final sample ($n = 96$) is presented below. Of these, data from 20 BD and 15 HC participants were reported previously in (Leibenluft et al., 2007). Data from 61 participants ($n = 12$ BD, 26 SMD, 17 ADHD, 6 HC) have not been presented previously.

Stop Signal Task

We used a stop signal task modified from Logan and colleagues (Logan, Schachar, and Tannock, 1997). Trials consisted of the central presentation of a white fixation cross (500ms), followed by a white “X” or “O” (target stimulus; 1000ms), on a black background. Participants pressed “1” or a “2” when they saw an “X” or an “O”, respectively, unless the “stop” signal appeared (i.e., the background color changed from black to red). During go trials (75% of trials) the background color did not change and participants were instructed to respond. During stop trials (25% of trials) the stop signal appeared and participants were instructed to inhibit their response. The delay between target and stop signal onsets (inhibit delay) varied to ensure an overall accuracy of approximately 50% on stop trials and, therefore, to control for performance differences between groups. Specifically, correct inhibition decreased the inhibit delay by 50 ms, but failed inhibition increased the inhibit delay by 50 ms (for details, see Leibenluft et al., 2007). Total trial length was held constant at 1500 ms with a 750 ms inter-trial interval.

Participants completed 4 runs (44 go, 20 stop, and 22 fixation trials randomly presented). Active task-related scanning time was approximately 13 minutes.

Scanning acquisition

Scans were conducted in a General Electric Signa 3T magnet. Participants viewed stimuli through Avotec Silent Vision Glasses (Stuart, FL) positioned in the head coil above the subject's eyes. A high-resolution T1 weighted anatomical image following standardized magnetization prepared gradient echo sequence was collected (180 1 mm sagittal slices; FOV = 256; NEX = 1; TR = 11.4 ms; TE = 4.4 ms; matrix = 256 × 256; TI = 300 ms; bandwidth = 130 Hz/pixel, 33 kHz/256 pixels). Gradient echo planar images (23 contiguous 5 mm axial slices/brain volume; parallel to anterior commissure posterior line; single shot gradient echo T2* weighting [matrix 64×64; TR = 2000 ms; TE = 40ms; FOV = 240mm; voxels were 3.75 × 3.75 × 5mm]) were collected following manual shim and sagittal localization procedures.

Data Analyses

Participant Demographics—Univariate analyses of variance (ANOVA) were used to compare BD, SMD, ADHD and HC youths on age and IQ. Univariate ANOVAs were also used to compare BD and SMD youths on the number of current medications, number of comorbid diagnoses, and CDRS variables. Differences in sex distribution were explored using a Chi square analysis.

Behavioral data—Correct go trials were those in which the participant pressed the appropriate response button during the presentation of the target stimulus (i.e., “1” for “X” or “2” for “O”). Correct stop trials were those in which the participant withheld a motor response. For each group, we computed means for the percentage of accurate go and stop trials; response time (RT) on go trials (GoRT); and, on stop trials, the interstimulus interval between the target and the stop signal (i.e., inhibit delay). The stop signal reaction time (SSRT) represents the speed at which a participant can inhibit a motor response and is thus the primary behavioral measure of inhibition ability. When participants correctly inhibited responses on 50% of the trials, the SSRT was calculated by subtracting the mean inhibit delay from the mean GoRT value (Logan et al., 1997). If a participant's stop trial accuracy rate did not equal 50%, an interpolation algorithm was used to calculate the SSRT. This algorithm involved identifying the GoRT value that corresponded to the participant's stop trial accuracy. For example, the SSRT value of an individual with a stop accuracy rate of 60% was calculated by identifying the GoRT value at the 60th percentile, and subtracting the mean inhibit delay from that value. Group differences in the mean percent accuracy (on stop

and go trials), GoRT, inhibit delay, and SSRT were tested separately using univariate analysis of covariance (ANCOVA) with *Group* (BD, SMD, HC) as the between-group factor. Sex was included as a covariate.

Imaging data—SPM8 (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK; <http://www.fil.ion.ucl.ac.uk/spm>) and Matlab 7 (The MathWorks, Natick, MA) were used to analyze imaging data. Preprocessing included slice timing correction, motion correction, spatial normalization to Montreal Neurological Institute (MNI) space, and smoothing (kernel FWHM = 8). We estimated three separate events using general linear models: stop incorrect, go, and stop correct. The small number of incorrect go trials rendered it impossible to estimate this trial type reliably, so they were excluded. Individual contrast images were created using pair-wise comparisons of event-related response amplitudes, which were then entered into second-level random-effects group analyses. A high pass filter (0.0078 Hz) was used.

The primary analysis consisted of three contrasts: stop correct-go; stop correct-stop incorrect; and stop incorrect-go. In the stop correct-go contrast, trials are matched for successful task completion, but differ on task demands and motor response and may identify regions associated with successful inhibition. In the stop correct-stop incorrect contrast, trials are matched for task demands but differ on motor-response, and therefore identify the regions associated with successful inhibition. In the stop incorrect-go contrast, trials are matched for motor-response but not task demands and may identify regions associated with failed motor inhibition, independent of the actual motor response. We examined several regions of interest (ROIs) highlighted in neuroimaging studies of motor inhibition: the bilateral putamen, caudate, nucleus accumbens, ACC, and VLPFC. These ROIs represent anatomically based regions that were hand drawn on the coronal plane of the single subject's canonical structural MRI image supplied by SPM99. MedEx software (Medical Numerics, Sterling, Virginia) and standard anatomical criteria (Szeszko et al., 1999) were used to define the ROI's, which were then applied to the subjects' normalized brains. At the group level, binary masks, consisting of voxels that demonstrated a measurable BOLD response in all participants, were created for each ROI (for details see Leibenluft et al., 2007).

We examined group (BD, SMD, and HC) differences for each of these three contrasts using a factorial ANOVA with sex included as a covariate in SPM8 followed by small volume corrections (SVC) for each ROI. For each contrast, we (1) identified clusters whose peak surpassed a corrected threshold for significance ($p < .05$) using the SVC procedure in SPM8; (2) averaged the estimated contrast values across these clusters for each participant; (3) conducted univariate ANCOVAs in SPSS with sex as a covariate to clarify group activation differences in the identified clusters.

We then conducted analyses to determine whether the differences that we observed between BD and HC youths could be due to the presence of comorbid ADHD in some BD youths. To address this question, we: (1) compared the entire sample of BD youths to our second control group, youths with ADHD but no mood disorder; and (2) compared BD youths without comorbid ADHD to youths with ADHD but no mood disorder. These analyses were conducted only in those regions where, in the primary analysis, there were significant activation differences between BD, SMD, and HC youths. We conducted separate, secondary analyses with the independent ADHD group, rather than including this group in our primary three-group comparison, to maximize statistical power in our primary analysis.

Finally, we conducted separate post-hoc analyses to examine two potential confounding variables in the BD group: mood state (euthymic/non-euthymic) and medication status. The details of these analyses and the results are included in the supplementary material.

Results

Participants

Twenty-eight (87.5%) of the participants in the BD group met criteria for BD-I and the remainder for BD-II. Nineteen (59.4%) were euthymic ($YMRS \leq 12$ and $CDRS \leq 40$), nine (28.1%) were hypomanic ($YMRS = 12-24$ and $CDRS \leq 40$), one (3.1%) was manic ($YMRS > 24$ and $CDRS \leq 40$), two (6.3%) were in a mixed state ($YMRS > 12$ and $CDRS > 40$), and one (3.1%) was depressed ($YMRS \leq 12$ and $CDRS > 40$). Seventeen (53.1%) BD and 18 (81.8%) SMD youths were medicated (information missing for 1 BD and 4 SMD youths). Eight (47.1%) ADHD youths were medicated regularly with short-acting stimulants but medication was withheld for 48 hours before scanning (See Table 1). Univariate ANOVAs and a Chi Square analysis indicated that groups did not differ on age, IQ, or sex (Table 1).

Behavioral Data

No group differences were observed for any behavioral variable (see Table 2).

Imaging Data

Group differences were examined on all three contrasts (stop correct vs. go; stop correct vs. stop incorrect; and stop incorrect vs. go), but only one of the three contrasts, the stop incorrect versus go comparison, generated between-group differences surpassing our statistical threshold (Table 3). Specifically, differences were observed in the right ACC and right nucleus accumbens, with trends in the left VPFC and left ACC. In the right ACC, ($F(2,75) = 14.44, p < .002$) and right nucleus accumbens, ($F(2,75) = 6.07, p < .05$), Bonferroni corrected pairwise comparisons indicated that BD participants exhibited less activation than SMD and HC youths ($ps < .01$) who did not differ from each other.

Secondary Analyses Comparing BD to ADHD

To investigate whether the significant differences between BD and HC youths observed in the primary analyses were attributable to symptoms of ADHD, we first compared activation between youths with BD and an independent sample of youths with ADHD in the regions identified in the primary analyses. BD youths exhibited a trend towards less activation than the ADHD comparison group during failed inhibition in the right ACC ($F(1,46) = 3.45, p < .07$) but no difference in the right nucleus accumbens ($p > .70$). Second, we compared activation between BD youths without ADHD ($n=14$) to the ADHD youths in the same regions as above. BD youths without ADHD did not differ from the ADHD youths in either region ($F_s < 2.0, ps > .15$).

Discussion

Results from this study add to longitudinal and family history data, as well as to one previous fMRI study, suggesting that SMD is not a developmental presentation of BD (Brotman et al., 2007; Brotman et al., 2010; Stringaris et al., 2010; Stringaris et al., 2009). Specifically, on a task assessing inhibitory processes relevant to the symptoms of both BD and SMD, BD youths differed from both SMD and HC youths in having reduced activation in the right ACC and right nucleus accumbens during failed inhibition. SMD youths did not differ from HC youths in any region. No group differences were observed when contrasting successful and unsuccessful inhibition or successful inhibition versus correct “go” responses. Additional analyses (see supplemental material) suggest that mood state and medication do not account for the primary findings of reduced activation in BD youths relative to SMD and HC participants.

A unique strength of our study was the comparison of clinical groups sharing overlapping clinical features. Both BD and SMD participants suffer from severe mood disorders, but in BD symptoms of abnormal mood and arousal are episodic (i.e., present during episodes of mania or depression), whereas in SMD these symptoms are chronic and persistent. Given that chronic irritability has been suggested to be a developmental presentation of BD (Biederman et al., 1998), the observed neural activation differences between BD and SMD while performing a psychological operation (motor inhibition) that is highly relevant to the symptoms of both illnesses, supports the argument that these conditions represent unique clinical disorders rather than variations in the developmental presentation of BD. Considering our data in concert with that from an fMRI study using a face processing task (Brotman et al., 2010), we have demonstrated that BD and SMD youths differ in recruitment of the right ACC, right nucleus accumbens, and left amygdala – regions typically associated with behavioral, cognitive, and emotion regulation. Interestingly, the present study did not identify any areas of common dysfunction in the BD and SMD groups. While this is surprising given the overlap in clinical symptoms between the two groups, it may be related to the limited statistical power associated with the three group comparison. Future research comparing and contrasting these populations will provide valuable information about how the pathophysiology of these two clinical presentations differs; such information would be valuable in ultimately guiding diagnosis and treatment.

Increasing evidence indicates that SMD is not a developmental phenotype of BD and yet little is known about the pathophysiology of children with this clinical presentation, even though their degree of clinical impairment is comparable to that of youths with BD (for review Leibenluft, 2011). In the present study, youths with SMD did not differ from healthy comparison children on either behavioral or neural activation measures. This was surprising given that a) most of our youths with SMD meet criteria for ADHD (> 70%); b) youths with ADHD demonstrate impaired behavioral and neural findings on motor inhibition tasks (Rubia et al., 1998; Schachar et al., 2000) and c) clinical symptoms of disinhibition are important elements of the SMD syndrome (Leibenluft, Blair, Charney, and Pine, 2003). Null findings are always difficult to interpret, especially in the context of neuroimaging studies with multiple group comparisons and limited statistical power. However, there is evidence that the pathophysiology of ADHD occurring in the setting of a mood disorder (e.g., SMD or BD with comorbid ADHD) is different from the pathophysiology of uncomplicated ADHD (Brotman et al., 2010; Dickstein et al., 2005), which may indicate a unique interaction between mood and attention problems. For example, youths with SMD may engage limbic, rather than attention related circuitry, to perform this motor inhibition task. Indeed, a recent study using a working memory task with emotional faces found that BD youths recruited limbic circuitry while youths with ADHD employed more prefrontal circuitry (Passarotti et al., 2010b). Future research could examine whether SMD youths also engage limbic, rather than attentional, circuitry.

The goals of the current study were to identify differences in neural circuitry function among BD, SMD, and HC and, secondarily, to address questions raised by our previous work concerning the impact of comorbid ADHD on neural activation in BD youths during motor inhibition. However, future work should compare directly SMD, ADHD without mood symptoms, and HC during motor inhibition and other relevant behavioral tasks.

The present findings in BD are consistent with our previous results in a partially overlapping sample (Leibenluft et al., 2007), and with findings from an independent sample of unmedicated youths in a manic state (Passarotti et al., 2010c). These two previous studies both found abnormalities in anterior cingulate, ventral prefrontal, and striatal function among BD youths during motor inhibition tasks. In pediatric BD, a number of studies have shown abnormalities in ACC volume as well as in ACC function on a variety of tasks (Bora,

Fornito, Yucel, and Pantelis, 2010; Chang et al., 2004; Passarotti, Sweeney, and Pavuluri, 2010a; Passarotti, Sweeney, and Pavuluri, 2010b; Singh, Spielman et al., 2010), suggesting dysfunction in this population in a region critical to emotional and cognitive integration (Yucel et al., 2003) that has also been associated with impulsivity (Matsuo et al., 2009). Striatal abnormalities, evidenced here by hypoactivation during failed inhibition among BD youths relative to the healthy children in the right nucleus accumbens, but across the striatum in our prior study with an overlapping sample (Leibenluft et al., 2007), may reflect deficits in recruiting this area to appropriately implement correct motor responses during changing contingencies (Hikosaka and Isoda, 2010). Therefore, the dysfunctional recruitment of these regions among the BD youths may contribute to the motor, cognitive, and emotional difficulties frequently observed in this population. Recent work indicates that abnormal recruitment of emotional circuitry during cognitive tasks may be an important biomarker for BD (Passarotti, Sweeney, and Pavuluri, 2010b) suggesting that future studies of brain functioning in BD youths would benefit from paradigms examining the impact of emotional stimuli on non-emotional cognitive tasks.

There are several possible explanations for our failure to replicate all of the deficits in BD youths that we reported in our prior study which included an overlapping sample (Leibenluft et al., 2007). First, since the present study included three groups, it may have less statistical power than the prior two-group study. The present study also included sex as a covariate, which may have reduced our power further. Third, the two studies used different analytic software (SPM99 versus SPM8) and methods (comparing peak voxel activation versus mean activation across the cluster).

An unanswered question from our prior study (Leibenluft et al., 2007) is the possible contribution of ADHD to the hypoactivation observed in BD youths during failed inhibition. Therefore we conducted a secondary analysis comparing the BD youths (the entire sample as well as a restricted subset of BD youths without comorbid ADHD) to an independent sample of youths with ADHD. Results indicate that the answer is still unclear. Youths with BD and those with ADHD differed in activation in the ACC at a trend level, but we were unable to demonstrate differences between the BD and the ADHD groups in the right nucleus accumbens. In addition, no differences from ADHD youths emerged when the BD group was restricted to those without comorbid ADHD. Therefore, we cannot rule out the possibility that comorbid ADHD in the BD group is responsible for our findings although, if ADHD symptoms were driving the observed neural activation patterns, we would have expected similar activation in the SMD youths who had high rates of comorbid ADHD. An important caveat to this discussion is the fact that the ADHD participants were medication-free at the time of scanning (stimulant medications were withheld for 48 hours before scanning) while, for ethical reasons, the BD youths remained medicated. While future research is necessary to examine the exact role of psychotropic medications on neural activation in pediatric populations, data suggest that medication status might not explain our findings. Specifically, secondary analyses (see supplemental material) documented impairments, at a significant or trend level, among unmedicated BD youths relative to both SMD and HC youths.

One possible limitation of our study is that the major index of inhibitory ability (SSRT) did not differ between groups. On the one hand, this indicates that the algorithm maintaining accuracy on stop trials worked correctly. On the other hand, a lack of behavioral differences on go trials as well as on the primary index of inhibition ability (SSRT), suggest no differences in ability to inhibit responses. Therefore the observed neural differences in BD youths were not associated with deficient motor inhibition, and may instead reflect neural inefficiency. However, the lack of behavioral differences between groups also confers an advantage, in that group activation differences were not secondary to performance

discrepancies. Other imaging studies using similar pediatric populations and tasks have observed group differences in neural activity in the absence of behavioral deficits (Finger et al., 2008; Pliszka et al., 2006; Singh, Chang et al., 2010), suggesting that the scanning environment may minimize group differences on behavioral measures.

A final methodological concern is the age range of our participants (8–18 years). Significant structural changes, including in regions supporting motor inhibition processes, occur during this time period (Giedd, et al., 1999; Gogtay et al., 2004). Our participant groups did not differ on mean age, therefore, we do not believe our findings represent an effect of participant age. However, it is possible that the wide age range of our participants reduced our ability to detect differences between participant groups. Future research should consider examining whether at what developmental stage group differences emerge or disappear when considering a more limited age range of participants.

In conclusion, this study comparing youths with BD, SMD, and healthy children provides further support for the uniqueness of the pathophysiology of BD versus SMD, despite significant overlapping symptoms relevant to motor inhibition. Our findings also suggest that the motor inhibition deficits observed previously in BD youths on out-of-scanner tasks may arise from disorder-specific neural activation processes. However, the neural activation patterns that underlie inhibition deficits among chronically irritable youths with hyperarousal symptoms remain unknown.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Tested motor inhibition in youths with BD or SMD
- BD exhibited reduced activation in several regions versus SMD and healthy children
- Neural activation differed between two phenotypically related illnesses
- SMD youths did not differ from healthy children in any comparison

Figure 1.

Activation on stop incorrect versus go trials of patients with bipolar disorder, severe mood dysregulation, and healthy volunteers in the right anterior cingulate cortex (Panel A: MNI coordinates $x = 10, y = 42, z = -2$) and right nucleus accumbens (Panel B: MNI coordinates $x = 8, y = 16, z = 0$). BD = bipolar disorder; SMD = severe mood dysregulation; HC = healthy children).

Table 1

Demographic and clinical characteristics of youths with bipolar disorder, severe mood dysregulation, attention deficit hyperactivity disorder or no psychiatric illness

Characteristic	BD (N = 32)		SMD (N = 26)		ADHD (N = 17)		Healthy Children (N = 21)	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	F (df) ^{††}	p
Age (years)	14.5 (2.5)	13.4 (1.9)	13.5 (2.6)	13.8 (2.0)	13.7 (14.2)	1.4 (3, 92)	> .25	
WASI two-scale IQ	108.5(14.7)	109.1 (8.9)	115.2 (13.9)			1.4 (3, 92)	> .20	
YMRS	10.8 (7.5)	---	---	---	---	---	---	
CDRS [†]	26.1 (9.2)	29.0 (7.2)	---	---	---	1.7 (1, 53)	> .20	
Number of Medications [†]	1.7 (1.7)	2.0 (1.3)	---	---	---	6.5 (1.67)	≤ .01	
Number of Comorbid Diagnoses	1.9 (1.5)	2.6 (1.1)	0.5 (0.8)	---	---	4.1 (1, 56)	≤ .05	
	N (%)	N (%)	N (%)	N (%)	N (%)	χ ² (df)	p	
Male	15 (46.9)	18 (69.2)	12 (70.6)	13 (61.9)	4.05 (3)	> .25		
BP I	28 (87.5)	---	---	---	---	---		
BP II	4 (12.5)	---	---	---	---	---		
Comorbid Diagnoses								
ADHD	18 (56.3)	22 (84.6)	---	---	---	---		
Unipolar Depression	---	6 (23.1)	---	---	---	---		
ODD or CD	11 (34.4)	17 (65.4)	1 (5.9)	---	---	---		
Anxiety	13 (40.6)	13 (50.0)	2 (11.8)	---	---	---		
Medication [†]								
Unmedicated	14 (45.2)	4 (18.2)	9 (52.9)	21 (100)	---	---		
Atypical Antipsychotic	12 (38.7)	6 (27.3)	---	---	---	---		
Lithium	6 (19.4)	3 (13.6)	---	---	---	---		
Antiepileptic	13 (41.9)	12 (54.6)	---	---	---	---		
Antidepressant	8 (25.8)	8 (36.4)	---	---	---	---		
Stimulants	6 (19.4)	10 (45.5)	8 (47.1)	---	---	---		

Note: BD = Bipolar Disorder; SMD = Severe Mood Dysregulation; ADHD = Attention Deficit Hyperactivity Disorder. WASI = Weschler Abbreviated Scale of Intelligence (two-scale IQ); CDRS = Children's Depression Rating Scale; ODD = Oppositional Defiant Disorder; CD = Conduct Disorder. ADHD participants withheld stimulants in the 48 hrs prior to scanning.

^{††} Statistics for demographic variables reflect the comparison between all four participant groups. For number of medications, they reflect the comparison between BD, SMD, and ADHD youths. For CDRS and number of comorbid diagnoses, they reflect a comparison between BD and SMD youths.

[‡] Data were not available for all participants for these variables. The following subsample of data was included for BD participants: medication status (n=31). For SMD participants: CDRS (n=23) and medication status (n=22). When data are missing, percentages are based on the number of participants with data for this variable.

Behavioral performance of youths with bipolar disorder, severe mood dysregulation, attention deficit hyperactivity disorder or no psychiatric illness

Table 2

Characteristic	BD (N = 32)		SMD (N = 26)		ADHD (N = 17)		Healthy Children (N = 21)		3 group comparison		4 group comparison	
	Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)		F (2,75)		F (3,91)	
Percent Accuracy Go Trials	83.16 (12.15)		82.34 (9.77)		80.29 (12.36)		83.92 (11.40)		0.12		0.38	
Percent Accuracy Stop Trials	48.59 (8.41)		47.91 (12.20)		50.22 (10.00)		53.36 (10.80)		1.85		1.30	
Mean Go Response Time	658.13 (74.97)		674.44 (96.09)		686.32 (110.08)		696.81 (109.35)		1.32		1.00	
Stop Signal Response Time	196.87 (49.11)		206.34 (51.31)		210.14 (36.05)		196.52 (40.93)		0.40		0.59	
Inhibit Delay	441.97 (102.16)		454.39 (134.33)		474.24 (122.31)		503.70 (123.50)		1.88		1.36	

Note: Values presented represent raw data. 3 group comparison reflects statistics from the primary analyses comparing BD, SMD and healthy children only with sex included as a covariate. Four group comparison reflects statistics from the secondary analysis comparing all four participant groups with sex included as a covariate. No group differences emerged for any variable in either comparison. BD = Bipolar Disorder; SMD = Severe Mood Dysregulation; ADHD = Attention Deficit Hyperactivity Disorder.

Table 3

Between-group differences in activation on the stop incorrect versus go contrast

Area of Activation	Side	cluster size [†]	MNI coordinates			F (2,75)	p <	Between-group differences
			x	y	z			
Anterior Cingulate Cortex	R	<u>245</u>	10	42	-2	<u>14.44</u>	<u>.002</u>	BD<SMD ^{**} ; BD<HC [*]
	L	<u>254</u>	4	44	0	<u>8.72</u>	<u>.06</u>	
Nucleus accumbens	R	<u>80</u>	8	16	0	<u>6.07</u>	<u>.05</u>	BD<SMD [*] ; BD<HC [*]
Ventrolateral Prefrontal Cortex	L	<u>451</u>	-24	32	-6	<u>7.82</u>	<u>.08</u>	

*
p < .01,
**
p < .001

BD = bipolar disorder, SMD = severe mood dysregulation, ADHD = attention deficit hyperactivity disorder, HC = healthy children. x, y, and z coordinates and F and p statistics refer to the voxel with maximum signal intensity

[†] determined using a significance threshold of p < .05, corrected for the number of voxels in each region and with sex entered as a covariate