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Neural correlates of reversal learning in severe mood dysregulation and pediatric bipolar disorder

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Abstract

Objective—Outcome and family history data differentiate children with severe mood dysregulation (SMD), a syndrome characterized by chronic irritability, from children with "classic," episodic bipolar disorder (BD). Nevertheless, the presence of cognitive inflexibility in both SMD and BD highlights the need to delineate neurophysiological similarities and differences between the two patient groups. We used fMRI to examine neural correlates of cognitive flexibility deficits in SMD and BD vs. healthy volunteers (HV).

Method—During fMRI, subjects completed a response reversal task that assesses cognitive flexibility (N=22 SMD, 26 BD, 34 HV). We examined task effects in four regions of interest: caudate, cingulate gyrus, inferior frontal gyrus (IFG), and ventromedial prefrontal cortex.

Results—Diagnosis-by-accuracy interactions emerged in caudate and IFG. In these regions, we calculated the difference in activation between incorrect vs. correct trials. In caudate, this value

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was smaller in both SMD and BD than in HV. In IFG, however, this value was smaller in SMD than in both BD and HV. Post-hoc analyses indicate that comorbid ADHD in patients may influence the caudate findings. Exploratory whole-brain analysis confirmed the caudate and IFG findings. In addition, other regions differentiating SMD and BD were identified (e.g., superior parietal lobule/precuneus and inferior temporal gyrus).

Conclusions—In response to errors, similar perturbations occur in the caudate for SMD and BD youth relative to HV youth. IFG deficits, in contrast, manifest in SMD, but not BD, youth.

Keywords

functional MRI; response reversal; Bipolar disorder; severe mood dysregulation; pediatric

Introduction

Debate centers on whether severe chronic irritability is a developmental presentation of bipolar disorder (BD). Leibenluft et al. operationalized severe mood dysregulation (SMD) to capture children with chronic, non-episodic irritability[1]. Outcome and family history data[2–4] differentiate youth with SMD from those with 'classic,' episodic BD. Nevertheless, the two conditions share some neuropsychological deficits. For example, on *behavioral* measures of face-emotion labeling and emotion regulation, SMD and BD patients both differ from healthy volunteers (HV). Importantly, however, these shared behavioral deficits reflect disorder-specific *neural* profiles[5,6]. The demonstration of disorder-specific neural dysfunction, in the context of similar-appearing behavioral deficits, highlights the importance of utilizing neuroimaging to probe differences between SMD and BD. Examining neural activity in SMD and BD could isolate syndrome-specific dysfunction, ultimately leading to better diagnosis and treatment.

Clinically significant irritability is common in both patient groups, although in SMD it is persistent, whereas in BD it is episodic[1]. Irritability manifests as a low threshold for anger in response to negative stimuli, and it can be precipitated by frustration[7]. Frustration occurs when an action fails to elicit an expected outcome[8]. Individuals with deficits in adapting to changing contingencies are at increased risk for frustration. Such deficits can be identified using cognitive flexibility paradigms, including reversal learning tasks. In such tasks, two stimuli, "A-B", are presented, and participants learn by trial-and-error that "A," but not "B," is rewarded (acquisition phase). Then, without warning, the stimulus/reinforcement relationship reverses, so that participants must learn that now "B," but not "A," is rewarded (reversal phase).

Behavioral deficits in reversal learning are prominent in BD youth and may occur in SMD youth[9–11]. Prior work also finds frontal and parietal hyperactivation in BD vs. HV during reversal learning[12]. However, since no imaging studies examine reversal learning in SMD, research is needed comparing the neural correlates of reversal learning in SMD and BD.

Imaging studies focused on clearly-defined neuroanatomical circuits often use a region-of-interest (ROI) approach, especially when examining psychopathology[13–16]. This approach maximizes a study's ability to identify between-group differences, and it directly extends prior work linking behaviors to specific circuits across a range of species. The anatomical circuit mediating reversal learning has been precisely mapped in humans, non-human primates, and rodents. The circuit encompasses ventromedial prefrontal cortex (vmPFC)[8,17–23], cingulate gyrus[22,24–27], inferior frontal gyrus (IFG)[28–37], and caudate nucleus[28,38–40]. In this circuit, the vmPFC represents reinforcement information[28,41] and encodes the value of actions[42]. The cingulate gyrus, IFG, and caudate act together to respond to errors[28]. Specifically, the cingulate gyrus registers the need to resolve response

conflict signaled by errors[43], whereas IFG facilitates such conflict resolution through motor response selection[28], response inhibition[44], and attention control[45]. The caudate nucleus supports motor learning, thus allowing adaptation to errors[46]. Work implicating these four regions in reversal learning justifies their selection in the current study as *a priori* ROIs. Nevertheless, for completeness, we also report results from an exploratory whole-brain analysis.

We tested the hypothesis that neural activity during reversal learning differentiates SMD, BD, and HV youths. Given evidence of reversal-learning deficits in SMD and BD[9,11], we examined the diagnosis-by-phase-by-accuracy interaction to test for group differences in response to reversal errors. Additionally, we modeled the diagnosis-by-phase interaction to investigate group differences across the reversal phase, including both correct and incorrect trials. Finally, given reports of abnormal error signals[47] and contingency-learning deficits in pediatric BD[10,48], we examined the diagnosis-by-accuracy interaction to elucidate group differences in response to errors regardless of phase.

Method

Data from 82 subjects were included: 22 SMD, 26 BD, and 34 HV (15 BD and 15 HV published previously[12]). Subjects provided informed consent/assent. Full recruitment and diagnostic methods are described previously[1,5].

Childhood Depression Rating Scale (CDRS)[49] and Childhood Global Assessment Scale (CGAS)[50] were administered to patients. Young Mania Rating Scale (YMRS)[51] was administered to BD, but not SMD as hypo/mania is exclusionary. The Wechsler Abbreviated Scale of Intelligence (WASI)[52] and Tanner self-report measure[53,54] were administered to all subjects.

In-Scanner Task

This probabilistic response reversal task elicits fronto-striatal activity[12,56] using six 6.5-minute, 135-trial runs. Each 2500ms trial (1600ms stimulus presentation, 900ms feedback) presented objects in pairs, and subjects were instructed to choose the “correct” object. Subjects were told that one object would tend to be correct but that the contingencies might reverse, as detailed previously[12,56] (and see Supplement 1, available online).

Behavioral Analysis

We used a three (diagnosis: SMD, BD, HV) by two (phase: acquisition, reversal) repeated-measures ANOVA for accuracy. ANOVA also compared groups on number of non-response trials.

MR Imaging

Images were acquired on a 1.5-T GE scanner using gradient echo-planar imaging (TR=2500ms, TE=30ms, 24×24 FOV, flip angle=90°) and 29 4-mm slices, across 147 time-points. A high-resolution scan was acquired (1.5-mm slices, 3-dimensional FSPGR, 20° flip angle, 256×192 matrix, 24cm FOV).

fMRI Analysis

Analysis used Analysis of Functional Neuroimages (AFNI)[57]. Preprocessing involved (1) despiking, (2) alignment, (3) anatomical coregistration, (4) spatially smoothing data (6mm rms deviation Gaussian blur), (5) masking, and (6) intensity-scaling, producing data in Talairach space. TRs with extreme motion were censored, and motion parameters were included as covariates. TRs n and n-1 were censored if the normed motion vector between

time-points was greater than 2mm. Subjects with more than 10% of TRs censored were excluded. SMD had a higher percentage of censored TRs than BD (p=0.005) or HV (p=0.003).

As detailed elsewhere[12,56], trials were categorized by phase (acquisition or reversal), accuracy (correct or incorrect, based on subject response), and reinforcement (reward or punishment), yielding nine events: (1) acquisition correct win ("acquisition correct"); (2) acquisition correct lose; (3) acquisition incorrect win; (4) acquisition incorrect lose ("acquisition incorrect"); (5) reversal correct win ("reversal correct"); (6) reversal correct lose; (7) reversal incorrect win; (8) reversal incorrect lose ("reversal incorrect"); (9) no response. For parsimony, correct trials with lose feedback and incorrect trials with win feedback are excluded; therefore, correct-win trials are referred to as "correct," and incorrect-lose trials as "incorrect." Individual modeling was performed using a GAM model for each event type regressor plus motion parameters. Beta coefficients and associated t-statistics were calculated for each voxel and each regressor. We were interested in four regressors: acquisition correct, acquisition incorrect, reversal correct, and reversal incorrect.

AFNI's GroupAna was used to run a 3×2×2 ANOVA: diagnosis (SMD, BD, HV) X phase (acquisition, reversal) X accuracy (correct, incorrect). The following interactions were examined: 1) diagnosis-by-phase-by-accuracy; 2) diagnosis-by-phase; 3) diagnosis-by-accuracy. Given extensive prior literature, group-level analyses adopted two approaches[58]. First, we examined four ROIs: caudate, cingulate gyrus, IFG, and vmPFC, delimited with bilateral masks created using the Talairach dataset in the AFNI Draw Dataset tool, re-sampled to 3×3×3mm, and thresholded at p<0.005. Monte Carlo simulation determined cluster-extent thresholds at p<0.05 corrected in each ROI: caudate: 7; cingulate: 23; IFG: 23; vmPFC: 20. Because we were interested in event-specific between-group differences, we decomposed the interactions. Mean BOLD signal in each significant cluster was extracted for each subject for all event types of interest. Difference scores for activity to specific events were compared across groups.

As in previous studies, an exploratory whole-brain analysis using a lower statistical threshold than the ROI analyses[15] was also conducted. Criteria for statistical significance included individual voxel height intensity of p<0.005 and cluster extent threshold of k>20 voxels[59].

Finally, because of a main effect of diagnosis on the number of total correct trials, we re-ran the primary ROI ANOVAs as ANCOVAs, with total correct trials as a covariate. Using Spearman's correlations, we examined correlations between accuracy and activation.

Post-Hoc Analyses: Comorbidity, Mood, Pubertal Effects, and Age

Given high rates of comorbid Attention Deficit Hyperactivity Disorder (ADHD) and anxiety, and the difference in the rate of Oppositional Defiant Disorder (ODD) between patient groups, we examined possible effects of comorbidity using post-hoc repeated-measures ANOVAs. Again, we decomposed significant interactions by calculating difference scores and comparing them with independent t-tests. We also examined possible effects of puberty and mood on the primary results by conducting Spearman correlations using average Tanner[60], mood (CDRS, YMRS) and impairment (CGAS) scales correlated with signal extractions from the significant clusters. As we did not have a priori hypotheses for these analyses, these correlations were Bonferroni-corrected. Because of the subjects' large age range, we ran Spearman correlations between activation and age across all subjects and in each diagnostic group separately, comparing the latter with Fisher r-to-z transformations.

Results

Participants

Groups did not differ in age, IQ, or gender (Table 1). Groups tended to differ on Tanner scores (ANOVA p=0.096), with lower scores in SMD vs. HV (p=0.062) and BD (p=0.053). SMD had higher rates of ODD (p=0.008) and tended to be more impaired on CGAS (p=0.09) than BD. All SMD and 16 BD were euthymic (YMRS<12, CDRS<40). SMD had lower CDRS scores than BD (p=0.043).

Behavior

Groups did not differ in non-responses. Repeated measures ANOVA revealed no diagnosis-by-phase interaction. There was a main effect of diagnosis (p=0.005); SMD had fewer total correct trials than HV (p=0.001) or BD (p=0.027).

Imaging

ROI—No clusters exhibited diagnosis-by-phase-by-accuracy or diagnosis-by-phase interactions. Two clusters exhibited diagnosis-by-accuracy interactions (Figures 1, 2): right caudate (459mm^3, p=0.002) and right IFG (621mm^3, p=0.001).

Diagnosis-by-accuracy

In caudate, the interaction reflected smaller difference scores (incorrect – correct) in SMD (p<0.001) and BD (p=0.007) relative to HV (Figure 1b); SMD and BD did not differ. In IFG, the interaction reflected an abnormal response only in SMD. Specifically, SMD had smaller difference scores than both BD (p=0.035) and HV (p<0.001; Figure 2b). HV and BD did not differ (p=0.073). In the ANCOVA co-varying for total number of correct trials, both diagnosis-by-accuracy interactions remained significant (caudate: p=0.007, IFG: p=0.006), suggesting that performance differences did not account for the between-group activation differences.

Across all subjects, total-number correct correlated with difference score in both ROIs (IFG: Spearman's r=0.30, p=0.007; caudate: Spearman's r=0.35, p=0.001). Thus, engagement of IFG and caudate relates to task performance.

Exploratory Whole-Brain Analysis—Significant clusters were evident for diagnosis-by-phase-by-accuracy, diagnosis-by-phase, and diagnosis-by-accuracy interactions (Table 2 and Table S1, available online).

Diagnosis-by-phase-by-accuracy

Diagnosis-by-phase-by-accuracy interactions were evident in three parietal regions, reflecting aberrant responses in SMD during incorrect reversal trials. In these three regions, SMD had greater activation than HV to incorrect reversal trials; SMD also showed hyperactivation vs. BD in two of these regions. There was also a three-way interaction in superior temporal gyrus (STG)/insula, where SMD and BD showed hyperactivation relative to HV during incorrect acquisition trials.

Diagnosis-by-phase

Diagnosis-by-phase interactions were found in five temporal regions and right middle frontal gyrus. Difference scores (acquisition minus reversal) were greater for SMD than HV in every region (e.g., see Figure 3), and in SMD than BD in all regions except left STG/insula.

Diagnosis-by-accuracy

Diagnosis-by-accuracy interactions were found in frontal and cerebellar regions and right caudate. Generally, as in the ROI analyses, while HV response differentiated incorrect vs. correct trials, response in SMD did not differentiate incorrect vs. correct trials (in four of five regions), and the pattern in BD was mixed. Notably, the diagnosis-by-accuracy interactions identified in right caudate and right IFG in the ROI analyses were replicated in the whole-brain analysis (as shown in bold in Table 2). Specifically, in caudate, both SMD and BD difference scores (incorrect minus correct) were smaller than those of HV ($p<0.001$ and $p=0.017$, respectively). However, in IFG, SMD difference scores were lower than those of both BD and HV ($p=0.016$ and $p<0.001$, respectively).

Post-Hoc Analyses—All post-hoc analyses were conducted on the results in caudate and IFG from the primary ROI analysis.

Anxiety

Repeated measures ANOVAs used three groups: HV (n=34), SMD and BD participants with anxiety (+Anx, n=22 [12 BD, 10 SMD]), SMD/BD without anxiety (−Anx, n=26 [14 BD, 12 SMD]). There were group-by-accuracy interactions in both regions (caudate: $p=0.003$; IFG: $p=0.002$). In caudate, +Anx and −Anx had smaller difference scores than HV ($p=0.008$ and $p<0.001$, respectively); +Anx and −Anx did not differ. In IFG, +Anx and −Anx again had smaller difference scores than HV ($p<0.001$ and $p=0.050$, respectively); +Anx and −Anx did not differ. Therefore, group differences in our primary analyses were not driven by comorbid anxiety disorders.

ODD

Repeated measures ANOVAs used three groups: HV (n=34), SMD and BD patients with ODD (+ODD, n=24 [8 BD, 16 SMD]), SMD/BD patients without ODD (−ODD, n=24 [18 BD, 6 SMD]). There were group-by-accuracy interactions in both regions (caudate: $p=0.003$; IFG: $p=0.004$). In caudate, both +ODD and −ODD had smaller difference scores than HV ($p=0.003$ for both comparisons); +ODD and −ODD did not differ. In IFG, +ODD and −ODD had smaller difference scores than HV (p=0.002 and 0.025, respectively); +ODD and −ODD did not differ. These findings suggest that between-group differences in our primary analyses were not driven by comorbid ODD in patients.

ADHD

Repeated measures ANOVAs compared three groups: HV (n=34); SMD and BD participants with ADHD (+ADHD, n=31 [14 BD, 17 SMD]); SMD/BD participants without ADHD (−ADHD, n=17 [12 BD, 5 SMD]) (Figure 4). There were group-by-accuracy interactions in both regions ($p<0.001$). In caudate, +ADHD had smaller difference scores than both HV ($p<0.001$) and −ADHD ($p=0.030$); −ADHD tended to have smaller difference scores than HV ($p=0.084$). In IFG, +ADHD had smaller difference scores than HV ($p<0.001$) but did not differ from −ADHD; −ADHD tended to have a smaller difference scores than HV ($p=0.085$).

We also used independent-sample t-tests (without correction for multiple comparison) to compare the difference scores of SMD and BD subgroups based on ADHD comorbidity: SMD with ADHD (SMD+ADHD, n=17), SMD without ADHD (SMD−ADHD; n=5, given small N, this group was excluded from analyses), BD with ADHD (BD+ADHD, n=14), BD without ADHD (BD−ADHD, n=12). SMD+ADHD and BD+ADHD did not differ in caudate, but there was a trend difference in the IFG ($p=0.076$) (Figure 4). Additionally, SMD+ADHD also tended to have smaller IFG difference scores than BD−ADHD

(p=0.068). BD patients with and without ADHD did not differ from each other in either ROI. These results suggest that comorbid ADHD is not likely to be driving the observed differences between SMD and BD in the IFG.

Mood, Impairment, Puberty, and Age

There were no correlations between mean Tanner, CDRS, YMRS, or CGAS scores and activation to correct or incorrect trials in either ROI.

There were no correlations between age and difference scores in caudate, whether this was analyzed across all subjects or separately by group. However, IFG difference scores correlated with age across all subjects (Spearman's r=0.34; p=0.002), and similar correlations were seen in each group separately (Spearman's r between 0.29–0.40, p's between 0.044–0.096). Fisher r-to-z transformation showed that the group correlation coefficients did not differ (all p's>0.65).

Discussion

This is the first study comparing brain function during reversal learning in SMD, BD, and HV. We examined diagnosis-by-phase-by-accuracy, diagnosis-by-phase, and diagnosis-by-accuracy interactions. In the ROI analyses, only the diagnosis-by-accuracy interaction resulted in significant clusters; subsequent analyses demonstrated that the most salient neural differences between SMD, BD, and HV were in response to errors, regardless of phase. To elucidate these findings, the difference in activation during incorrect vs. correct trials was calculated. In caudate, this value was smaller in SMD and BD than in HV. In IFG, however, this value was smaller in SMD than in both BD and HV. Post-hoc analyses indicated that comorbid ADHD might influence these findings, particularly in caudate. Whole-brain analysis confirmed the IFG and caudate findings.

Behaviorally, SMD made more errors across the entire task than did the other two groups; their deficit was not limited to the reversal phase. Some out-of-scanner work in larger samples demonstrates specific reversal-learning deficits in both SMD and BD[9–11]; thus, our study resembles others that, across a variety of paradigms, find intact in-scanner performance despite in-clinic deficits[56,61]. Taken together, current and prior data suggest that behavioral deficits observed in the scanner in SMD and in out-of-scanner testing in SMD and BD[9,11] reflect deficient engagement of IFG in SMD and of caudate in both SMD and BD following errors. Neither SMD nor BD exhibited the normative increase in caudate activity to incorrect trials, suggesting both have difficulty learning from errors, an important caudate function[46] that could reflect dopamine dysfunction. Dopamine signaling modulates reward-based[38] and feedback-dependent[62] learning; such learning deficits can result in perseveration[63].

Unlike caudate dysfunction, which manifested in both groups, SMD, but not BD, failed to show the expected, normal increase in IFG activity during incorrect trials. Thus, while caudate dysfunction characterized both SMD and BD, frontal dysfunction was unique to SMD. Frontal projections modulate striatal activity, so IFG and caudate are part of a circuit that adjusts behavior following an error[28,64]. IFG also mediates functions necessary for response selection, including attention maintenance and representation of contingencies, context, and goals. Right IFG plays an important role in response inhibition[44], and a recent study indicates that IFG activity is modulated by the response control demands of a motor task[65].

Speculatively, chronic SMD symptomatology may result from persistent fronto-striatal dysfunction, while episodic impairment in BD may reflect intermittent prefrontal

dysfunction. SMD exhibited IFG and caudate dysfunction, as well as fewer correct trials than the other groups. In BD, on the other hand, IFG response and task performance are more similar to HV; perhaps intact IFG function enables BD subjects to compensate for basal ganglia dysfunction. Most patients were euthymic when scanned; while IFG dysfunction is amongst the most consistently reported finding in BD, a recent metaanalysis suggested such IFG dysfunction may be present during mania but not euthymia or depression[66]. Future longitudinal studies of BD patients in different mood states are required to test this possibility.

Our results are consistent with prior work. Using the stop signal task in a partially overlapping sample, we found that, relative to controls, BD had hypoactivation in IFG and striatum during unsuccessful attempts to inhibit motor responses[47] (i.e., in response to error). Thus, using first a motor inhibition task in BD[47] and then a response reversal task in BD and SMD, we identified neural dysfunction that may compromise the ability of both groups to adapt their behavior in response to changing contingencies, causing an increased propensity to experience frustration and irritability[67].

Post-hoc analyses suggest that comorbid ADHD may contribute to our caudate findings: patients with ADHD differed from those without ADHD in response to incorrect vs. correct trials, and patients without ADHD more closely resembled controls. In IFG, patients with ADHD did not differ from those without ADHD in response to incorrect vs. correct trials, rendering it less likely that the between-group differences we observed were secondary to ADHD. Our caudate results here are consistent with our previous stop signal findings, where we could not rule out the role of comorbid ADHD in the aberrant neural responses of BD patients during unsuccessful inhibition[47]. A study using the same response reversal paradigm as here and a different analytic strategy found no neural deficits in ADHD patients[56], but other data suggest abnormal activation in ADHD during related cognitive tasks (e.g., behavioral deficits and aberrant IFG and caudate activity in ADHD during response inhibition[68–70]).

The role of ADHD in our findings is difficult to ascertain because ADHD is present in 77% of the SMD sample; SMD inclusion criteria require three “hyperarousal” symptoms common to ADHD and mania. However, it is unclear whether the pathophysiology of ADHD in the context of SMD or BD is the same as that of ADHD without irritability. Studies report different neural activity[5] and neurological symptoms[71] in SMD or BD (including those with comorbid ADHD) vs. ADHD alone, again suggesting the importance of using behavioral and neuroimaging data, in addition to symptoms, to differentiate syndromes. Importantly, the current study was not designed to ascertain explicitly the impact of ADHD on the pathophysiology of SMD or BD, since to do so one would need to compare patients with “pure” ADHD without comorbid irritability to patients with SMD, BD, and HV[5].

A major strength of this study is the comparison of two clinical populations to each other and a healthy group. Most psychiatric imaging studies compare one clinical population to a healthy group, and thus cannot differentiate disease-unique and disease-common abnormalities in diagnoses with overlapping symptoms. The extent to which SMD and BD children differ from controls but resemble each other indicates overlapping disease substrates. Here, both disorders exhibit striatal dysfunction. On the other hand, differences between clinical groups may indicate disorder-specific abnormalities with important diagnostic and treatment implications; here, we found differences between patient groups in prefrontal cortex function. However, there may be a dimensional component to IFG dysfunction in this task: like SMD, BD may not increase IFG response to incorrect trials as much as HV; the comparison between BD and HV is at a trend level and therefore

equivocal. Nonetheless, direct comparison between SMD and BD indicates a categorical between-group difference in IFG activity.

Exploratory whole-brain analyses confirmed the IFG and caudate ROI findings and identified dysfunction in other regions. Like the ROI results, whole-brain results suggest dysfunction in SMD in regions that mediate detecting and learning from errors and executing an alternative response (e.g. superior/medial frontal gyrus[72,73], right IFG, caudate). Also similar to the ROI analyses, the whole-brain analysis found that dysfunction was more consistent and pervasive in SMD than BD. Comparing BD and HV, our results are similar to Dickstein et al., who used a partially overlapping sample[12]. Specifically, in BD vs. HV, both studies found parietal hyperactivation during incorrect reversal trials and hyperactivation to all incorrect trials in superior frontal gyrus.

The study has limitations. First, though larger than those in most pediatric fMRI studies, the sample sizes used here are small. Second, we did not obtain frustration ratings in the scanner, and therefore cannot correlate activation and affective response. Adding such measures would have limited comparability with other studies and altered the psychological processes engaged, perhaps activating top-down regulatory regions. Studies suggest that caudate and IFG mediate switching responses after negative feedback[28,64], but we cannot rule out the possibility that the between-group differences we observed are associated with psychological processes not measured by the task, such as increased frustration in response to negative feedback or decreased motivation in patients vs. controls. Also, because we lack dimensional symptom measures for comorbid disorders such as ADHD and ODD, we cannot correlate such symptoms with activation. Finally, many patients were medicated; ethical concerns preclude withdrawing ill children from medication for research. However, data suggest that medication may increase noise, rather than bias towards false positive errors[74]. While not all subjects were euthymic, most were, and post-hoc analyses suggest that mood state does not account for our findings (see supplement 1, avaliable online). Although post-hoc analyses suggest that the higher ADHD comorbidity, higher error rates, and slightly younger age of the SMD group are not driving between-group differences, these three factors may have interacted to influence the results.

This study is the first to examine the neural underpinnings of response reversal in children with SMD and BD compared to controls, finding deficits in both groups in response to errors. Hypoactivation during incorrect responses occurs in caudate in both SMD and BD and in IFG in SMD. Such hypoactivation to errors may reflect deficits in response inhibition signaling or new response selection, which may result in increased frustration and irritability. Future work should elucidate the role of comorbid ADHD, specifically in the caudate, in error-processing deficits in SMD and BD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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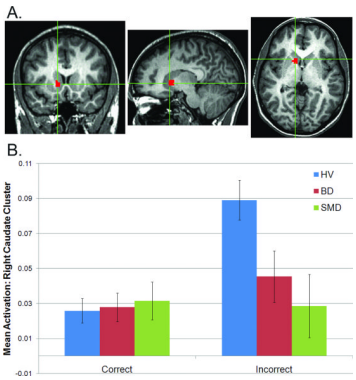

Figure 1.

Diagnosis-by-accuracy interaction in right caudate: (**A**) location (peak: 11, 11, 2; images in radiological convention, left=right); (**B**) mean responses to correct and incorrect trials. Note: BD=Bipolar Disorder; HV=Healthy Volunteers; SMD=Severe Mood Dysregulation.

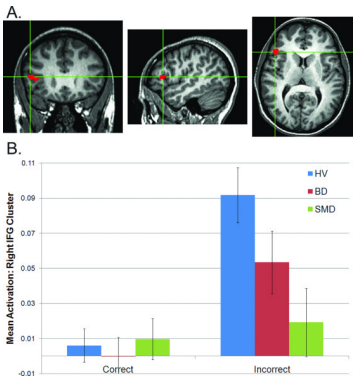

Figure 2.

Diagnosis-by-accuracy interaction in right inferior frontal gyrus (IFG): (**A**) location (peak: 44, 26, 11; images in radiological convention, left=right); (**B**) mean responses to correct and incorrect trials. Note: BD=Bipolar Disorder; HV=Healthy Volunteers; SMD=Severe Mood Dysregulation.

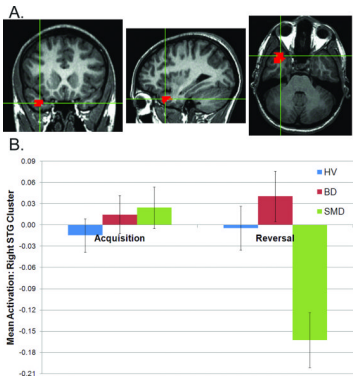

Figure 3.

Diagnosis-by-phase interaction from whole-brain analysis in right superior temporal gyrus: (**A**) location (peak: 32, 23, -31; images in radiological convention, left=right); (**B**) mean responses to acquisition and reversal trials. Note: BD=Bipolar Disorder; HV=Healthy Volunteers; SMD=Severe Mood Dysregulation.

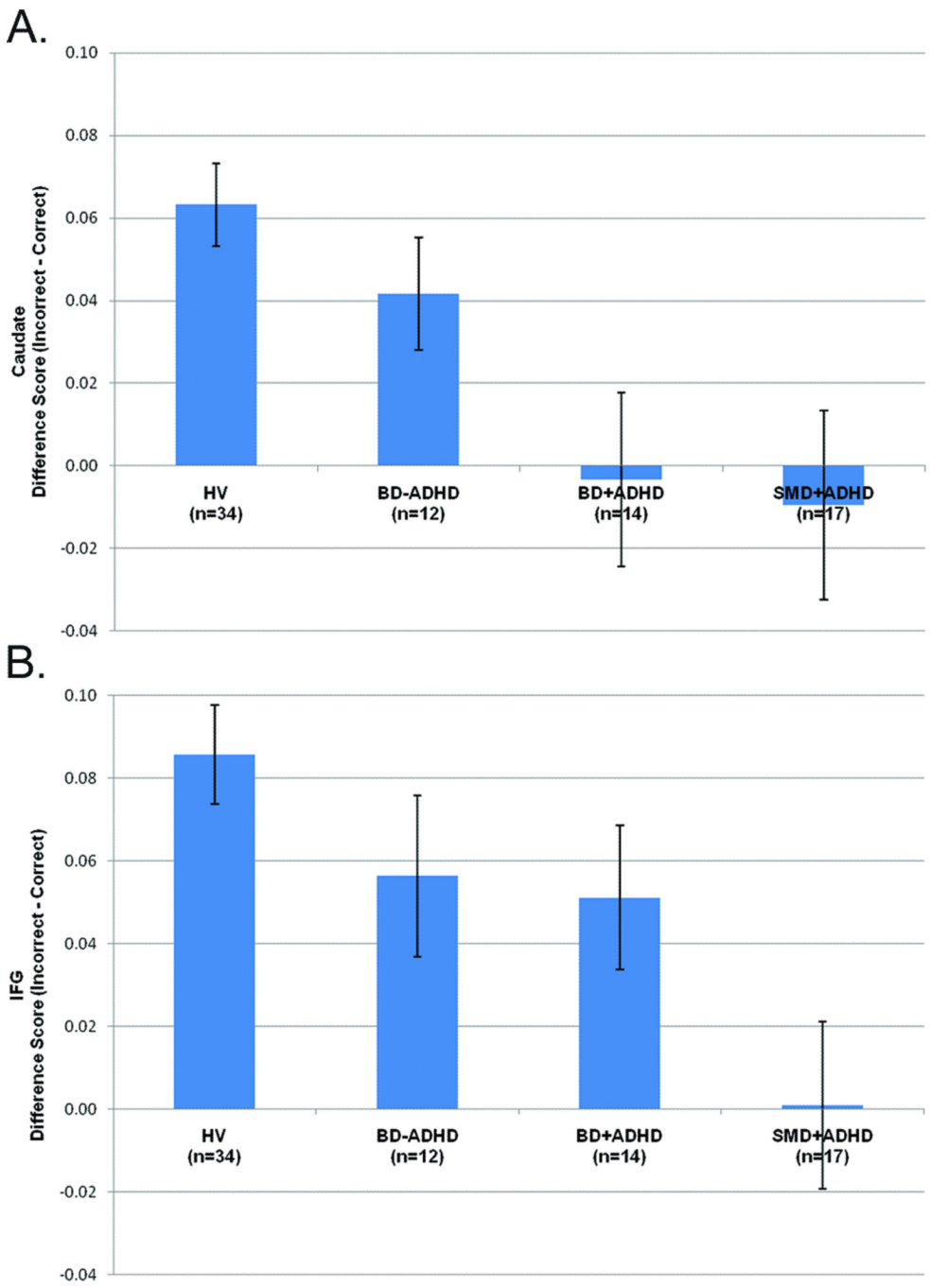

Figure 4.

Difference scores (incorrect minus correct trials) in (**A**) right caudate and (**B**) right inferior frontal gyrus (IFG). Note: BD−ADHD=Bipolar Disorder without comorbid Attention Deficit Hyperactivity Disorder; BD+ADHD=Bipolar Disorder with comorbid Attention Deficit Hyperactivity Disorder; HV=healthy volunteers; SMD+ADHD=Severe Mood Dysregulation with Attention Deficit Hyperactivity Disorder.

Table 1

Study Subject Demographics

	Healthy Volunteers (n=34)	Bipolar Disorder (n=26)	Severe Mood Dysregulation (n=22)
	Mean ± SD	Mean ± SD	Mean ± SD
Gender	17 male (50%)	14 male (53.8%)	17 male (77.3%)
Age	14.17 ± 2.33	14.34 ± 2.59	13.25 ± 2.07
Tanner stage[a,b]	3.72 ± 1.19	3.81 ± 1.47	3.00 ± 1.38
IQ	111 ± 15.10	109 ± 16.33	109 ± 10.61
Young Mania Rating Scale	---	10.12 ± 6.42	---
Childhood Depression Rating Scale[a,c]	---	28.81 ± 11.18	22.05 ± 10.57
Childhood Global Assessment Scale[a,d]	---	53.74 ± 14.01	47.73 ± 8.74
No. Comorbid Diagnoses	---	1.92 ± 1.55	2.36 ± 1.53
	N (%)	N (%)	N (%)
Bipolar Disorder-I	---	23 (88.5)	---
Bipolar Disorder-II	---	3 (11.5)	---
Mood State			
Euthymic[e]	---	16 (61.5)	22 (100)
Depressed	---	4 (15.4)	0 (0)
Hypomanic/Manic	---	8 (30.8)	---
Mixed	---	2 (7.7)	---
Medication			
Unmedicated	---	6 (23.1)	8 (36.4)
Lithium	---	6 (23.1)	3 (13.6)
Antidepressant	---	5 (19.2)	5 (22.7)
Stimulant	---	9 (34.6)	9 (40.9)
Non-Stim ADHD Med	---	2 (7.7)	3 (13.6)
Antipsychotic	---	13 (50)	8 (31.8)
Anti-epileptic	---	12 (46.2)	8 (36.4)
Anxiolytic/Sedative	---	2 (7.7)	1 (4.5)
Other	---	5 (19.2)	6 (27.3)
Comorbid Diagnoses			
Any Anxiety Disorder	---	12 (46.2)	10 (45.5)
Major Depressive Disorder	---	---	3 (13.6)
Obsessive Compulsive Disorder	---	2 (7.7)	2 (9.1)
Attention Deficit Hyperactivity Disorder	---	14 (53.8)	17 (77.3)
Oppositional Defiant Disorder[f]	---	8 (30.8)	16 (72.7)
Post-Traumatic Stress Disorder	---	3 (11.5)	0 (0)
Conduct Disorder	---	2 (7.7)	0 (0)

Note:

[a] Scores unavailable for Tanner: 5 healthy volunteers (HV), 5 bipolar disorder (BD), 1 severe mood dysregulation (SMD); Childhood Depression Rating Scale (CDRS): 2 SMD; Childhood Global Assessment Scale (CGAS): 3 BD.

[b] Analysis of Variance p=0.096

[c] Between-group p=0.043

[d] Between-group p=0.091

[e] Fisher's exact test p=0.001

[f] Fisher's exact test p=0.008

Table 2

Exploratory Whole Brain Results

Cluster Region (Brodmann Area)	No. voxels in cluster (Vol. in mm^3)	Talairach Coords of Cluster Peak		
		x	*y*	*z*
Diagnosis-by-phase-by-accuracy:				
R SPL/Precuneus (7/19)	56 (1512)	29	−73	50
L STG (22) and Insula (13)	30 (810)	−49	−13	−7
L SPL/Precuneus (7)	25 (675)	−25	−67	56
R SPL/Precuneus (7/19)	21 (675)	26	−64	59
Diagnosis-by-phase:				
R STG (38)	62 (1674)	32	23	−31
L STG/insula (22/13)	56 (1512)	−46	−16	−13
R ITG/MTG/fusiform (20/21)	35 (945)	62	−19	−19
L ITG/MTG/fusiform (20/21)	30 (810)	−49	−10	−31
R MFG (6)	29 (783)	35	2	53
R ITG/MTG/fusiform (20/21)	27 (729)	47	−4	−28
Diagnosis-by-accuracy:				
R/L superior/medial frontal gyrus (6)	92 (2484)	2	14	65
R IFG/insula (45/13)	**51 (1377)**	**35**	**20**	**5**
L fusiform/declive (18)	25 (675)	−19	−88	−22
R cerebellum	23 (621)	53	−58	−28
R caudate	**23 (621)**	**8**	**11**	**2**

Note: Clusters indicated in bold are similar to the two clusters identified from the region of interest (ROI) analysis. ; ITG=Inferior Temporal Gyrus; L=left; MFG=Middle Frontal Gyrus; MTG=Middle Temporal Gyrus; R=right; SPL=Superior Parietal Lobule; STG=Superior Temporal Gyrus.