Cognitive Flexibility in Phenotypes of Pediatric Bipolar Disorder

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ABSTRACT

Objective: Clinicians and researchers debate whether children with chronic, nonepisodic irritability should receive the diagnosis of bipolar disorder (BD). To address this debate, we evaluated cognitive flexibility, or the ability to adapt to changing contingencies, in three groups of children: narrow-phenotype BD (NP-BD; full-duration manic episodes of elevated/expansive mood; $N = 50$; 13.1 ± 2.9 years), severe mood dysregulation (SMD; chronic, nonepisodic irritability; $N = 44$; 12.2 ± 2.1 years), and healthy controls ($N = 43$; 13.6 ± 2.4 years). Cognitive flexibility is relevant to symptoms of BD involving dysfunctional reward systems (e.g., excessive goal-directed activity and pleasure-seeking in mania; anhedonia in depression). **Method:** We studied simple and compound reversal stages of the intra-/extradimensional shift task and change task that involves inhibiting a prepotent response and substituting a novel response. **Results:** On the simple reversal, NP-BD youths were significantly more impaired than both the SMD group and controls. On the compound reversal, NP-BD and SMD youths performed worse than controls. On the change task, NP-BD youths were slower to adapt than SMD subjects. **Conclusions:** Phenotypic differences in cognitive flexibility may reflect different brain/behavior mechanisms in these two patient populations. *J. Am. Acad. Child Adolesc. Psychiatry,* 2007;46(3):341–355.
Key Words: bipolar disorder, neuropsychological tests, cognition.

Bipolar disorder (BD) is among the most disabling psychiatric illnesses afflicting children and adolescents, often resulting in academic and social dysfunction along with suicidality (Dickstein et al., 2005c; Wilens et al., 2003). The diagnosis remains the subject of much debate, centering on two issues. First, because irritability is a nonspecific symptom common to many pediatric psychiatric disorders, should elevated/expansive mood be required for a diagnosis of mania or is there a particularly severe or distinct form of irritability found in prepubertal mania? Second, given that *DSM-IV-TR* defines a manic episode as a "distinct period of abnormal mood" (American Psychiatric Association, 2000), is pediatric BD characterized by distinct mood episodes or is there a developmental presentation of BD characterized instead by a chronic, nonepisodic course (Carlson et al., 2003; Leibenluft et al., 2003b; National Institute of Mental Health, 2001).

Irritability is one of the most common presenting symptoms of children brought by their caregivers for psychiatric care. Not only is it an explicit *DSM-IV-TR* criterion for several psychiatric disorders, including major depressive episode, manic episode, and generalized anxiety disorder, but it is common in children with other disorders, including attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), and pervasive developmental disorder (Carlson, 1998; Leibenluft et al., 2003a; Mick et al.,

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2005). Determining the diagnosis of a child with irritability depends on the child's other associated symptoms. For example, a child with irritability secondary to a pervasive developmental disorder spectrum disorder would also exhibit deficits in social interactions or language and/or stereotypies, whereas one with irritability secondary to a major depressive episode would also exhibit anhedonia, fatigue, feelings of worthlessness, appetite changes, suicidality, and so forth. In the case of a manic episode, irritability is associated with the B criteria for the disorder, some of which are unique to mania (e.g., decreased need for sleep, excessive involvement in pleasurable activities with high potential for painful consequences) and some of which overlap with ADHD (e.g., pressured speech in mania and blurts out answers in ADHD). Adhering to the *DSM-IV-TR* criteria, one can differentiate an irritable child with ADHD from one with mania because in the case of the former, irritability (and the symptoms of ADHD) should be present consistently, whereas in mania, irritability should occur (or at least worsen markedly) episodically, at the same time that the B symptoms occur. However, it has been suggested that in children and adolescents, mania can present not as an episodic illness, but rather as an illness characterized by chronic irritability. In turn, this makes the distinction between mania, on the one hand, and ADHD-like symptoms accompanied by severe, chronic irritability, on the other hand, problematic (Carlson, 1998; Leibenluft et al., 2003b; National Institute of Mental Health, 2001).

To facilitate research on this question, Leibenluft et al. (2003b) suggested a system of putative BD phenotypes that differ in the presence of euphoria versus irritability and episodic versus chronic course. This system allows clinically distinct presentations, each of which may or may not be found ultimately to represent a bipolar spectrum disorder, to be compared longitudinally and pathophysiologically. The most clearly bipolar of these presentations is the so-called narrow phenotype of pediatric BD (NP-BD), which includes children with a history of at least one episode of mania or hypomania meeting *DSM-IV-TR* duration criteria (i.e., 4–7 days), during which time elevated or expansive mood (euphoria) predominates (American Psychiatric Association, 2000). In contrast, children with a chronic, nonepisodic course of severely impairing irritable mood and ADHD-like symptoms are called severely mood dysregulated (SMD) in the Leibenluft et al., 2003b phenotyping system. It is unclear whether children with SMD have a developmental presentation of BD, an illness along the depressive spectrum (Leibenluft et al., 2006), or another disorder. This question is the focus of current research.

Comparative studies of NP-BD and SMD subjects have the potential to address the fundamental question of whether these two groups have the same underlying pathophysiology. The only comparative study showed that NP-BD subjects had more suicidality, a higher prevalence of psychiatric hospitalization, and a higher prevalence of comorbid anxiety disorders than SMD youths. Additionally, SMD youths were of a significantly younger age at symptom onset than NP-BD subjects (Dickstein et al., 2005c). Thus, this study showed that NP-BD and SMD subjects differ on clinical features apart from those related directly to BD phenotype.

It is important to complement clinical description with an understanding of the brain/behavior mechanisms underlying the phenotypes of pediatric BD. One approach is to study cognitive flexibility in NP-BD and SMD youths. Cognitive flexibility is the ability to adapt one's thinking and behavior in response to changing environmental conditions, such as rewards (Cools et al., 2004; Stemme et al., 2005). Adaptation to rewards and cognitive flexibility are highly relevant to BD because clinical features of BD may reflect altered reward processing (Ernst et al., 2004). For example, mania is a hyperhedonic state with aberrant reward processing resulting in manic symptoms, including excessive involvement in pleasurable activities with high potential for painful consequences, increased goal-directed activity, and inflated self-esteem or grandiosity. In contrast, depression is a hypohedonic state involving decreased responsivity to rewards, manifested by diminished interest and pleasure in daily activities, anhedonia, and feelings of worthlessness. In either case, patients are unable to respond and adapt appropriately to emotional stimuli. Indeed, cognitive flexibility is mediated by areas of the brain that have been implicated in BD, including the ventral prefrontal cortex, amygdala, and ventral striatum (Alexander et al., 1986; Baxter et al., 2000). Moreover, three previous studies demonstrate that NP-BD subjects have impaired cognitive flexibility compared to typically developing controls (Dickstein et al., 2004; Gorrindo

et al., 2005; McClure et al., 2005). However, previous studies of cognitive flexibility in children and adolescents with non-BD psychopathology, such as depression, ADHD, ODD, high-functioning autism, or Tourette's syndrome, have yielded mixed results relative to typically developing controls (Geurts et al., 2005; Goldberg et al., 2005; Happe et al., 2006; Kempton et al., 1999; Kyte et al., 2005; Oosterlaan and Sergeant, 1998; Verte et al., 2006). Thus far, no studies have evaluated cognitive flexibility in SMD subjects.

To address this lack of knowledge, we evaluated cognitive flexibility in SMD subjects compared to both NP-BD and typically developing youths. Previously, we used the intradimensional/extradimensional shift (ID/ED) task of the Cambridge Neuropsychological Testing Automated Battery (CANTAB; Cambridge Cognition Ltd., Cambridge, UK) and the change task to show impaired cognitive flexibility in NP-BD versus control youths (Dickstein et al., 2004; McClure et al., 2005). We sought to determine the specificity of these deficits by administering both tasks to a newly recruited sample of SMD subjects and to an expanded sample of NP-BD and control youths. Based on our previous work in demonstrating clinical impairment in SMD subjects (Dickstein et al., 2005c), the high rate of psychopathology in SMD subjects, and our previous findings on measures of cognitive flexibility in NP-BD versus control subjects, we hypothesized that SMD subjects would perform worse than controls on cognitive flexibility measures. However, given the lack of previous work in this area, we did not advance specific hypotheses regarding possible differences between SMD and NP-BD subjects.

METHOD

Subjects

NP-BD and SMD subjects were enrolled in two institutional review board–approved studies at NIMH. After the studies were explained and before participation, parents gave written informed consent and children gave written assent. Subjects were recruited through advertisements placed on support groups' websites and distributed to psychiatrists nationwide.

NP-BD (n = 50) inclusion criteria were meeting *DSM-IV-TR* criteria for BD, including history of at least one episode meeting full-duration criteria for hypomania (≥4 days) or mania (≥7 days) wherein the child exhibited abnormally elevated or expansive mood accompanied by at least three other *DSM-IV* criterion B mania symptoms; involvement with ongoing mental health treatment; and presence of a primary caretaker to grant consent and participate in the research process. Children with irritability only without elevated or expansive mood were excluded from this group (Geller et al., 1998; Leibenluft et al., 2003b).

SMD (n = 44) inclusion criteria were abnormal mood (anger or sadness), present at least half of the day most days; hyperarousal (≥3 of insomnia, agitation, distractibility, racing thoughts or flight of ideas, pressured speech, intrusiveness); markedly increased reactivity to negative emotional stimuli manifest verbally or behaviorally; and symptoms causing severe impairment in at least one setting (home, school, or peers) and at least mild impairment in a second setting. SMD symptom onset must occur before age 12 and must be present for at least 12 months without symptom-free periods longer than 2 months (Leibenluft et al., 2003b).

Exclusion criteria for both patient groups were age younger than 7 or older than 18 years, IQ ≤70, autism or Asperger's syndrome, psychosis interfering with the child's capacity to comply with study procedures, medical illness that is unstable or could cause the symptoms of BD, pregnancy, and substance abuse within 2 months. Additional SMD exclusion criteria were presence of cardinal bipolar symptoms including elevated/expansive mood, grandiosity/inflated self-esteem, or episodically decreased need for sleep and distinct episodes lasting longer than 4 days.

Following a telephone interview to ascertain relevant symptoms, potential NP-BD or SMD subjects were invited to the NIMH. Onsite screening included the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) with an additional SMD supplement, designed in collaboration with Joan Kaufman, Ph.D., to ascertain whether children met criteria for this syndrome. All diagnostic measures were administered individually to parent and child by trained graduate-level clinicians with established interrater reliability ($\kappa \geq 0.9$, including distinguishing between SMD and NP-BD; Kaufman et al., 1997). All diagnoses were based on best-estimate procedures (Leckman et al., 1982) generated in a consensus conference of research staff led by two psychiatrists with extensive experience evaluating children with NP-BD and SMD.

In the NP-BD sample, diagnoses comorbid to BD were assessed with the K-SADS-PL by inquiring about symptoms during a time of relative euthymia to ensure that such comorbidities were not merely NP-BD symptoms counted toward another diagnosis. In contrast, because SMD is not a *DSM-IV-TR* diagnosis, the K-SADS-PL was used to assess *DSM* diagnoses, and a separate module was used to assess for the SMD syndrome. We also administered the following mood and functional ratings in both NP-BD and SMD subjects: Young Mania Rating Scale (YMRS; Young et al., 1978), Children's Depression Rating Scale (CDRS; Emslie et al., 1990), Children's Global Assessment of Severity (CGAS; Shaffer et al., 1983), and Full Scale IQ (FSIQ) from the Wechsler Abbreviated Scale of Intelligence (WASI). Although the YMRS was administered and scored in the same standard way for both NP-BD and SMD subjects, SMD subjects' YMRS scores should not be interpreted as a measure of mania severity per se, but rather as a measure of the severity of the criteria B symptoms of their illness because by definition, SMD subjects do not fulfill *DSM-IV-TR* mania criteria.

Typically developing child controls (n = 42) were also evaluated with an initial telephone screen followed by an onsite K-SADS-PL administered by graduate-level clinicians. Inclusion criteria were age 7–17 years, negative psychiatric history in control subject and first-degree relatives, and an identified primary care physician. Exclusion criteria were age younger than 7 or older than 18 years, IQ ≤70, ongoing medical illness, regular medication use, pregnancy, past or present psychiatric disorder or substance abuse, and history of abuse.

Cognitive Flexibility Paradigms

Cognitive flexibility was assessed with the ID/ED shift and change tasks.

ID/ED Task

The ID/ED task (Fig. 1A) is a computerized set-shifting task modeled after the Wisconsin Card Sorting Task. Subjects select one of two geometric shapes presented simultaneously on a touch screen without any explicit instruction about which shape is correct. The task has nine stages, and subjects must successfully complete six trials in a maximum of 50 attempts to advance to the next stage or the task is discontinued. Stage 1 is a simple discrimination stage, requiring subjects to learn from trial and error what initial construct (e.g., preference for purple squares rather than purple circles) is being reinforced by winning points. Stage 2 is a simple reversal, requiring subjects to adapt to the reversal of stage 1's stimulus/reward relationships (e.g., now purple circles rather than purple squares) are rewarded. In stages 3 through 9, white line designs are added to the purple shapes of stages 1 and 2 to form compound stimuli. However, throughout stages 1 through 7, reinforcement

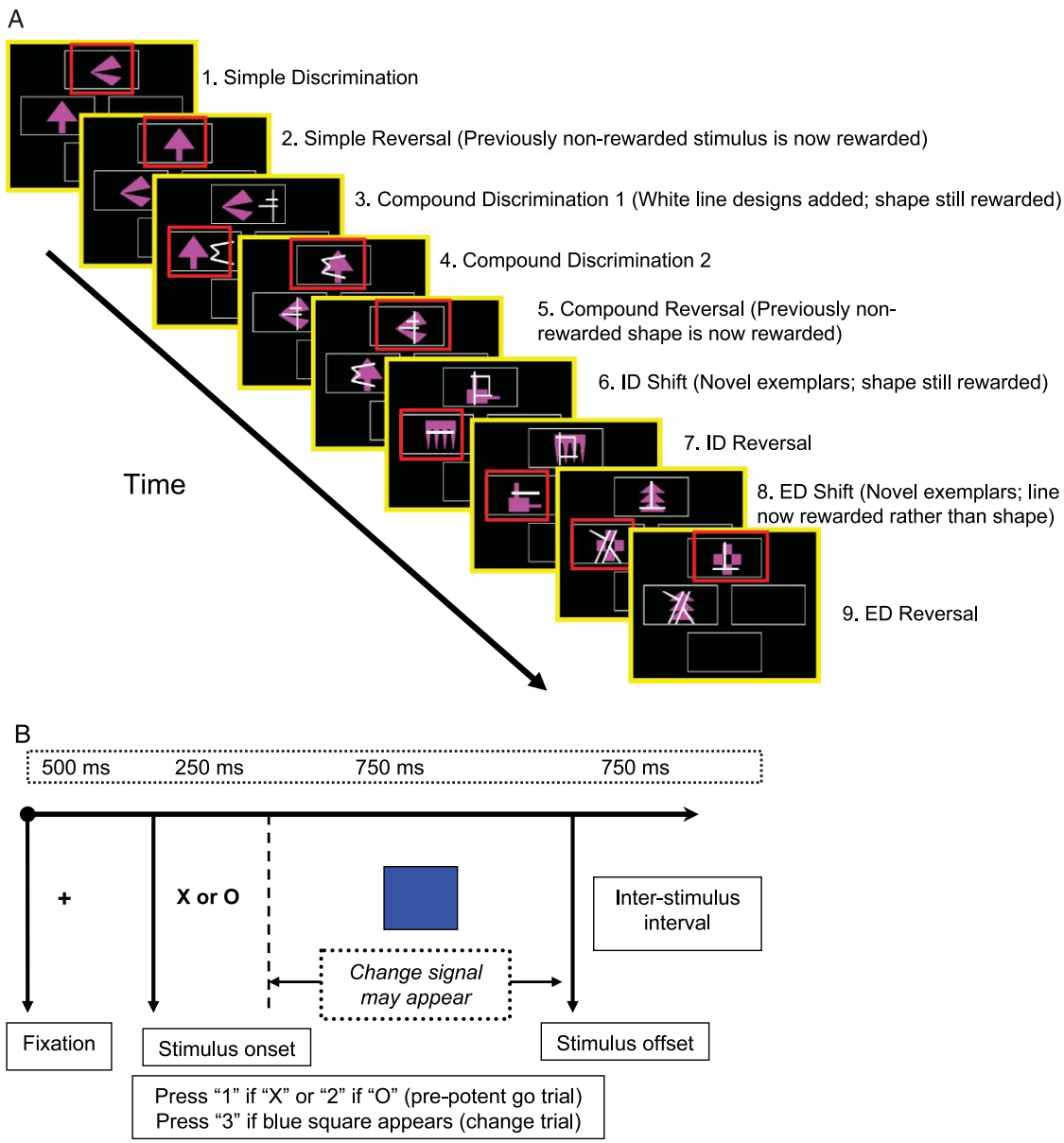

Fig. 1 (A) Subjects must determine by trial and error which stimulus is correct/rewarded at each stage. For this figure, the correct stimulus is indicated by a red box. Stimulus pairs are randomly presented in 2 of 4 white squares. Cambridge Neuropsychological Test Automated Battery (Cambridge Cognition Ltd., Cambridge, UK). (B) To ensure that "go" responses are prepotent, there were twice as many go trials as change trials. The difficulty of each trial adjusts automatically on a trial-by-trial basis to each subject's performance. A blank screen is displayed during interstimulus interval. ID = intradimensional; ED = extradimensional.

depends on purple shapes, and the white lines are irrelevant. Stage 6 is known as the ID shift because, although the old stimuli are replaced with novel exemplars of the purple shape/white line stimuli, reward continues to be based on the purple shape rather than white lines. Stage 8 is the ED shift because it is the first stage at which the previously irrelevant construct (i.e., white line design) is rewarded.

Outcome measures for the ID/ED task include errors, latency, and number of trials to reach criteria (six correct trials per stage) for all trials before the ED shift (pre-ED shift, stages 1–7) and at the ED shift. Errors, latency, and number of trials to reach criteria can also be extracted for each stage. Based on our previous study in a smaller sample showing that NP-BD subjects were impaired on the simple reversal stage (Dickstein et al., 2004), here we focused on the simple and compound reversal stages of the ID/ED task. Unlike the previous study, we included only subjects who completed all nine stages of the ID/ED task because we wanted to ensure a minimal competency in the task, especially given that a disproportionate number of SMD subjects, relative to NP-BD subjects, were tested while medication free. The present report contains CANTAB ID/ED data from 9 previously published and 17 novel NP-BD subjects and 13 previously published and 20 novel controls. The SMD CANTAB data (n = 33) have not been published previously.

Change Task

The change task requires subjects to inhibit a prepotent response (i.e., a response performed habitually so that it dominates all others) after it has been cued and to substitute a novel response for the prepotent one. This computerized paradigm consists of go and change trials (Fig. 1B; Logan et al., 1997). Subjects are instructed to press 1 if they see X or 2 if they see O (go trials); however, if the background changes to blue (change trials), they are to press 3. They are also told to respond before the X or O disappears from the screen (i.e., within 1,000 milliseconds). To ensure that go responses are prepotent, there are twice as many go as change trials. Moreover, task difficulty adjusts to subject performance on a trial-by-trial basis. On the first trial, the change signal occurs 250 milliseconds after the go signal. If the subject is successful on this trial (i.e., presses 3), then the change signal occurs 50 milliseconds later on the next change trial, making the task more difficult because the subject must then inhibit the prepotent response longer while awaiting the potential change signal. If the subject is unsuccessful (presses 1 or 2 or does not respond), then the change signal occurs 50 milliseconds earlier on the subsequent change trial, making the task easier because the subject must inhibit the prepotent response for a shorter duration. This timing adjustment continues throughout the task, matching performance (i.e., percentage of correct change trials) across groups and allowing calculation of the speed at which subjects execute the flexible change response (see below). Blank trials are included randomly to provide comparability with behavioral data obtained in functional magnetic resonance imaging studies. Each subject completed four runs of the 3.5-minute change task for a total of 176 go trials and 80 change trials.

Outcome measures for the change task included go and change accuracy; mean inhibit delay (MID); and change signal reaction time (CSRT). MID is the interval between the go and change signals and is an index of task difficulty. CSRT is a measure of the speed at which one can execute the flexible response, incorporating both speed and accuracy, and is not simply the reaction time on change trials (Williams et al., 1999). When a subject successfully changes on 50% of change trials, the CSRT is the mean change task reaction time minus the MID (Logan et al., 1997). We used an interpolation algorithm to calculate CSRT, such that CSRT = go-signal reaction time at the Xth percentile minus mean MID, where X is the subject's percentage of accuracy on change trials. Change task data from 34 of 46 NP-BD subjects and 22 of 22 controls published (McClure et al., 2005) are also used in the analysis here; data from the SMD subjects (n = 32) have not been published previously.

Statistical Analyses

We conducted repeated-measures multiple analyses of covariance with the Statistical Package for Social Sciences (version 13.0, SPSS Inc., Chicago, IL) using diagnosis (NP-BD, SMD, control) as the fixed factor, task-specific outcome variables as dependent measures, and age as a covariate because this differed significantly between groups. Significance was set at .05, with results Bonferroni corrected for multiple comparisons. Where the multiple analyses of covariance showed a significant main effect of diagnosis, we determined significant between-group differences with post hoc pairwise t tests and calculated effect sizes with Cohen's d. Post hoc analyses using the same methodology were conducted to evaluate the impact of mood state, comorbidity, and medication status on our results. Last, although the major goal of this study was to examine the specificity of impaired cognitive flexibility in NP-BD versus SMD youths, we have added enough new NP-ND subjects to the CANTAB data set to allow us to also determine whether we could use these new cases to replicate the findings in our original study (Dickstein et al., 2004).

RESULTS

Subject Characteristics

The three subject groups did not differ significantly in FSIQ or sex (Table 1). However, they differed significantly in age $F_{2,133} = 3.22$, $p = .04$ with SMD subjects being younger than controls ($p = .04$). Therefore, all of the analyses were covaried for age.

Both patient samples were moderately impaired, with SMD subjects significantly more impaired than NP-BD youths (NP-BD mean CGAS: 57.7 ± 13.8; SMD mean CGAS: 48.4 ± 7.3; $t = 4.07$; $p = .00$). There was no significant difference in mean YMRS or CDRS scores (Table 1). In the NP-BD sample, 24 of 50 (48%) were euthymic (YMRS ≤12 and CDRS <40), 17 of 50 (34%) were hypomanic (YMRS = 13–24 and CDRS <40), 3 of 50 (6%) were depressed (YMRS ≤12 and CDRS ≥40), 6 of 50 (12%) were mixed hypomanic (YMRS ≤12 and CDRS ≥40), and 0 were manic (YMRS ≥25 and CDRS <40). Among SMD children, 2 of 44 (4.5%) were depressed (YMRS ≤12 and CDRS ≥40). Regarding medication status, 38 of 50 (76%) NP-BD subjects and 17 of 44 (39%) SMD subjects were tested while on their usual outpatient psychotropic medications. Although no subjects were medication

TABLE 1
Subject Demographics

	Group						Analysis	
	NP-BD (n = 50)		SMD (n = 44)		NC (n = 42)			
	Mean	SD	Mean	SD	Mean	SD		p
Age	13.1	2.9	12.2	2.1	13.6	2.4	$F_{2,133}$ = 3.22	.04
FSIQ	110.2	13.5	105.7	14.3	111.0	12.7	$F_{2,128}$ = 1.90	NS
CGAS	52.7	14.8	48.4	7.3	—	—	t = 4.10; df = 77[a]	.00
YMRS	10.2	8.5	10.6	6.1	—	—	t = −0.25; df = 90[a]	NS
CDRS	30.3	11.5	29.2	7.2	—	—	t = 0.62; df = 85[a]	NS
No. of current K-SADS-PL diagnoses	3.0	1.4	2.8	1.3	—	—	t = 0.74; df = 92	NS
	No.	%	No.	%	No.	%	Pearson χ^2	p
Gender								
Female	21	42	13	30	15	36		
Male	29	58	31	70	27	64		
BD								
Type I	41	82						
Type II	9	18	—	—	—			
Current diagnoses[b]								
ADHD	27	54	36	82	—		12.5	.00
Any anxiety disorder	27	54	22	50	—		0.5	NS
Generalized anxiety	17	34	15	34	—		0.3	NS
Separation anxiety	9	18	11	25	—		0.2	NS
Simple phobia	9	18	6	14	—		0.2	NS
Social phobia	6	12	4	9	—		0.1	NS
Depression	15	30	11	25	—		1.7	NS
ODD	12	24	35	80	—		24.6	.00

Note: FSIQ data were not obtained for three NP-BD and one SMD subjects and one control. NP-BD medication (N [%]): lithium, 15 (30%); valproate, 14 (28%); other antiepileptic drug, 24 (48%); atypical neuroleptic, 29 (58%); antidepressant, 13 (26%); psychostimulant, 11 (22%); medication free for four drug half-lives, 12 (24%). SMD medication (N [%]): lithium, eight (18%); valproate, two (5%); other antiepileptic drug, six (14%); atypical neuroleptic, seven (16%); antidepressant, four (9%); psychostimulant, 8 (18%); medication free for four drug half-lives, 27 (61%). NP-BD = narrow-phenotype bipolar disorder; SMD = severe mood dysregulation; NC = normal control; FSIQ = Full Scale IQ; CGAS = Children's Global Assessment of Severity; YMRS = Young Mania Rating Scale; CDRS = Children's Depression Rating Scale; K-SADS-PL = Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version; ADHD = attention-deficit/hyperactivity disorder; NS = not significant; ODD = oppositional defiant disorder.

[a] Degrees of freedom modified because of a significant Levene test for equal variances (i.e., not assumed).

[b] Current diagnoses included bipolar disorder in the NP-BD sample only.

naïve, 12 of 50 (24%) NP-BD subjects and 27 of 44 (61%) SMD subjects were tested medication free (meaning free of each of their usual psychotropic medication for at least four half-lives).

CANTAB ID/ED Task Results

There was a significant main effect of diagnosis on the ID/ED task results (Table 2). Specifically, there was a main effect of diagnosis on pre-ED shift errors $F_{2,88}$ = 6.70; p = .002. Post hoc pairwise comparisons of pre-ED shift errors showed that NP-BD subjects made significantly more errors than NC (p = .001), and there was a trend toward NP-BD subjects making more errors than SMD subjects (p = .06); however, SMD subjects did not differ significantly from controls (p = .6). There was also a main effect of diagnosis on number of trials required to complete all stages of the ID/ED task $F_{2,88}$ = 3.92; p = .02, with post hoc analyses demonstrating that NP-BD subjects required significantly more trials to complete all stages of the task than controls (p = .03).

Focusing on reversal stages, NP-BD subjects were impaired relative to both SMD and control groups on the simple reversal stage. There was a significant main

TABLE 2
Cognitive Flexibility Results

	Group						Analysis			
	NP-BD (n = 26)		SMD (n = 33)		NC (n = 33)					
Test	Mean	SD	Mean	SD	Mean	SD	F	p	Post hoc	Cohen's d
ID/ED shift										
Completed stage trials	95.4	26.7	87.3	18.2	81.9	14.5	3.92 (2,88)	.02	NP-BD > NC p = .03	0.63
Completed stage errors	20.9	11.6	18.9	9.4	16.7	7.2	1.63	NS		
Pre-ED shift errors	12.6	8.2	9.2	7.4	6.5	3.0	6.70	.002	NP-BD > NC, p = .001;	0.99
									NP-BD > SMD, p = .06	0.44
ED shift errors	5.4	6.1	8.2	7.0	8.6	6.3	1.61	NS		
Total trials	97.3	30.4	91.8	22.8	83.5	18.6	2.91	.06		
Total errors	21.9	13.7	21.2	11.8	17.5	9.8	1.16	NS		
Simple reversal stage										
Trials	12.8	8.6	9.9	6.8	8.4	3.0	3.71	.03	NP-BD > NC, p = .03	0.68
Errors	3.1	3.2	1.9	2.0	1.4	0.9	4.98	.009	NP-BD > NC, p = .01;	0.72
									NP-BD > SMD, p = .04	0.45
Latency	1,413.00	509.38	1,202.79	421.07	1,046.55	268.72	6.38	.003	NP-BD > NC, p = .002;	0.90
									NP-BD > SMD, p = .05	0.45
Compound reversal stage										
Trials	10.3	5.6	10.0	5.5	7.4	1.5	3.99	.02	NP-BD > NC, p = .03	0.68
Errors	2.2	1.6	2.3	2.5	1.2	0.5	3.56	.03	SMD > NC, p = .05;	0.61
									NP-BD > NC, p = .08	0.84
Latency	1,599.62	576.01	1,522.70	763.06	1,153.18	315.55	4.84	.01	NP-BD > NC, p = .01	0.96
	Group						Analysis			
	NP-BD (n = 46)		SMD (n = 32)		NC (n = 22)					
	Mean	SD	Mean	SD	Mean	SD	F	p	Post hoc	Cohen's d
Change task										
Change signal reaction time	292.69	91.07	254.26	86.39	253.14	55.84	3.32 (2,96)	.04	NP-BP > SMD, p = .04;	0.43
									NP-BD > NC, p = .4	0.52
% Go accuracy	79.4	16.1	74.6	16.0	91.2	5.7	6.16	.003	NC > NP-BD, p = .02;	0.98
									NC > SMD, p = .003	1.38
% Change accuracy	53.3	18.6	54.6	20.3	54.4	12.3	0.34	NS		
Mean inhibit delay	417.11	130.94	413.40	105.51	488.39	129.01	1.66	NS		
Mean go reaction time go	784.85	104.71	759.88	105.94	753.50	104.17	0.87	NS		
Mean change reaction time	919.26	121.53	870.16	120.13	900.09	101.39	1.38	NS		

Note: Multiple analyses of covariance were used with diagnosis as a fixed factor, task as a dependent variable, and age as the covariate. Bonferroni correction was used for multiple comparisons; significance set at ≤.05. NP-BD = narrow-phenotype bipolar disorder; SMD = severe mood dysregulation; NC = normal control; ID/ED = intradimensional/extradimensional; NS = not significant.

effect of diagnosis on the number of trials required to complete this stage: $F_{2,88}$ = 3.71, p = .03; errors $F_{2,88}$ = 4.98, p = .009; and latency, $F_{2,88}$ = 6.38, p = .003. Post hoc pairwise comparisons revealed that NP-BD subjects, compared with controls, required more trials to complete the simple reversal stage (p = .03), made more errors (p = .01), and had longer latency (p = .002). Similar analyses demonstrated that NP-BD subjects, compared with SMD youths, made significantly more errors (p = .04) and had longer latency (p = .05).

The results of the compound reversal stage demonstrated a less specific pattern of impairment, with both NP-BD and SMD youths performing worse than controls (Fig. 2). There was a significant main effect of diagnosis on number of trials: $F_{2,88}$ = 3.99, p = .02; errors, $F_{2,88}$ = 3.56, p = .03; and latency, $F_{2,88}$ = 4.84,

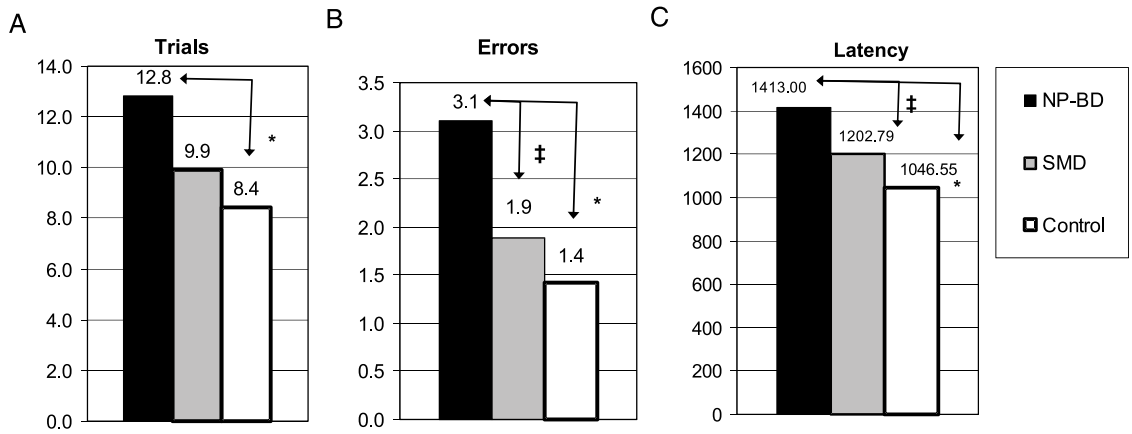

Fig. 2 Method: Cambridge Automated Neuropsychological Testing Battery (CANTAB, Cambridge, U.K.). Intradimensional/extradimensional shift task. Results covaried for age. Post hoc pairwise analyses are Bonferroni corrected *p* values. (A) Trials: $F_{2,88} = 3.71$, $p = .03$. Post hoc: NP-BD > NC, $p = .03$ (Cohen's $d = 0.68$). (B) Errors: $F_{2,88} = 4.98$; $p = .009$. Post hoc: NP-BD > NC, $p = .01$ (Cohen's $d = 0.72$). NP-BD > SMD, $p = .04$ (Cohen's $d = 0.45$). (C) Latency: $F_{2,88} = 6.38$, $p = .003$. Post hoc: NP-BD > NC, $p = .002$ (Cohen's $d = 0.90$); NP-BD > SMD, $p = .05$ (Cohen's $d = 0.45$). *NP-BD > NC. ‡NP-BD> SMD. NP-BP = narrow-phenotype bipolar disorder; SMD = severe mood dysregulation.

$p = .01$. Post hoc pairwise comparisons showed that NP-BD subjects, compared with controls, required significantly more trials ($p = .03$) and longer latency ($p = .01$) and tended to make more errors ($p = .08$) to complete this stage. SMD youths, compared with controls, made significantly more complex reversal errors ($p = .05$).

Change Task Results

Change task data indicate that although both patient groups were slower and less accurate than controls on change trials, NP-BD patients took significantly longer than SMD patients to change their response on those change trials that were completed successfully. Specifically, there was a significant main effect of diagnosis on CSRT ($F_{2,96} = 3.32$, $p = .04$) and on percentage of accuracy on go trials ($F_{2,96} = 6.16$; $p = .003$). Post hoc pairwise comparisons demonstrated that CSRT was significantly longer for NP-BD than SMD subjects ($p = .04$), but there was no significant difference between NP-BD and control subjects ($p = .4$; Fig. 3). Post hoc pairwise comparisons showed that controls had significantly greater percentage of accuracy on go trials than either NP-BD ($p = .02$) or SMD ($p = .003$)

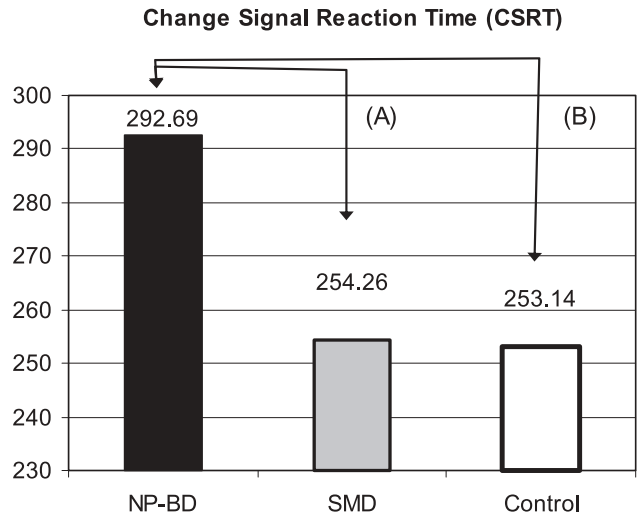

Fig. 3 Method: CSRT = go signal reaction time at the Xth percentile − mean inhibit delay = (change signal − go signal). X is the subject's percentage of accuracy on change trials ($F_{2,96} = 3.32$; $p = .04$). Post hoc pairwise analyses: NP-BD > SMD, $p = .04$ (Cohen's $d = 0.43$) (A). NP-BD > control, $p = .4$ (Cohen's $d = 0.52$) (B). NP-BP = narrow phenotype bipolar disorder; SMD = severe mood dysregulation.

subjects, but NP-BD and SMD subjects did not differ from one another.

Post Hoc Analyses: Mood State

We conducted post hoc analyses to evaluate the effects of mood state, comorbid ADHD, and medications. Regarding mood state, in the NP-BD sample, there were no significant correlations between either YMRS or CDRS and the ID/ED simple or compound reversal stage or change task measures. In the SMD sample, the only significant correlations with either YMRS or CDRS and ID/ED or change task variables were between compound reversal stage trials and YMRS (r = 0.35, p = .05). To further evaluate the effect of mood, we evaluated cognitive flexibility in euthymic NP-BD subjects (YMRS ≤12 and CDRS <40), nondepressed SMD subjects (CDRS <40), and controls. On the ID/ED task, there was a main effect of diagnosis on simple reversal stage latency ($F_{2,62}$ = 6.76, p = .002) and on the compound reversal stage latency ($F_{2,62}$ = 6.87, p = .002). Post hoc pairwise comparisons showed that euthymic NP-BD subjects (n = 13) had greater simple reversal stage latency than either nondepressed SMD subjects (n = 20; p = .03) or controls (n = 33; p = .002) and greater compound reversal stage latency than either nondepressed SMD subjects (p = .05) or controls (p = .001). On the change task, there was a main effect of diagnosis on the percentage of accuracy during go trials ($F_{2,63}$ = 5.56; p = .006), with both euthymic NP-BD subjects (n = 24; p = .03) and nondepressed SMD subjects (n = 21; p = .009) being less accurate than controls (n = 22). In brief, these post hoc analyses of cognitive flexibility in euthymic NP-BD and SMD subjects versus controls are consistent with the results of the overall sample, suggesting that mood state heterogeneity does not have a significant impact on our results.

Post Hoc Analyses: Comorbid Anxiety and ADHD

We also conducted post hoc analyses to evaluate associations with comorbid anxiety disorders and ADHD, the most common comorbid disorders in NP-BD and SMD subjects. Because roughly half of the NP-BD and SMD subjects did not have any anxiety disorders, we attempted to parse the effect of comorbid anxiety by restricting our sample to those without any anxiety disorders. On the ID/ED task, we found a main effect of diagnosis on the simple reversal latency ($F_{2,59}$ = 8.96, p = .00) with nonanxious NP-BD subjects (n = 12) more impaired than either controls (n = 33; p = .00) or nonanxious SMD subjects (n = 18; p = .009). We also found a main effect of diagnosis on the compound reversal trials ($F_{2,59}$ = 4.45, p = .02), errors ($_{F2,59}$ = 4.16, p = .02), and latency ($F_{2,59}$ = 7.58, p = .001); further analysis showed that nonanxious SMD subjects required more trials (p = .01) and made more errors (p = .02) than controls on the compound reversal stage, whereas nonanxious NP-BD subjects had longer latency than controls (p = .001) on the compound reversal stage. On the change task, we found a main effect of diagnosis on the percentage of accuracy of go trials ($F_{2,56}$ = 4.71, p = .01) but not the CSRT, with nonanxious SMD subjects less accurate than controls (p = .01). Taken as a whole, this suggests that comorbid anxiety does not have an impact on ID/ED task performance, but it may affect change task performance: Whereas the entire NP-BD sample was less accurate than controls, there was no difference in accuracy between nonanxious NP-BD subjects and controls.

With regard to ADHD, there were insufficient numbers of SMD subjects without ADHD (8/44; 18%) to conduct similar analyses. However, comparing NP-BD subjects with ADHD and those without ADHD did not reveal any significant differences on either the simple and compound reversal stages of the ID/ED task (NP-BD with ADHD [n = 12]; NP-BD without ADHD [n = 14]) or change task (NP-BD with ADHD [n = 25], NP-BD without ADHD [n = 21]).

Post Hoc Analyses: Psychotropic Medications

To examine the effect of medications, we compared unmedicated SMD and medicated SMD subjects, but we did not find any significant differences on the simple or compound reversal stages (unmedicated SMD [n = 19]; medicated SMD [n = 14]) or change task (unmedicated SMD [n = 21]; medicated SMD [n = 11]). Unfortunately, similar within-group analyses were not conducted in the NP-BD sample because of an insufficient number of unmedicated NP-BD subjects.

Post Hoc Analyses: Replication of Previous CANTAB

We conducted analyses to determine whether our present CANTAB ID/ED results represent a replication of our previous study, in which we found impaired simple reversal stage performance in NP-BD subjects

versus controls (Dickstein et al., 2004). Novel NP-BD subjects (n = 17) were significantly more impaired than novel controls (n = 20) on simple reversal stage latency ($F_{1,34}$ = 4.91, p = .03) but not on either trials or errors. Because there were no significant differences on the simple reversal stage measures between the previously published controls (n = 13; 3 of 16 previously published controls had not completed all 9 ID/ED task stages) and novel controls (n = 20), we merged both into a single group of controls (n = 33). Compared with this merged group of controls, novel NP-BD subjects required more trials ($F_{1,47}$ = 6.07, p = .02), made more errors ($F_{1,47}$ = 6.44, p = .02), and had longer latency ($F_{1,47}$ = 10.5, p = .002) on the simple reversal stage. Thus, as in Dickstein et al., 2004, we once again found impaired simple reversal stage latency in NP-BD versus controls.

DISCUSSION

The present study extends our previous reports that NP-BD subjects have deficits in cognitive flexibility compared with controls (Dickstein et al., 2004; McClure et al., 2005) by demonstrating the extent to which these deficits differentiate NP-BD from SMD subjects. Our primary findings are that NP-BD subjects are impaired on simple reversal learning compared to both SMD subjects and controls and that NP-BD subjects are worse at executing an alternative, nonprepotent motor response than are SMD subjects. We also found that both patient groups have impaired performance compared with controls on the ID/ED compound reversal and on simple motor execution in the change task. Our work suggests that reversal learning is relatively independent of minor mood state heterogeneity and, to at least some extent, of comorbid anxiety disorders and ADHD. However, further work is needed with larger samples to determine definitively whether impaired reversal learning, or a specific neural dysfunction mediating it, is a trait marker for pediatric BD. Additional work could also determine whether the deficit is familial and heritable, thus qualifying as an endophenotype of pediatric BD (Gottesman and Gould, 2003).

Although impaired reversal learning is a consistent finding in NP-BD youths, the neural basis for this deficit remains unknown. Studies in nonhuman primates and adult human controls show that reversal learning is mediated by a distributed neural circuit encompassing the ventral prefrontal cortex, amygdala, and ventral striatum. The components of this circuit appear to have dissociable roles. In particular, neuroimaging studies of healthy adults suggest that the ventral prefrontal cortex adapts behavior to the changing valence and salience of emotional stimuli, the ventral striatum translates stimulus information into motor responses, and the amygdala processes the reward value of stimuli (Arana et al., 2003; Cools et al., 2002, 2004; Monchi et al., 2001; Rogers et al., 2000). Lesion studies in nonhuman primates confirm that cognitive flexibility in response to changing rewards requires interaction among all three of these regions (Baxter et al., 2000; Dias et al., 1997; Izquierdo et al., 2004; Schultz et al., 2000).

In contrast, we know little about the underlying brain mechanisms mediating reversal learning in phenotypes of pediatric BD. At present, there are no published neuroimaging studies comparing NP-BD youths to SMD youths. Moreover, there are only three published functional magnetic resonance imaging studies comparing BD youths to controls, none of which examined reversal learning (Blumberg et al., 2003b; Chang et al., 2004; Rich et al., 2006). Structural magnetic resonance imaging studies of pediatric BD subjects report volumetric alterations in the amygdala-striatal-prefrontal cortex circuit (Blumberg et al., 2003a; Chang et al., 2005; DelBello et al., 2004; Dickstein et al., 2005b; Sanches et al., 2005; Wilke et al., 2004), the same circuit involved in reversal learning in healthy adults and nonhuman primates.

In addition to specific deficits on the simple reversal learning task, we found that NP-BD subjects are significantly slower than SMD subjects in executing an alternate, nonprepotent motor response. The CSRT differed between NP-BD and SMD patients, but not between NP-BD patients and controls. The change task is complex, requiring both the inhibition of a prepotent response and the substitution of an alternate one. Successful performance on this task is likely to involve both the ventral prefrontal cortex, which mediates inhibition (Aron et al., 2004; Durston et al., 2002; Rubia et al., 2003), and the dorsolateral prefrontal cortex, which exerts top-down control over regions that mediate motor response to rewards, such as the striatum (Casey et al., 2002). Although the neural basis for NP-BD subjects' impairment on the change task remains

unknown, previous work demonstrates decreased volume of the dorsolateral prefrontal cortex and striatum in NP-BD subjects compared with controls (Dickstein et al., 2005b).

Our third finding is that although NP-BD subjects have deficits on the ID/ED simple reversal compared with both SMD and control youths, both NP-BD and SMD youths have poorer performance than controls on the ID/ED compound reversal stage. Whereas the simple reversal stage measures only reversal learning, the compound reversal stage measures both reversal learning and selective attention because subjects must ignore the irrelevant white line designs and reverse the stimulus/reward associations of the purple shapes. Despite similar behavioral performance, deficits on the compound reversal stage may nonetheless result from different neural mechanisms in NP-BD and SMD youths. For example, NP-BD subjects' impairments in both simple and compound reversal stages may be caused by an impaired ability to adapt to altered stimulus/reward associations. In contrast, the SMD subjects' impairment on compound but not simple reversal may reflect impaired selective attention because complex reversal is associated with significantly greater attentional demands. Consistent with this, SMD youths have a higher prevalence of ADHD than do NP-BD patients (80% SMD; 48% NP-BD). Future neuroimaging studies of cognitive flexibility comparing NP-BD and SMD subjects are required to determine what neural differences underlie these behavioral differences.

It is also important to compare our findings in SMD and NP-BD with other forms of psychopathology. At present, five studies have used the CANTAB ID/ED task to study cognitive flexibility in children and adolescents with illnesses other than BD or SMD, including some with disorders characterized by irritability. Of those, only one found differences between patients and controls. Specifically, Kempton et al. (1999) demonstrated that unmedicated ADHD subjects performed worse than either medicated ADHD or control subjects. In contrast, no such differences were identified, relative to controls, in depressed adolescents (Kyte et al., 2005) or in youths with either ADHD or high-functioning autism (Goldberg et al., 2005; Happe et al., 2006). A fifth study failed to identify ID/ED task performance differences in subjects with early-onset schizophrenia compared with those with nonaffective psychosis (Fagerlund et al., 2006). However, of these studies, only that of Kyte et al. in depressed adolescents specifically examined reversal stages of the ID/ED task. Thus, although additional comparative studies of the ID/ED task's reversal stages are required, impaired simple reversal stage performance may distinguish pediatric NP-BD subjects from children and adolescents with other forms of psychopathology.

In contrast, three previous studies of the change task in youths with psychopathology other than BD or SMD have yielded mixed results. Oosterlaan and Sergeant (1998) found no main effect of diagnosis on CSRT when comparing youths with ADHD, disruptive behavior disorder (i.e., ODD and CD), anxiety disorder, and control youths; however, they did find that youths with either ADHD and disruptive behavior disorders had significantly worse accuracy and greater variability of reaction times during the change task. Similarly, a subsequent study using the change task failed to find differences in CSRT between children and adolescents with ADHD combined type, ADHD inattentive type, and controls, but found that combined type ADHD youths had significantly worse accuracy than controls (Geurts et al., 2005). Finally, a recent study found that children with high-functioning autism had CSRT and accuracy deficits compared with children with no psychopathology, Tourette's syndrome, or high-functioning autism plus Tourette's syndrome (Verte et al., 2006). Thus, change task performance does not appear to be a unique behavioral marker of pediatric BD, but instead may be shared by several forms of psychopathology characterized by irritability and/or ADHD. Further comparative studies of change task performance using both behavioral and neuroimaging techniques are required to fully evaluate possible specificity.

Clearly, more research is needed to identify specific behavior/brain markers for psychiatric disorders in children and adolescents. As illustrated by the previous two paragraphs, a number of studies have taken the first step of identifying differences between a single group of patients and controls. The next step, determining the specificity of these deficits relative to other psychopathologies, requires using the same behavior/brain measure and data analytic approach in adequately powered samples of youths with different disorders. For example, only three published studies of brain/behavioral measures have compared BD with other

forms of psychopathology in pediatric samples. Two out of three studies have used magnetic resonance spectroscopy to evaluate neurometabolite differences in the anterior cingulate cortex. The first of the two spectroscopy studies found increased myoinositol (a second messenger implicated in several medications' antimanic activity [O'Donnell et al., 2003]) in pediatric BD subjects compared with both patients with intermittent explosive disorder and healthy controls (Davanzo et al., 2003). The second spectroscopy study demonstrated higher ratios of glutamine plus glutamate (markers of the major excitatory neurotransmitter) to myoinositol in subjects with ADHD versus those with ADHD and BD or controls (Moore et al., 2006). The third comparative study compared BD, ADHD, and control youths on neurological examination abnormalities, also known as soft signs. In this study, NP-BD youths were distinguished from both ADHD subjects and controls by impairments on sequential motor tasks (a deficit that may be associated with cognitive inflexibility), whereas ADHD subjects were distinguished from NP-BD and controls by impairments on repetitive motor tasks (a deficit that may be associated with response disinhibition; Dickstein et al., 2005a). Such comparative studies are needed to identify specific behavior/brain markers for BD and other forms of psychopathology.

Limitations

Our study has four chief limitations: psychotropic medications, between-group age differences, mood state heterogeneity, and manner of assessing ADHD. Regarding medication status, comparing medicated and unmedicated SMD subjects, we did not find significant differences on our principal outcome variables (i.e., those obtained during the simple or compound reversal stages of the ID/ED task) or the CSRT. Although such within-group analyses in the NP-BD sample lacked sufficient power, several factors suggest that the differences we observed between NP-BD and SMD subjects do not result simply from more NP-BD than SMD subjects taking psychotropic medications. First, if psychotropic medications improve function, then NP-BD subjects should perform better, not worse, than SMD subjects; yet NP-BD subjects performed worse than SMD subjects on some but not all tasks, such as the ID/ED simple reversal. In contrast, if medications worsen function (e.g., by causing psychomotor slowing), then we would expect NP-BD subjects to be globally impaired on all measures relative to both controls and also the largely unmedicated SMDs; however, this was not borne out by our results. Nevertheless, further study is needed to determine how different medications may affect cognitive flexibility.

Another limitation is age; SMD subjects were significantly younger than NP-BD subjects and controls. In our present study, we address this by covarying for age in all of the analyses, although a preferred approach would involve well-matched samples. Additional work is necessary to ascertain how development affects cognitive flexibility, especially in light of studies demonstrating maturation of the prefrontal cortex through adolescence (Casey et al., 2000; Gogtay et al., 2004).

Mood state heterogeneity is a third limitation of our present study. This is more of an issue in the NP-BD sample because NP-BD subjects were presented in a variety of mood states, including euthymia (48%), hypomania (34%), depression (6%), and mixed hypomania (12%). Among SMD children, 4.5% were depressed. We examined this issue through post hoc correlations between mood ratings and cognitive flexibility measures; the only significant finding was in the SMD sample, between compound reversal stage trials and YMRS. We also constrained our sample to euthymic NP-BD subjects, nondepressed SMD subjects, and controls. The results of the latter analyses, although complicated by a disproportionate reduction in the NP-BD sample size relative to either SMDs or controls, are largely in concert with our overall results, with euthymic NP-BD subjects being impaired on simple and compound reversal latency, SMD subjects being impaired on compound reversal trials and errors, and both NP-BD and SMD subjects being impaired on accuracy during prepotent go trials. Thus, although our present work suggests that cognitive flexibility may be a trait impairment, further comparative studies of large samples of euthymic, manic, and depressed youths are necessary to fully determine whether cognitive flexibility impairments are state or trait deficits in pediatric BD.

The fourth limitation of our study is comorbidity because studies show that co-occurring psychiatric disorders can affect the clinical course of pediatric BD (Masi et al., 2001; Wilens et al., 2003) as well as possibly influencing neurobiological measures (Adler et al., 2005). With regard to comorbid anxiety disorders,

we had sufficient power to examine NP-BD and SMD subjects without anxiety disorders relative to one another and controls. Those analyses showed largely the same results on the ID/ED reversal stage but suggested the possibility that comorbid anxiety may worsen NP-BD subject accuracy on the change task. In contrast, we lacked sufficient power to conduct similar analyses in ADHD because 80% of SMD subjects had ADHD. Furthermore, we could not evaluate the effect of ADHD subtypes on our results because of those NP-BD or SMD subjects with ADHD, most had combined type (>85%). Given that previous studies using either the ID/ED or change tasks have not yielded consistent cognitive flexibility deficits in ADHD subjects, our results may be specific to BD spectrum disorders.

Therefore, future work to determine the specificity of cognitive flexibility deficits will require samples with greater homogeneity with respect to comorbid psychiatric disorders, mood state, and medication status; larger samples facilitating adequately powered post hoc examinations of these factors; and/or studies comparing youths with BD spectrum disorders to those whose primary psychiatric diagnosis is that commonly comorbid in BD (i.e., primary anxiety or primary ADHD).

Clinical Implications

Using the ID/ED and change tasks, we have reproduced in the laboratory one of the major clinical features of BD, namely, how aberrant reward-related processes affect decision-making (Clark et al., 2004; Ernst et al., 2004; Rolls, 2000). Many cardinal symptoms of mania and depression that are experienced by patients, as well as observed by parents, teachers, and clinicians, may reflect such aberrant reward processing, including excessive goal-directed activity and pleasure-seeking during mania and anhedonia during depression. Similarly, it is possible that irritability present in mania and depression may reflect an impaired ability to adapt to social feedback and rewards (i.e., praise or reprimand) from peers and adults, resulting in functional impairment at home or school. Thus, identifying potential behavioral markers of BD, such as cognitive flexibility, may advance the diagnosis of pediatric BD from the current reliance solely on clinical features to a complementary grounding in neurobiology. There may also be important treatment implications from our findings. For example, some psychotherapies may be less effective in BD youths or require BD-specific modifications because BD children may be less able to respond to rewards essential to the psychotherapies' mechanism of change; in other words, token economy in behavior therapy (explicit reward) or inability to identify or to change dysfunctional automatic thoughts in cognitive-behavioral therapy (implicit reward). Additionally, it is unknown whether medications currently used to treat BD, as well as novel agents, may enhance or hinder cognitive flexibility (Chamberlain et al., 2006). Thus, further study of the diagnostic and therapeutic implications of impaired cognitive flexibility in pediatric BD is clearly warranted.

In conclusion, our study demonstrates that compared with both SMD and control youths, NP-BD subjects have specific impairments in cognitive flexibility. This suggests that these two putative phenotypes of pediatric BD may differ pathophysiologically. Additional research is necessary to determine whether treatments designed to increase cognitive flexibility will also ameliorate symptoms of BD in these children and adolescents.

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Food-Related Advertising on Preschool Television: Building Brand Recognition in Young Viewers Susan M. Connor, PhD

Objectives: This study used content analysis to explore how much and what type of advertising is present in television programming aimed at toddlers and preschool-aged children and what methods of persuasion are being used to sell products and to promote brands to the youngest viewers. *Methods:* Four randomly selected, 4-hour blocks (9 AM to 1 PM) were recorded in spring 2005 from each of 3 stations airing programming aimed specifically at toddlers and preschool-aged children (Public Broadcasting Service, Disney, and Nickelodeon). All content that aired in the spaces between programs was examined. Data recorded for foodrelated advertisements included the primary appeals used to promote products or brands, whether advertisements were aimed at children or adults, whether advertisements used primarily animation or live action, whether advertisements showed food, and whether licensed characters were used. *Results:* In 96 half-hour blocks of preschool programming, the 3 stations had a total of 130 food-related advertisements (1.354 food advertisements per half-hour). More than one half of all food advertisements (76 of 130 advertisements) were aimed specifically at children, and the majority of those were for fast food chains (50 advertisements) or sweetened cereals (18 advertisements). The primary advertising appeals used associated products with fun and happiness and/or with excitement and energy. Fast food advertisements in particular seemed to focus on building brand recognition and positive associations, through the use of licensed characters, logos, and slogans. *Conclusions:* The majority of child-oriented food advertisements viewed seemed to take a branding approach, focusing on creating lifelong customers rather than generating immediate sales. Promotional spots on advertisement-supported (Nickelodeon) and sponsor-supported (Public Broadcasting Service and Disney) networks took similar approaches and used similar appeals, seeming to promote the equation that food equals fun and happiness. **Pediatrics** 2006;118:1478–1485.