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Inhibition and attention in adolescents with nonmanic mood disorders and a high risk for developing mania

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Abstract

This study examines psychomotor inhibition, sustained attention, and inhibitory attentional control in adolescents (ages 12–18 years) with a nonmanic mood disorder and with a first-degree relative with bipolar I disorder (MD, $N = 20$) and demographically matched healthy children of parents without any psychiatric disorder (HC, $N = 13$). MD participants showed abnormal performance in stop signal reaction time and latency ($d = 1.28$ and 1.64, respectively), sustained attention response bias ($d = 0.75$), and color naming speed ($d = 0.88$). The results indicate that MD participants exhibit psychomotor disinhibition, marginal cognitive slowing and cautious response biases, but no formal deficits in sustained or selective attention.

Keywords

Disinhibition; Attention; High risk; Bipolar disorder; Depression; Neurocognition

INTRODUCTION

Across the lifespan, individuals with bipolar disorder exhibit impaired disinhibition and attention. Specifically, dysfunction in inhibition or attention has been reported during manic, hypomanic, depressed, and euthymic mood states (Martinez-Aran et al., 2004), and in medicated and unmedicated children, adolescents, and adults with bipolar disorder (Pavuluri et al., 2006), even after controlling for co-occurring attention-deficit hyperactivity disorder (ADHD; Dickstein et al., 2004; Doyle et al., 2005; Leibenluft et al., 2007; Rucklidge, 2006). However, few studies have examined dysfunction in inhibition or attention in offspring of bipolar parents, and those that have are somewhat contradictory (Duffy, Grof, Kutcher, Robertson, & Alda, 2001; Klimes-Dougan, Ronsaville, Wiggs, & Martinez, 2006; McDonough-Ryan et al., 2002; Meyer et al., 2004). One way to address such contradictions is to examine already symptomatic offspring of bipolar parents who do not yet fully meet DSM-IV-TR (*Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition, Text*

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Revision; American Psychiatric Association, 2000) defined criteria for bipolar I disorder. The underlying assumption is that if disinhibition and inattention are trait-related deficits of bipolar disorder, they should be present in this ultra-high-risk sample.

With these considerations in mind, we compared inhibition and attention in a sample of adolescents with nonmanic mood disorders and a familial risk for developing bipolar I disorder and demographically matched and psychiatrically healthy offspring of healthy parents. Adolescents with nonmanic mood disorders and a family history of bipolar disorder are at ultra high risk for developing full blown mania and might exhibit trait-related neurocognitive deficits that precede the onset of mania. Based on recent evidence that the underlying neurophysiology of disinhibition and inattention may serve as cognitive vulnerability indicators that predispose adolescents to bipolar disorder (Klimes-Dougan et al., 2006; McDonough-Ryan et al., 2002; Zalla et al., 2004), we hypothesized that offspring of bipolar parents with nonmanic mood symptoms would exhibit abnormalities in motor inhibition, sustained attention, and inhibitory attentional control. In contrast to prior studies, this study characterizes specific components of inhibition and attention in participants at familial risk for bipolar I disorder who were unmedicated at the time of neuropsychological assessment.

METHOD

This study was approved by the University of Cincinnati (UC; Cincinnati, Ohio) Institutional Review Board. All study participants and their parents provided written assent and consent, respectively, prior to participating in study procedures.

Participants

Adolescents of ages 12–18 years with a nonmanic mood disorder who had at least one first-degree relative (parent or sibling) with bipolar I disorder were recruited (MD, $N = 20$). A comparison group of healthy children of parents free of DSM-IV-TR Axis I psychopathology was also recruited (HC group, $N=13$) from advertisements and schools in the communities from which the MD participants resided. All adolescents were evaluated using the Washington University in St. Louis Kiddie-Schedule for Affective Disorders and Schizophrenia (WASH-U KSADS; Geller, Zimmerman, Williams, & Frazier, 1996), administered separately to parents and adolescents, by raters blind to diagnostic group, with established symptom and diagnostic reliability (kappa > 0.9). All diagnoses were determined by a consensus conference attended by a child and adolescent psychiatrist (M.P.D.) and the WASH-U KSADS interviewer, after both parent and child interviews were completed. A diagnosis of bipolar disorder–not otherwise specified (BP-NOS) was made if the participant was missing only one DSM-IV-TR criterion for mania or had all criteria but did not meet duration for a DSM-IV-TR-defined manic episode (Birmaher et al., 2007; Del-Bello, Adler, Whitsel, Stanford, & Strakowski, 2007). Mood symptom severity in MD participants was assessed using the Young Mania Rating Scale (YMRS; Young, Biggs, Ziegler, & Meyer, 1978) and the Children's Depression Rating Scale–Revised Version (CDRS–R; Poznanski, Cook, & Carroll, 1979) by raters with established symptom reliabilities (intra-class correlation coefficient > 0.9). Parent or sibling diagnosis of bipolar disorder was confirmed using the Structured Clinical Interview for DSM-IV–Patient Version (SCID-P, if >18 years old; First, Spitzer, Gibbon, & Williams, 1996) or the WASH-U KSADS (if <18 years old), by raters who were blind to diagnostic group and who had established diagnostic interrater reliability (kappa > 0.9).

Participants were excluded from the HC group by the presence of a lifetime diagnosis of any DSM-IV-TR Axis I disorder in themselves, their parents, or any first-degree relative of their parents. Exclusion criteria for both groups included pregnancy or lactation, hospitalization

for a psychiatric disorder, lifetime substance (other than nicotine) use disorder, and an unstable medical or neurological illness as determined by a study physician. None of the participants were taking medication at the time of the neuropsychological assessments (DelBello, Adler, Whitsel, Stanford, & Strakowski, 2007). Fluoxetine was discontinued at least 28 days prior, antidepressants, anticonvulsants, antipsychotics, and atomoxetine were discontinued at least 7 days prior, and psychostimulants were discontinued 48 hours prior to testing for participants previously taking these medications.

Cognitive assessment

All participants were administered the Wechsler Abbreviated Scale of Intelligence (WASI; Psychological Corporation, 1999) to assess intellectual functioning. Participants performed three neurocognitive tasks: a Stop-Signal Task (SST; Logan, Schachar, & Tannock, 1997), Conners's Continuous Performance Test (CPT; Conners, 1995), and the Delis–Kaplan Executive Function System Color–Word Interference Test (CWIT; Delis, Kaplan, & Kramer, 2001), to evaluate possible abnormalities in psychomotor inhibition, sustained attention, and inhibitory attentional control, respectively. Tasks were administered by trained psychometricians who were blind to subject group.

The SST is a computerized measure that assesses psychomotor inhibition. Adapted from Logan (Logan et al., 1997) and Nigg (1999), this 20-minute task consists of one of two letters (X or O), presented centrally, and participants must indicate which letter appears by pressing one of two keys as quickly and accurately as possible using their dominant index or middle finger. Additionally, participants are instructed not to respond on trials in which the letter is followed by a brief auditory tone (stop signal). They are told that they should not wait for the tone and that it will not be possible to stop every time they hear the tone. The latency between the onset of the go signal (X or O) and the stop signal (tone) is automatically varied based on the accuracy of performance on the previous stop trial (with longer latencies making it increasingly difficult to stop successfully); this variation provides information about the amount of time that participants require to make a successful stop response. Following two sets of three practice trials (Logan et al., 1997; Nigg, 1999), participants complete four blocks of 64 trials (with 2-minute rest periods between blocks) for which 25% of the go signals are followed by a stop signal. The stop signal latency is initially set to 250 ms and then either increases or decreases by 50 ms on the next trial, depending on whether the participant did or did not stop successfully, respectively. Longer latencies represent better performance (i.e., better ability to inhibit a motor response longer after response selection and/or initiation), and the stop signal latency is automatically adjusted so that participants inhibit 50% of the time by task conclusion. The primary measure of interest is stop signal reaction time, which is calculated as the difference between mean go reaction times (mean reaction times to the go signal), and the stop signal latency (the number of ms between the onset of the go and stop signals at task conclusion). Stop signal reaction times have been shown to increase with impulsivity (Logan et al., 1997) and represent a failure to inhibit a motor response when a stop signal is presented.

The Conners's CPT is a computerized test of vigilance or sustained attention (Conners, 1995). Participants are instructed to press a key when a letter other than "X" appeared on the screen and not to press when an "X" appeared on the screen (10% probability). Each of the 360 stimuli appear for 250 ms with a 2,000-ms average interstimulus interval, resulting in a 13.5-min vigil. The CPT measures of interest are signal detection indices including attentiveness (d'), which measures the ability to discriminate between targets and nontargets, response bias (β), which measures tendencies towards either a low-frequency cautious response style or high-frequency impulsive responding, and psychomotor processing speed and efficiency for correct responses through hit reaction time (hit RT).

The CWIT is a Stroop-like task composed of four conditions: color naming, word reading, inhibition, and inhibition/switching. The first three conditions are comparable to most Stroop tasks. Administration and scoring considerations are provided in the examiner's manual (Delis et al., 2001). In the final, more novel inhibition/switching condition, 50 color words (i.e., red, blue, or green) are printed in five rows of 10 stimuli each on a single page in an incongruent ink color (e.g., red printed in blue ink), with half of the stimuli appearing in a box. Participants are instructed to switch between reading the word if it appeared in a box and naming the ink color if it did not appear in a box. The measure of interest for all CWIT conditions is the total number of seconds required to complete the page regardless of errors, with faster times representing better performance (i.e., better ability to switch between conceptual categories and to inhibit the prepotent reading response).

Data analysis

Wilcoxon rank sum and Fisher's exact tests were used to compare demographic variables, and *t* tests were used to compare neurocognitive performance between groups. Post hoc analyses of covariance (ANCOVAs) were performed to examine group comparisons in neurocognitive measures after adjusting for IQ scores. Effect size, Cohen's *d*, was calculated for neurocognitive measures (Cohen, 1977). Spearman correlations were performed to assess relationships between Full Scale IQ scores and neurocognitive performance, as well as between neurocognitive performance and YMRS and CDRS–R scores. To assess whether co-occurring ADHD or anxiety contributed to any identified group differences in neurocognitive performance, post hoc ANCOVAs on all IQ-adjusted measures were performed after removal of MD participants with a diagnosis of ADHD ($n = 7$) or an anxiety disorder ($n = 4$) . Due to a reduction in sample size for these subgroup analyses, effect sizes were calculated for differences between MD and HC groups across all neurocognitive measures, in the presence and absence of co-occurring ADHD or anxiety. All statistical analyses were performed using Statistical Analysis System software, Version 9.1 (SAS Institute, Cary, NC).

RESULTS

Demographic and clinical characteristics of MD and HC groups are listed in Table 1. The MD group had significantly lower average Verbal ($p = .008$) and Full Scale IQ scores ($p = .03$) than did the HC group; however, both groups were at or above average relative to the normative sample for this test.

Table 2 summarizes group differences in neurocognitive functioning in the MD and HC groups after adjusting for Full Scale IQ. The MD group exhibited shorter stop signal latency, $F(1, 19) = 15.93$, $p = .0008$, $d = -1.64$, and longer stop signal reaction time, $F(1, 19) = 9.65$, $p = .006$, $d = 1.28$, than did the HC group. The MD group had faster mean go reaction times in the SST task than those of the HC group, $F(1, 19) = 11.9$, $p = .003$, $d = 1.42$. The MD group showed a trend for abnormal CPT performance (higher response bias scores), $F(1, 18) = 3.44$, $p = .08$, $d = 0.75$, in the presence of similar reaction times and marginal deficits in cognitive processing speed (slower CWIT color naming), $F(1, 16) = 4.51$, $p = .05$, $d = 0.88$, compared with the HC group.

Submeasures within the CWIT, CPT, and SST tasks were highly correlated ($|r| \leq .86$, $p \leq .0001$), and strong correlations were observed between SST and CPT as well as CPT and CWIT subscales ($|r| \leq .56$, $p \leq .003$). MD participants with higher Full Scale IQ scores demonstrated higher scores on certain CWIT measures (word reading, $r = -.50$, $p < .007$; inhibition, $r = -.48$, $p < .012$; and inhibition/switching $r = -.59$, $p < .0009$). No statistically significant correlations were found between symptom scores and performance on attentional tasks (YMRS, $|r| \leq .27$, $p \leq .2$; CDRS, $|r| \leq .25$, $p \leq .4$).

A total of 7 (35%) of the MD participants were diagnosed with ADHD. After removing MD participants with co-occurring ADHD, MD group impairments in psychomotor inhibition remained statistically significant: shorter stop signal latency, mean = 283 ms, $SD = 196$, versus mean = 495 ms, $SD = 138$ ms; $F(1, 14) = 6.98$, $p = .02$, $d = -1.24$; and longer stop signal reaction time, mean = 163 ms, $SD = 105$, versus mean = 68 ms, $SD = 77$; $F(1, 14) = 4.57$, $p = .05$, $d = 1.03$. Group differences in IQ-adjusted cognitive-processing speed became more significant (slower CWIT color naming, mean = 39 s, $SD = 11$, vs. mean = 27 s, $SD = 6.7$); $F(1, 11) = 9.52$, $p = .01$, $d = 1.43$; but CPT performance became less significant (higher response bias scores, mean = 0.33, $SD = 0.33$, vs. mean = 0.14, $SD = 0.2$; $F(1, 13) = 2.73$, $p = .12$, $d = 0.75$), after removing MD participants with ADHD. Effect sizes for group differences were similar for all comparisons with and without the ADHD participants, with the exception of increased effect sizes identified for IQ-adjusted CWIT raw inhibition scores from small to large ($d = 0.43$ to 0.80) and inhibition/switching scores from small to medium ($d = 0.39$ to 0.60).

A total of 4 (20%) of the MD participants were diagnosed with a co-occurring anxiety disorder. Removing participants with co-occurring anxiety did not change the effect sizes for the neuropsychological measures obtained.

DISCUSSION

The results of this preliminary study indicate dysfunction in certain domains of inhibition and attention in adolescents with nonmanic mood disorders and a familial risk for developing bipolar I disorder. Specifically, we report medium to large effects for group differences between MD and HC participants in psychomotor inhibition, sustained attention, and inhibitory attentional control. Relative to HC participants, MD participants had longer stop signal reaction times (i.e., mean go reaction times minus stop signal latency), which may be associated with impulsivity (Logan et al., 1997). In addition, MD participants had shorter stop signal latencies than HC participants, indicating difficulty inhibiting motor responses unless the stop-signal onset asynchrony was very short. MD participants also demonstrated a relatively more cautious response tendency, for which they attempted to minimize false positive responses on the CPT, and a trend for slower cognitive processing speed on CWIT color naming. Taken together, these patterns are consistent with the view that psychomotor disinhibition may be a trait-related deficit in bipolar disorder but primary measures of sustained attention and inhibitory control of selective attention are not significantly impaired in patients at risk for bipolar disorder (Fleck, Shear, & Strakowski, 2005; Meyer et al., 2004). Furthermore, our results suggest that slower cognitive processing speed and more conservative and cautious responding may represent compensatory mechanisms to overcome psychomotor disinhibition. Correlations between tasks confirm the influence of processing speed and response style on dysfunctional patterns of inhibition.

Our results are consistent with two previous studies of offspring of bipolar parents, which identified spatial and speeded processing abnormalities rather than formal attentional deficits (Duffy et al., 2001; McDonough-Ryan et al., 2002). In a cohort of 8- to 12-year-old children of parents with bipolar I disorder, McDonough-Ryan and colleagues found discrepancies between verbal and performance intelligence quotients as compared to children of healthy parents, suggesting deficiencies associated with spatial processing and speeded psychomotor integration (McDonough-Ryan et al., 2002). However, in contrast to their study, our study only sampled high-risk offspring and siblings who met criteria for active nonbipolar I mood disorders and were from an older age cohort. Another study found that psychiatrically ill 10- to 25-year-old offspring of bipolar parents were perceived as having greater inattention than those without a lifetime psychiatric illness including affective

disorders; however, they exhibited no objective evidence of attentional dysfunction on the Talland Letter Cancellation Test (Duffy et al., 2001).

Formal deficits in attention and executive functioning have been identified in other high-risk samples (Klimes-Dougan et al., 2006; Meyer et al., 2004). One study (Klimes-Dougan et al., 2006) found that offspring of mothers with bipolar disorder showed deficits in sustained attention and aspects of executive functioning. Although our study indirectly assessed executive functioning with CWIT Inhibition and Inhibition/Switching, these are also measures of selective attention. Additionally, a naturalistic study of young adult offspring of mothers with a mood disorder showed that 67% of those who later developed bipolar disorder had attention deficits and executive dysfunction during adolescence, although in this study mood symptoms were absent in the offspring at the time of their assessment (Meyer et al., 2004). Differences among studies in sample sizes, demographics, and clinical status may have contributed to differences in findings.

There are several limitations to consider when interpreting our results. First, correlations among certain neurocognitive tasks combined with a small sample size may have limited the power to detect some subgroup differences and increase the risk of type II error. Second, the HC group had higher Full Scale IQ scores than the MD group, suggesting that IQ may be confounding attentional performance. However, IQ is often underestimated in the presence of clinically significant mood symptoms, and even in this context the MD group scored at the population mean, and adjusting for IQ did not change our results. Moreover, there were no significant correlations between IQ and most of the performance measures, making it less likely to contribute significantly to group differences found. Third, although participants were excluded by the presence of bipolar I disorder, there was no exclusion of participants based on the presence of other psychopathology that, therefore, may be affecting our results. Most relevant to this study is the presence of a diagnosis of ADHD or anxiety. Group differences in attentional performance were attenuated on certain parameters and accentuated in others with removal of MD participants with co-occurring ADHD. However, replication with larger sample sizes are needed to determine whether the presence of ADHD is mediating the attentional dysfunction characterized in this study.

CONCLUSION

This study demonstrates that unmedicated adolescents with nonmanic mood disorders and a familial risk for bipolar I disorder exhibit significant psychomotor disinhibition and marginal levels of cognitive slowing and cautious response biases in the presence of mood symptoms. However, traditional measures of selective (CWIT Inhibition and Inhibition/Switching) and sustained attention (CPT d' and hit RT) remained intact. Therefore, patients at the greatest relative risk for developing mania did not exhibit characteristic cognitive deficits of bipolar disorder, calling into question the assumption that disinhibition and inattention are trait-related deficits. This pattern indicates, instead, that an inability to inhibit motor responses once they have begun may be a trait deficit of bipolar disorder. Importantly, MD patients, despite a possible cognitive vulnerability to attention deficits, showed signs of compensating by slowing performance and adopting a cautious response style, thereby trading processing inefficiency for attentional performance quality. Further studies of attentional dysfunction, as well as other neurocognitive domains in larger samples of at-risk individuals are needed. Furthermore, additional investigations examining the differential contributions of nonspecific constructs such as psychomotor processing speed, processing efficiency, and impulsivity on cognitive functioning in individuals with and at high risk for bipolar disorder are-warranted (Fleck et al., 2005; Wilder-Willis et al., 2001; Swann, Pazzaglia, Nicholls, Dougherty, & Moeller, 2003). Prospective assessment of

neurocognitive functioning over time is also warranted and may identify predictors of illness course and treatment response in this high-risk population.

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TABLE 1

Demographic, clinical, and IQ characteristics of MD and HC groups

Variable	MD (N=20)	HC (N=13)
Age, mean (*SD*), years	15 (2)	15 (1)
Sex, *N* (%) female	8 (40)	5 (38)
Ethnicity, *N* (%) White	18 (90)	9 (69)
DSM-IV-TR Axis I Diagnosis, *N* (%)		N/A
Mood disorders		
Bipolar disorder–NOS	11 (55)	
Bipolar II disorder	3 (15)	
Cyclothymia	2 (10)	
Dysthymia	3 (15)	
Major depressive disorder	1 (5)	
Co-occurring disorders		
ADHD	7 (35)	
Anxiety disorder	4 (20)	
Oppositional defiant disorder	5 (25)	
Conduct disorder	3 (15)	
YMRS, mean (*SD*)	18.1 (5.5)	N/A
CDRS–R, mean (*SD*)	38.2 (9.8)	N/A
WASI		
Full Scale IQ[a]	100 (12)	111 (10)
Verbal Scale IQ[b]	99 (13)	114 (9)

Note. MD=at risk with nonmanic mood disorder. HC=healthy control. *d*=effect size. *DSM-IV-TR=Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition-Text Revision.* ADHD=attention-deficit hyperactivity disorder. YMRS=Young Mania Rating Scale. CDRS–R=Child Depression Rating Scale–Revised. WASI = Wechsler Abbreviated Scale of Intelligence. IQ=intelligence quotient. NOS=not otherwise specified.

[a] $t(21)=2.31$, $p=.03$, $d=1.00$.

[b] $t(21) = 3.05$, $p = .008$, $d = 1.34$.

TABLE 2

Full Scale IQ-adjusted mean neurocognitive performance in MD versus HC groups

Neurocognitive test	MD (N ≤ 20)	HC (N ≤ 13)	p	d
SST				
Stop Signal Latency (ms)[a]	223 (190)	506 (153)	0.0008	1.64
Stop Signal RT (ms)[b]	225 (133)	71 (107)	0.006	1.28
Go RT (ms)[b]	448 (101)	577 (81)	0.003	1.42
CPT				
d' [a]	1.54 (1.3)	2.08 (1.01)	0.26	0.47
β[c]	0.32 (0.3)	0.13 (0.2)	0.08	0.75
Hit RT (ms)[b]	332 (85)	321 (67)	0.73	0.14
CWIT				
Raw, Color Naming Score (s)[b]	35 (9)	27 (7)	0.05	0.88
Raw, Word Reading Score (s)[b]	25 (10)	26 (8)	0.89	0.06
Raw, Inhibition Score (s)[b]	65 (21)	57 (16)	0.31	0.43
Raw, Inhibition/Switching Score (s)[b]	73 (21)	66 (16)	0.37	0.39

Note. Standard deviations in parentheses. MD=at risk with nonmanic mood disorder. HC=healthy control. *d*=effect size. WASI=Wechsler Abbreviated Scale of Intelligence. IQ=intelligence quotient. CWIT=Color–Word Interference Test. CPT=Continuous Performance Task. d'=attentiveness. β=response bias index. RT=reaction time. SST=Stop Signal Task.

[a] Higher scores=better performance.

[b] Lower scores = better performance.

[c] Lower scores = a relatively more impulsive response style.