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Characterizing Impulsivity in Mania

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Abstract

Objective—To determine whether specific aspects of impulsivity (response disinhibition, inability to delay gratification, inattention) differ between healthy and bipolar manic subjects, and whether these aspects of impulsivity were associated with each other and severity of affective symptoms.

Methods—Performance of 70 bipolar I manic or mixed patients was compared to that of 34 healthy subjects on three tasks specifically designed to study response inhibition, ability to delay gratification, and attention; namely a stop signal task, a delayed reward task, and a continuous performance task respectively. Correlations among tasks and with symptom ratings were also performed.

Results—Bipolar subjects demonstrated significant deficits on all three tasks as compared to healthy subjects. Performance on the three tasks was largely independent. Task performance was not significantly associated with the severity of affective symptom ratings. However, measures of response inhibition and attention were sensitive to medication effects. Differences in the delayed reward task were independent of medication effects or symptom ratings. During the delayed reward task, although bipolar patients made their choices more slowly than healthy subjects, they were significantly more likely to choose a smaller, but more quickly obtained reward. Moreover performance on this task was not associated with performance on the other impulsivity measures. Manic patients showed more impulsive responding than mixed patients.

Conclusions—Bipolar I manic patients demonstrate deficits on tests of various aspects of impulsivity as compared to healthy subjects. Some of these differences between groups may be mediated by medication effects. Findings suggested that inability to delay gratification (i.e., delayed reward task) was not simply a result of the speed of decision making or inattention, but rather that it reflected differences between bipolar and healthy subjects in the valuation of reward relative to delay.

Keywords

Bipolar disorder; impulsivity; delayed reward; inattention; response inhibition

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BACKGROUND

Although impulsivity occurs in many psychiatric conditions, impulsive behaviors appear to be particularly common during the course of bipolar disorder (1–8). However, impulsivity is not a singular behavior, but rather a multi-faceted construct. Barratt and colleagues suggested that impulsivity consists of three independent behavioral factors, based on responses to the Barratt Impulsiveness Scale (9,10). First, Non-planning Impulsiveness refers to a present orientation or failure to consider the future. Second, Motor Impulsiveness refers to acting without thinking. Third, Attentional Impulsiveness refers to a tendency to shift attention quickly, leading to inappropriately rapid decisions. Dickman (11) identified three similar dimensions of impulsivity –reflection, disinhibition, and attentional – based upon an extensive review of human studies. Together, this work plus that of others (e.g., 12,13) suggests three aspects of impulsivity: 1) an inability to delay gratification for greater benefit, i.e., an inability to delay response for an immediate reward in order to gain a larger reward or prevent a negative consequence; 2) disinhibition, i.e., an inability to inhibit a prepotent response in favor of a better or correct response; and 3) inattention, i.e., an inability to maintain attention to complete a particular task rather than being distracted to an alternative task. These three behavioral components of impulsivity appear to be independent, based upon animal models, and they are mediated by semi-independent, although probably related, neural systems (12).

Mania, which is the defining phase of bipolar disorder, may represent the behavioral extreme of impulsivity (2). Although there is an extensive literature of continuous performance task (CPT) studies in mania (14), these only address one aspect of impulsivity, namely attention. Consequently, it is largely unknown whether the impulsive behaviors of mania span all three aspects of impulsivity or instead simply reflect attentional deficits or are merely an extension of mood symptoms. Clarifying these relationships could potentially inform neurophysiological models of bipolar disorder as well as suggest novel behavioral interventions.

With these considerations in mind, the aims of this study were to determine whether measures of inability to delay gratification, disinhibition, and inattention: 1) significantly differed between bipolar manic and healthy subjects; 2) were independent from each other in these populations; and 3) were associated with the severity of affective symptoms. To achieve these aims, we administered tasks designed to measure reward delay, inhibition, and attention to bipolar patients during an acute manic episode and demographically similar healthy subjects. Based on work described previously (1–8,12,14), we predicted that: 1) bipolar patients would exhibit significantly impaired performance on all three tasks compared with healthy subjects; and 2) performance among the three tasks would not be significantly correlated. Given the mixed literature and limited experience in mania with some of these tasks, we could not predict associations between symptoms and performance, so this aim should be viewed as exploratory.

METHODS

Subjects

Seventy patients with DSM-IV bipolar I disorder were recruited from the inpatient units of University Hospital and outpatient clinics at the University of Cincinnati Academic Health Center. Patients were required to meet DSM-IV criteria for bipolar disorder, currently in an acute manic or mixed episode. Additionally, patients had a Young Mania Rating Scale (YMRS; 16) $\geq$ 20. Bipolar patients were excluded if the manic/mixed episode was secondary to drug or alcohol intoxication or withdrawal, or if it was not possible to determine from evaluation whether the bipolar illness was secondary to a substance use disorder based on DSM-IV criteria. They were not excluded by other psychiatric comorbidities. Healthy subjects were recruited by advertisement and word-of-mouth from the same communities as the bipolar subjects. Healthy subjects were required to exhibit no history of any Axis I psychiatric disorder or any

history of affective or psychotic disorders in first degree relatives. Both subject groups were limited to adults 18 to 50 years old in order to minimize age confounds on cognitive measures. Subjects were excluded if they had a medical or neurological disorder that might potentially impact ability to perform the cognitive tasks; by an estimated IQ score <85; or if they were exhibiting symptoms or signs of drug or alcohol intoxication or withdrawal. All subjects signed written informed consent after procedures had been explained in full. This study was approved by the Institutional Review Board of the University of Cincinnati.

Clinical assessments

A DSM-IV diagnosis of bipolar I disorder, manic or mixed in patients, or no Axis I diagnosis in healthy subjects, was established using the Structured Clinical Interview for DSM-IV Axis I Disorders, Patient versions (SCID-I/P), performed by an extensively trained interviewer (17). Additionally, we identified the lifetime presence of Attention Deficit Hyperactivity Disorder (ADHD) using the SCID-I/P module. Diagnoses of current or past substance use disorders were also determined using the SCID-I/P. The investigators have established high inter-rater reliability among all interviewers ($\kappa > 0.90$). Diagnoses were then verified in a best estimate meeting of the investigators. Finally, age at onset of bipolar disorder was estimated from SCID-I/P based on the age at which patients developed their first affective episode. Duration of illness was then calculated as current age minus age at onset.

Ratings of psychiatric symptoms were obtained at the time of the index assessment. As noted, the YMRS was used to assess manic symptoms. Depressive symptoms were assessed using the Montgomery-Asberg Depression Rating Scale (MADRS) (18). The investigators have established high inter-rater reliability with these ratings scales (intraclass correlation coefficient, ICC>0.70 for total scores). Additionally, the Addiction Severity Index (ASI; 19) was completed for each subject to document specific drug and alcohol use during the previous month. In these samples, rates of substance use disorders other than alcohol and cannabis were too infrequent to be evaluated statistically.

In addition to symptom and diagnostic assessments, we obtained general measures of premorbid intellectual function (IQ) using the American Modification of the National Adult Reading Test (ANART; 20). The ANART provides an estimate of premorbid IQ that is known to be resilient to the influence of psychiatric symptoms in patients with schizophrenia (21) and mood state in those with bipolar disorder (41). Healthy subjects received a more comprehensive IQ assessment using the four-subtest version of the Wechsler Abbreviated Scale of Intelligence (WASI; 22).

Demographic information was collected through direct interview and review of the medical records. Medications being taken at the time of the testing were recorded and were categorized into general classes including: lithium, anti-epileptics (AEDs), atypical antipsychotics (AAPs) and benzodiazepines (BEN). Other medication classes were infrequently prescribed. Patients were tested more than 8 hours after receiving benzodiazepines.

Impulsivity assessments

The impulsivity tasks were completed in a quiet, darkened room using a Macintosh PowerMac G4 computer running OS 9.0.4. These tasks were programmed in PsychScope (23). Subjects were seated with their eyes approximately two feet from a 19” computer monitor, and they responded with their dominant hand using a mouse or button box attached to the computer.

Disinhibition

Disinhibition was assessed using the Logan Stop-Signal Task (SST; 24–28). The SST has been well validated (24–28). Subjects were presented a letter (X or O) at one second intervals, and

they responded by pressing a button corresponding to the displayed letter. During these trials, 25% of the 'go' signals were followed by an auditory 'stop' signal. The 'stop signal latency' was initially set at 250 msec (i.e., the tone followed the presentation of the letter by 250 msec), and then was either increased or decreased by 50 msec on the next stop trial, depending on whether the participant did or did not stop successfully, respectively. Using this iterative procedure, the proportion of successful stop responses becomes fixed at approximately 50% for each participant.

Subjects were first given two sets of 32 practice trials to become familiarized with the test procedures. Following the practice trials, participants completed four blocks of 64 trials (with 2-minute rest periods between blocks). Blocks were combined for analyses. The primary measure of interest was the "stop signal reaction time (SSRT)," calculated as the mean 'go' response time during trials with no stop signal minus the mean 'stop' signal latency when subjects successfully inhibited a response. Secondary measures of interest were the mean 'go' reaction time and mean 'stop' latency time. Subject performances were excluded for insufficient effort if less than 50% of the 'go' signals elicited a response and there were not at least two successful 'stops'; these criteria were necessary for the task to converge appropriately while being fairly liberal to ensure full representation of response patterns expected from subjects. A similar rationale was used for the other impulsivity tasks, as will be discussed with each. Based on these criteria, 30 (88%) of the healthy subjects and 49 (70%) of the bipolar subjects successfully performed this task (χ^2=4.2, df=1, p=.04) and were included in SST analyses. Because of the relatively high numbers of bipolar subjects who could not complete the SST, demographic, clinical and other task variables listed in Tables 1 and 2 were contrasted between those who did and did not successfully complete the SST. Patients who did not complete the SST were less educated (12 vs. 14 years; p<.02), and were less likely to use alcohol to intoxication in the previous month (0.6 vs. 2.0 days; p<.04) than completers; otherwise there were no significant differences on any other variable (p>.12 in all cases).

Inability to delay gratification

A delayed reward task (DRT) was administered to assess subjects' ability to delay gratification. This task is based on an adjusting reward schedule paradigm similar to those that have been used in animal studies (42) as modified for use in humans by Cherek et al (29). Several recent studies support the task's validity (29–31). During the DRT, subjects were presented with two response options: 1) the letter 'A', which was the impulsive response, and 2) the letter 'B', which was the self-control response. Each letter was the same size presented in right and left mirror locations of the computer screen. Subjects used a computer mouse to select either A or B for each trial. When A was selected, the B was immediately removed from the screen, and after a fixed 5 second delay, the A started to flash. The subject was instructed to respond using the right mouse button while the letter was flashing in order to receive 5 cents added to a reward counter. If the subject selected B, then the A was removed and after a variable delay, the B began to flash. Selecting the flashing B added a 15-cent reward to the counter. Because the number of trials was fixed, the maximal amount of money would be earned by always selecting response B. However, the length of the delay for response B was manipulated. Specifically, the initial delay for B was set at 15 seconds. Each time B was chosen, the delay for the next B choice was increased by 2 seconds. Each time A was chosen, the delay for the next B was decreased by 2 seconds to a minimum of 7 seconds, so that it was always greater than the delay for A. The delay for the A response was fixed at 5 seconds. Ten training trials preceded the actual session to familiarize subjects with the procedures and apparatus of the task. Then, a total of 25 trials were completed at each session. Trials were separated by two seconds. The subjects controlled the rate of trial presentation, since one letter did not disappear until after the other was selected, and the trial did not re-set until the second button push while the selected letter was flashing. The primary measure of interest was the percent of impulsive ('A')

responses; reaction time was also analyzed. Subject performances were excluded from analyses for insufficient effort if the task was not completed. All of the healthy subjects and 59 (84%) of the bipolar subjects successfully completed the task (χ^2=6.0, df=1, p=.01) and were included in analyses of the DRT.

Inattention

Inattention was measured using the degraded stimulus version of the CPT (DSCPT; 32). The DSCPT has been widely used to study attentional processing in healthy and psychiatric populations, including previous studies in bipolar disorder (15,33,34). In this task, subjects were presented a random series of numbers from 0 to 9. Each number was displayed for 35 msec, and numbers were presented at a rate of one per second. The numbers were perceptually degraded (i.e., blurred) to increase the difficulty (32). Subjects responded to the target stimulus (the number 0) by pressing a button. A total of 480 trials were presented, including 25% targets, divided into six successive blocks presented over 8 minutes. Prior to the actual session, subjects were given a brief training session of one block (80 numbers) to acquaint them with procedures. One measure of interest was sensitivity (A'), which is a nonparametric measure analogous to discriminability (d') and refers to the ability to discriminate between signal and noise. It is calculated as: A'=0.5+(y-x)(1+y-x)/4y(1-x), in which x is the probability of a false alarm and y is the probability of a hit (33). Additionally, the nonparametric version of response bias (B") was calculated. Response bias represents variables other than sensitivity that may influence performance, such as fatigue or motivation (33), and is calculated by: B"=y(1-y)-x(1-x)/y(1-y)+x(1-x). A smaller B" represents more impulsive responding. Finally, reaction time was calculated (34). Subjects failing to respond to at least two targets were excluded from analysis for insufficient effort. All of the healthy subjects and 68 (97%) of the bipolar subjects successfully performed this task (χ^2=1.0, df=1, p=.31) and were included in analyses of the DSCPT.

BIS-11

The Barratt Impulsiveness Scale, version 11 (9,10) was completed by each subject at the time of cognitive testing. The variables of interest were the 2nd order factors: Attentional Impulsiveness, Motor Impulsiveness and Nonplanning Impulsiveness. One healthy (3%) and four bipolar (6%; χ^2=0.5, df=1, p=.54) subjects did not complete the BIS-11.

Statistical Analyses

All analyses were performed using the Statistical Analysis System (SAS) for the Personal Computer (SAS Institute, Cary, NC 2006). Simple statistics (e.g., t-tests, chi-square tests) were used to contrast groups on demographic and clinical variables. Three separate analyses were performed for each of the three aspects of impulsivity. Specifically, for inability to delay gratification, Multivariate Analysis of Variance (MANOVA) was used to contrast the two groups on DRT measures of reaction time and fraction of impulsive responses. MANOVA was also used to contrast attentional measures between groups; the model included the DSCPT measures of sensitivity (A'), bias (B"), and reaction time. For disinhibition, the stop-signal measure of SSRT is a combination of the other two variables of interest (namely, mean 'go' time, and mean 'stop' latency time); consequently, MANOVA was not appropriate in this instance. Instead a one-way ANOVA for SSRT to examine group effects was performed. Significant differences between groups were defined as p<.05 for these three planned comparisons. If these initial analyses were significant, then individual variable's contributions to the overall group difference were identified by calculating effect sizes, *f*, from one-way ANOVA F-statistics in which *f*= square root of (F/N). Cohen has defined *f*=.1 as a small effect size, *f*=.25 as a medium effect size and *f*>.4 as a large effect size (35). The same general statistical approach was used to compare the BIS-11 factors between groups. To determine

whether the three tasks were measuring independent behaviors, correlations among the primary measures (SSRT from the SST, fraction of impulsive responses from the DRT, and A' from the DSCPT) were assessed using Pearson's r. Finally, associations among symptom measures (YMRS, MADRS), BIS-11 factors, and the primary impulsivity task measures were calculated also using Pearson's r. Other analyses were performed as needed for completeness. Of note, there were differential missing data between groups since the bipolar subjects were less likely to meet the liberal task requirements for completion. Rather than invoke more complex statistical procedures, because the missing data typically represented inability to perform the task we chose a more conservative approach of only analyzing subjects successfully performing the task.

RESULTS

Demographic and clinical characteristics

The demographic and clinical characteristics of the subjects are listed in Table 1. The groups were generally well matched on demographic variables. Although years of education significantly differed between groups (t=2.7, df=102, p=.007), the clinical meaningfulness of this two year difference is limited, particularly with the similar IQ scores. Nonetheless, to evaluate the potential impact of education on the measurements, years of education was correlated with the impulsivity measures. No significant associations were observed between any of the impulsivity measures and education ($|r| \leq 0.12$, $p > .2$) or IQ ($|r| < 0.17$, $p > .09$).

By definition, the bipolar patients exhibited significantly greater mania and depression ratings [YMRS (t=27.5, df=102, p<.0001), MADRS (t=8.5, df=102, p<.0001)]. As expected by exclusion criteria in healthy subjects, the bipolar patients exhibited higher rates of ADHD (χ^2=9.2, df=1, p=.002). The bipolar patients also exhibited higher lifetime rates of both alcohol (χ^2=14.1, df=2, p=.0009) and cannabis (χ^2=13.3, df=2, p=.001) use disorders. In particular, the patients were more likely to exhibit cannabis and alcohol dependence (Table 1). Despite differences in lifetime rates of alcohol use disorders, the number of days alcohol was used to intoxication in the month prior to index evaluation was similar between groups (t=0.3, df=96, p=.77). In contrast, the bipolar subjects used cannabis more frequently in the month prior to the index evaluation (t=2.2, df=95, p=.03). Nonetheless, the days of alcohol use to intoxication or any cannabis use in the prior month exhibited no significant correlations with the impulsivity measures ($|r| < 0.14$, $p > .21$).

IMPULSIVITY MEASURES (Table 2)

Group differences in Impulsivity measures—Bipolar patients exhibited significant differences from healthy subjects in SST performance [F(1,77)=4.6, p=.035]; n.b., because the groups demonstrated significantly unequal variances, the SSRT data were square-root transformed prior to analysis. Specifically, the patients exhibited a longer SSRT primarily due to a significantly shorter 'stop' latency.

Bipolar patients exhibited significant differences from healthy subjects in DRT performance [Multivariate F(2,90)=10.0, p=.0001]. The patients exhibited more frequent impulsive responses, although they were slower to respond overall.

Bipolar patients exhibited significant differences from healthy subjects in DSCPT performance [Multivariate F(3,98)=3.3, p=.02]. Although reaction times were similar between groups, the patients exhibited decreased sensitivity (A') and bias (B"); i.e., patients were less able to discriminate between targets and distractors, and they were more impulsive in their responding.

Associations between symptoms and impulsivity task measures—Within the bipolar group, YMRS total scores were not significantly associated with any of the primary impulsivity task measures ($|r|<0.17$, $p>.17$). MADRS total scores similarly were not significantly associated with the primary impulsivity task measures ($|r|<0.23$, $p>.12$). To extend this analysis, we examined correlations among the impulsivity task measures and duration of illness; in this analysis, there were only small nonsignificant associations ($|r|<0.27$, $p>.06$). The presence of psychosis was not significantly associated with any of the impulsivity measures ($z<1.83$; $p>.06$), although several trends were noted. Specifically, DSCPT bias was nonsignificantly lower in psychotic (mn=0.44 SD=0.4) than nonpsychotic (mn=0.64 SD=0.30) patients ($z=1.74$, $p=.08$). DRT reaction time was slower in psychotic (mn=1561 SD=1357 ms) than nonpsychotic (mn=1026 SD=800 ms) patients ($z=1.84$, $p>0.06$). Rates of impulsive responses on the DRT were lower in psychotic (42% SD=24%) than nonpsychotic (59% SD=35%) patients ($z=1.73$, $p>.08$).

Associations between BIS-11 factors and impulsivity task measures—Bipolar patients exhibited significantly greater scores on all three BIS-11 second-order factors (Attentional Impulsiveness, Motor Impulsiveness, Nonplanning Impulsiveness; Table 2) [Multivariate $F(3,95)=14.5$, $p<.0001$]. No significant associations were observed between BIS-11 factors and impulsivity task measures in the bipolar group ($|r|<0.30$, $p>.06$), although trends were noted for: Attentional Impulsiveness with the SSRT ($r=-0.28$, $p=.08$); Nonplanning Impulsiveness with the SSRT ($r=-0.29$, $p<.07$); and Motor Impulsiveness with DRT reaction time ($r=-0.23$, $p=.08$). None of the BIS-11 factors were significantly correlated with YMRS scores ($|r|<0.12$, $p>.34$). Attentional Impulsiveness was significantly associated with MADRS scores ($r=0.38$, $p=.002$), whereas Motor Impulsiveness ($r=0.17$, $p>.17$) and Nonplanning Impulsiveness ($r=0.20$, $p>0.10$) where not.

Mixed vs. manic patients—In an exploratory analysis, we compared performance on the impulsivity tasks between patients in a mixed state (N=20, 29%) to those who were manic (N=50, 71%). These subgroups did not significantly differ in measures from the SST [$F(1,47)=0.38$, $p=.54$] or the DSCPT [Multivariate $F(3,64)=0.33$, $p=.81$]. However, mixed and manic patients significantly differed in DRT performance [Multivariate $F(2,56)=3.70$, $p=.03$], even after controlling for MADRS scores [Multivariate $F(2,55)=6.8$, $p=.002$]. Specifically, the manic patients had higher rates of impulsive responding (49%, SD=29%) than the mixed patients (36%, SD=25%).

Associations among the primary measures—Correlations were calculated among the primary measures for each task. The SSRT from the SST and DSCPT - A' were significantly correlated in both the bipolar ($r=-0.34$, $p=.02$) and healthy ($r=-0.50$, $p=.005$) subjects. Therefore, in order to further explore our prediction that these measures were relatively independent, we performed an ANOVA of the group differences in SSRT controlling for A'. After controlling for A', the group difference observed in SSRT largely persisted [$F(1,74)=3.6$, $p=.06$]. The percent of impulsive responding in the DRT was not significantly associated with either of the other task primary measures ($r<0.18$, $p>.3$).

Effects of lifetime co-occurring syndromes—As noted, the bipolar group exhibited higher lifetime rates of alcohol and cannabis use disorders and ADHD. To evaluate the potential effects of these co-occurring conditions on differences observed in impulsivity task measures, we contrasted bipolar patients with each of these co-occurring disorders to those without using analyses as described for the overall group comparisons.

Patients with alcohol use disorders (N= 32) and those without (N=38) did not significantly differ in measures from the SST [$F(1,47)=0.28$, $p=.60$], DRT [Multivariate $F(2,56)=1.52$, $p=.23$], or the DSCPT [Multivariate $F(3,64)=0.62$, $p=.60$]. Similarly, patients with cannabis use

disorders (N=28) and those without (N=42) did not significantly differ in measures from the SST [F(1,47)=0.66, p=.42], DRT [Multivariate F(2,56)=0.14, p=.87], or the DSCPT [Multivariate F(3,64)=1.25, p=.30]. Finally, patients with a lifetime history of ADHD (N=16) compared to those without (N=56) did not significantly differ in measures from the SST [F (1,46)=0.06, p=.80], DRT [Multivariate F(2,54)=1.06, p=.35], or the DSCPT [Multivariate F (3,61)=1.85, p=.15].

Effects of medications—Potential medication effects were examined following several steps. First, associations were analyzed among the impulsivity measures and the presence or absence of the four classes of medications prescribed (lithium, AED, AAP, BEN) using general linear models (PROC GLM in SAS). Specifically each impulsivity variable was modeled as a function of the four medications (absent/present) in order to control for interactions among medications in patients receiving multiple drugs. In these models only lithium was significantly associated with any of the measures, namely DSCPT A' [F(1,63)=4.0, p=.05] and SSRT [F (1,44)=8.3, p=.006], in which patients on lithium performed the tasks less well (Table 3).

Second, because patients treated with lithium received significantly more total medications than patients not on lithium (Table 3), correlations were calculated between the total number of medications prescribed and impulsivity task performance. DSCPT A' was significantly correlated with the total number of medications prescribed (r=−.34, p=.004); no other impulsivity measure correlated significantly with the number of medications (|r|<0.23, p>.12). After controlling for the total number of medications, the association between the DSCPT A' and lithium no longer persisted [F(1,65)=0.7, p=.4]. In contrast, the association between the SSRT and lithium remained significant even after adjusting for the total number of medications [F(1,46)=5.9, p=.02].

Third, an ANOVA was performed contrasting SSRT for patients on and off of lithium and healthy subjects. The overall model demonstrated a significant group-by-lithium effect [F (2,76)=9.2, p=.0003]. Specifically, Tukey's HSD post-hoc test revealed that SSRT was significantly higher for patients on lithium (mean=257 sd=101 ms) than both patients not receiving lithium (mean=172 sd=67 ms) and healthy subjects (mean=150 sd=38 ms). Finally, contrasts in clinical variables between patients on or off lithium were performed to determine whether lithium might represent a proxy or mediating variable for another clinical effect (e.g., severity of illness; Table 3), in addition to total number of medications prescribed. Patients on or off lithium had similar YMRS and MADRS ratings and demonstrated no differences in rates of co-occurring syndromes or in age at onset. The lithium group had a significantly longer duration of illness. Differences among patients on and off lithium and healthy subjects on the SSRT were re-analyzed using ANCOVA adjusting for this variable and the significant lithium-by-group effects persisted [F(2,75)=5.0, p=.009].

DISCUSSION

This study was designed to examine differences between bipolar manic and healthy subjects in different aspects of impulsivity. Based on our specific aims, three predictions were tested in a sample of patients with mania using computerized delayed reward, response inhibition, and attention tasks. The first predication was supported; namely, that bipolar patients would exhibit significantly impaired performance relative to healthy subjects on all impulsivity tasks. During the delayed reward task, although bipolar patients made their choices more slowly than healthy subjects, they nonetheless were significantly more likely to choose a smaller, but more rapidly obtained reward. Moreover performance on this task was not associated with performance on the attentional measure (DSCPT). These observations suggest that inability to delay gratification is not simply a result of the speed of decision making or inattention, but rather that it reflects differences between bipolar and healthy subjects in the valuation of reward

relative to delay. This finding suggests that a feature of mania may be an alteration in reward processing in addition to inattention. Reward processing in healthy subjects involves medial prefrontal-anterior cingulate-striatal networks that appear to iteratively modulate behavioral responses to potential rewards (37,38). Previous neuroimaging work in bipolar disorder suggests abnormalities within the structures of this network (39). Consequently, differences between bipolar manic and healthy subjects in the delayed reward task in this neurocognitive study may represent behavioral correlates to findings from previous imaging studies. However, in the absence of direct neuroimaging of this task in bipolar disorder, the specific functional neuroanatomic underpinnings of our results cannot be determined.

Notably, mixed state patients performed differently than manic patients on this task, even after controlling for differences in depression severity. This finding, although *post-hoc* and therefore exploratory, suggests that reward processing differences may distinguish among bipolar mood states, independent of actual symptom differences. Additional studies that use this and other reward processing tasks across mood states in the course of bipolar disorder are therefore warranted as they might inform neurocognitive and neurophysiological models of changes among the phases of bipolar illness.

Group differences were modified by medication effects on two impulsivity measures. Specifically, in the response inhibition task (SST), the manic subjects receiving lithium exhibited significantly longer stop-signal reaction times (SSRTs), suggesting that lithium-treated patients had more difficulty inhibiting a prepotent ‘go’ signal than bipolar subjects not receiving lithium or healthy subjects. One interpretation of this finding is that lithium directly impairs performance on the SST, perhaps by inducing psychomotor slowing (36). However, the groups performed comparably on both measures of simple reaction time (‘go’ reaction time on the SST and mean RT on the DSCPT). Consequently, differences between groups were not entirely attributable to generalized psychomotor slowing in the patients on lithium.

Similarly, the number of medications prescribed was inversely correlated with DSCPT (attention) performance. Since many medications used for treating bipolar disorder are sedating, this finding appears intuitive. However, general measures of reaction time were similar between groups, again suggesting these differences were not simply due to psychomotor slowing. Because treatment was naturalistic the specific effects of medications on DSCPT performance could not be determined. Moreover, because no healthy subjects, but nearly all bipolar subjects were taking medications at the time of assessment, the effect of the number of medications on group differences cannot be determined. Regardless, our findings suggest that the bipolar group demonstrated poorer attentional sensitivity to target stimuli and a more liberal response bias, although some of this effect may be mediated by medications.

The second prediction, that these impulsivity measures would be largely independent assessments of behavior, was generally supported. Although significant correlations were observed between measures of attention (DSCPT A’) and inhibition (SSRT), group differences persisted after adjusting for this association, suggesting that both tasks provided independent assessments of aspects of impulsive behavior. The delayed reward task showed no significant or clinically meaningful correlations with the other two tasks.

The results of the third aim, to explore associations between task performances and symptoms, found little association. Previously, Wilder-Willis et al (40) reported CPT impairments in bipolar disorder that were independent of symptoms consistent with this study. In contrast, Sax et al (15) and Swann et al (1) observed changes with clinical state and manic symptoms in CPT measures suggesting an association of attentional impairment with the severity of symptoms. One possibility is that symptom effects on these cognitive measures are relevant until a specific threshold is met, e.g. a full manic syndrome, at which point the cognitive measures become

independent of symptom levels, perhaps due to the restricted range of symptoms in patients meeting criteria for a full manic or mixed syndrome. Alternatively, the measurements obtained in each of these studies differed sufficiently to impact the associations. For example, the attentional task used by Swann et al (1) was more complex than the CPT used in this study. Nonetheless, the findings in the current study suggest that these tasks might identify behaviors that are independent of acute symptom severity (i.e., YMRS $\geq$ 20), but not necessarily mood state (i.e., meeting syndrome criteria). The difference between mixed and manic patients in rates of impulsive responding on the delayed reward task, after adjusting for the severity of depressive symptoms, supports this interpretation. Finally, a number of nonsignificant trends suggested possible weak associations with the presence of psychosis; however, the fraction of nonpsychotic patients was relatively small, and coupled with a limited assessment of psychosis, statistical power for this assessment was limited.

In general, associations were modest between BIS-11 impulsiveness factors and the impulsivity task measures. These results mirror those of Swann et al, who found generally weak or nonsignificant associations between BIS-11 measures and the CPT (1,43). BIS-11 scores were not correlated with mania scores, although it is possible that the narrowed range of manic symptoms precluded significant associations. BIS-11 scores were associated with depression scores. Together, these data suggest that BIS-11 measures assess aspects of impulsiveness generally separate from cognitive tasks; as suggested by Swann et al. these differences may reflect state versus trait characteristics in mania (1,43).

As with all research, this study had limitations that must be considered when interpreting the results. Not all subjects successfully completed every task, particularly within the bipolar group. Consequently, some of the subjects with the worst performance were excluded, which may have minimized group differences. As noted, in this naturalistic study medications were prescribed by inpatient treatment teams based on clinical information that might not have been captured by our rating scales. Consequently, this clinical information may confound medication assignment with unmeasured but relevant clinical variables that affected task performance and that might identify subgroups of patients with specific attentional or response inhibition deficits. In other words, associations with lithium or multiple medications might reflect unidentified clinical characteristics that impacted both treatment assignment and task performance. Moreover, although a relatively large sample of bipolar subjects was studied, with uncontrolled medication assignment it was not possible to identify the potential affects of each medication used, limiting analyses to broad medication classifications. Previous studies in subjects with primary substance use disorders have suggested that greater impulsivity is associated with drug and alcohol abuse (e.g. 43, 44). This association was not observed in this study; however, it is likely that the overall impact of manic symptoms subjects limited our ability to detect the effects of substance use disorder comorbidity specifically. Moreover, the inclusion and exclusion criteria generally disqualified heavy, current drug and alcohol users. Finally, the tasks that were chosen have been validated in other clinical populations, but have been used relatively rarely to specifically assess impulsiveness in bipolar disorder; consequently, other tasks may provide more sensitive measures, e.g., extinction paradigms. Nonetheless, strengths of the study, including the large sample size, clinically well-characterized subjects, and independent laboratory measures of specific aspects of impulsivity balance these limitations.

The relative independence of the three aspects of impulsivity suggests that individual patients may have varying difficulty with different types of impulsive behaviors. This finding suggests that as part of the clinical assessment of bipolar patients, various types of impulsive behaviors be separately identified, rather than simply asking general questions about impulsivity. This specific information might then be useful for individualizing therapeutic goals, as well as focusing specific therapeutic interventions. For example, a patient identified with difficulties

delaying gratification may have different cognitive interventions (e.g., stop-delay types of strategies) than one whose primary problem is inattention (e.g., list making). Additional work is needed to determine whether these types of measures may lead to novel therapeutic strategies. Moreover, the finding that performance on the delayed reward task was independent of affective symptoms and other impulsivity measures, as well as different between manic and mixed patients, suggests that additional study of reward processing in mania might inform new neurocognitive or neurophysiologic models of bipolar disorder. An important next step in this line of work will be to extend the use of these types of tasks across mood states and into euthymia during the course of bipolar disorder to see if any of the measures represent a potential trait measure of this illness.

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Table 1

Demographic and clinical variables of 70 bipolar I manic/mixed and 34 healthy subjects completing measures of impulsivity.

Variable	Bipolar Subjects	Healthy Subjects	p-value
Age, years	30 (8)	30 (9)	.90
Sex, N(%) women	41 (59)	20 (59)	.98
Ethnicity, N(%) white	45 (64)	27 (79)	.12
Education, years	13(3)	15 (2)	.007
Intelligence Quotient (IQ)	107 (17)	112 (9)	.12
YMRS total score	27 (5)	1 (2)	<.0001
MADRS total score	12 (8)	1 (1)	<.0001
Mixed state, N(%)	20 (29)	n/a	
Psychosis present, N(%)	53 (76)	n/a	
Lifetime alcohol use disorder, N(%)			.0009
Alcohol abuse	10 (14)	5 (15)	
Alcohol dependence	22 (31)	0 (0)	
Lifetime cannabis use disorder, N(%)			.001
Cannabis abuse	18 (25)	2 (6)	
Cannabis dependence	10 (14)	0 (0)	
Days of alcohol use to intoxication, prior month	1 (2)	2 (2)	.77
Days of any cannabis use, prior month	5 (10)	1 (4)	.03
Lifetime ADHD, N(%)	16 (22)	0 (0)	.002
Age of bipolar onset, years	20 (8)	n/a	
Medications prescribed, N(%)*			
Lithium	13 (19)	n/a	
Anti-epileptic (AED)	21 (30)	n/a	
Atypical antipsychotic (AAP)	49 (70)	n/a	
Benzodiazepine (BEN)	15 (21)	n/a	

Values reported are means (SD) unless otherwise specified. YMRS=Young Mania Rating Scale, MADRS=Montgomery-Asberg Depression Rating Scale, ADHD=Attention-Deficit Hyperactivity Disorder. P-values were calculated using t-test for continuous variables and chi-squares tests for categorical variables.

*Some patients were receiving more than one medication.

Table 2

Results of impulsivity task performance in 70 bipolar I manic/mixed patients and 34 healthy subjects.

Variable	Bipolar Subjects	Healthy Subjects	*f* (p-value)
Disinhibition task (SST)[1]			
Stop-signal reaction time (SSRT)*, ms	186 (80)	150 (38)	0.24 (.04)
'go' reaction time*, ms	608 (87)	638 (143)	0.10 (.36)
'stop' latency, ms	422 (138)	488 (157)	0.22 (.05)
Delayed gratification task (DRT)[2]			
%Impulsive (A) responses	45 (28)	34 (21)	0.21 (.04)
Reaction time, ms*	1434 (1294)	808 (463)	0.31 (.003)
Attention task (DS-CPT)[3]			
Sensitivity, A'	0.82 (0.14)	0.88 (0.12)	0.22 (.03)
Bias, B"	0.48 (0.39)	0.65 (0.37)	0.20 (.04)
Reaction time, ms	548 (70)	532 (75)	0.11 (.28)
BIS-11 scores[4]			
Attentional impulsiveness factor	18 (4)	13 (3)	0.62 (<.0001)
Motor impulsiveness factor	26 (6)	20 (3)	0.56 (<.0001)
Nonplanning impulsiveness factor	25 (7)	21 (4)	0.37 (.0004)

Values reported are means (SD) unless otherwise specified. SST=stop signal task; DRT=delay reward task; DS-CPT=degraded stimulus continuous performance task; BIS-11=Barratt Impulsiveness Scale, v. 11; *f*=effect size based on one-way univariate ANOVA F-statistic.

[1] Significant difference between groups: F(1,77)=4.6, p=.035.

[2] Significant difference between groups: Multivariate F(2,90)=10.0, p=.0001.

[3] Significant difference between groups: Multivariate F(3,98)=3.3, p=.02.

[4] Significant difference between groups: Multivariate F(3,95)=14.5, p<.0001.

* Although raw data are listed for clarity, data were square-root transformed prior to analysis due to unequal variances between groups.

Table 3

Clinical characteristics and impulsivity measures of bipolar manic/mixed patients who were or were not receiving lithium therapy.

Variable	Lithium Treated (N=13)	No Lithium (N=57)	p-value
YMRS total score	27 (5)	26 (5)	.55
MADRS total score	11 (8)	12 (6)	.59
Mixed state, N(%)	4 (31)	16 (28)	.85
Psychosis present, N(%)	12 (92)	41 (72)	.12
Lifetime alcohol use disorder, N(%)	7 (54)	25 (44)	.51
Lifetime cannabis use disorder, N(%)	5 (38)	23 (40)	.90
Lifetime ADHD, N(%)	5 (42)	19 (35)	.64
Age of bipolar onset, years	19 (5)	20 (9)	.66
Illness duration, years	15 (12)	9 (8)	.04
Number of medications prescribed, N(%)	2.4 (0.9)	1.2 (0.7)	<.0001

Values reported are means (SD) unless otherwise specified.