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Iowa Gambling Task scores predict future drug use in bipolar disorder outpatients with stimulant dependence

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ABSTRACT

Poor decision-making is associated with poor recovery in persons with bipolar disorder and drug relapse in persons with stimulant dependence. Cognitive predictors of stimulant use in those with comorbid bipolar and stimulant dependence are surprisingly absent. Our goal was to determine if a single baseline assessment of decision-making (Iowa Gambling Task, IGT) would predict future drug use in bipolar disorder outpatients with comorbid stimulant dependence. Ninety-four men and women of multiple race/ethnic origins consented to participate in a 20-week study. Data analyses were performed on 63 comorbid bipolar outpatients completing at least four study weeks and 28 cocaine dependent volunteers without a mood disorder who participated as cocaine controls. There were no significant differences in IGT scores between comorbid patients and cocaine controls. In the comorbid group, IGT scores significantly predicted future drug use during the study. Age, sex, race, years of mental illness, or mood state did not significantly influence IGT scores. This is the first longitudinal study to show that IGT scores obtained at a single baseline assessment predicts future objective drug use in comorbid bipolar disorder outpatients with cocaine or methamphetamine dependence. Evaluating decision-making with the IGT may provide clinicians with valuable insight about the trajectory of their patients' risk for future drug use. These data suggest a need to augment existing treatment with cognitive restructuring to prevent slips and relapses in comorbid bipolar patients. The lack of a bipolar control group and a modest sample size may limit data interpretations.

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1. Introduction

Poor decision-making is a hallmark characteristic in persons with stimulant dependence (Bechara et al., 2001; Bechara, 2003; Aharonovich et al., 2003, 2006) and in those with bipolar disorder during manic, hypomanic, depression, and euthymic mood phases (Murphy et al., 2001; Clark et al., 2001; Martinez-Aran et al., 2004; Adida et al., 2011). The inability to make good decisions is associated with drug relapse and treatment attrition in those with substance use disorders (Bechara et al., 2001; Bechara, 2003; Aharonovich et al., 2003, 2006; Bowden-Jones et al., 2005), and poor functional recovery in those with bipolar disorder (Denicoff et al., 1999; Clark et al., 2002; Jaeger et al., 2007; Martino et al., 2009). However, decision-making in relation to drug use outcomes in those with comorbid bipolar and stimulant dependence is unknown.

The lifetime substance abuse rate in those with bipolar disorder is ~60% with ~30% of this subset consisting of stimulant use disorders (Regier et al., 1990; Goldberg et al., 1999; Strakowski and DelBello, 2000; Strakowski et al., 2000; Cassidy et al., 2001). Chronic substance use worsens bipolar illness, significantly interferes with recovery, and facilitates poorer prognostic outcomes than in those without comorbid substance abuse (Regier et al., 1990; Goldberg et al., 1999; Strakowski and DelBello, 2000; Strakowski et al., 2000; Cassidy et al., 2001). Thus, it is worthwhile to examine decision-making as a clinically relevant and therapeutic target in patients with comorbid bipolar disorder and stimulant dependence.

The most well-known and widely used decision-making assessment in addiction research is the Iowa Gambling Task (IGT). The consensus in the prevailing literature focuses on IGT comparison data, that is, in comparison to healthy controls those with addiction disorders make poorer, riskier decisions based on immediate rewards (Bolla et al., 2000; Bartzokis et al., 2000; Grant et al., 2000; Bechara et al., 2001, 2000; Bechara and Damasio, 2000; Bechara, 2003; Bolla et al., 2003; Bechara and Martin, 2004; Verdejo-Garcia et al., 2006, 2007; van der Plas et al., 2009; Buelow

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and Suhr, 2009; Toplak et al., 2010). Only four small studies have examined IGT scores as a '*predictor*' of future drug use in substance abusing populations. However, these investigations quantified drug use as binary 'yes or no' self-reports of drug use in abstainers versus non-abstainers (Bowden-Jones et al., 2005; De Wilde et al., 2013) or utilized subjective reports of drug use frequency (Schilt et al., 2009; Goudriaan et al., 2011). The IGT has never been used to predict an objective measure of drug use in a prospective, longitudinal design.

Further, only a few studies have examined IGT decision-making in bipolar disorder. Most are comparison studies, exclude comorbidities, and show little, if any, IGT performance differences between healthy controls and those experiencing acute or remitted manic states, depressed or euthymic mood states (Clark et al., 2001, 2002; Frangou et al., 2008; Yechiam et al., 2008; Adida et al., 2011; Martino et al., 2011). Together, the literature suggests a clear and present gap in our understanding about decision-making in relation to drug use in the comorbid bipolar population.

The high rate of stimulant abuse in bipolar disorder and the harmful effects that drug use has on illness recovery suggest a critical need to identify those who are prone to continue drug use, slip or relapse. Predicting the drug use potential in comorbid bipolar patients is an important prevention tool to avert poor prognoses. Using a single cognitive test to predict future drug use prior to treatment onset should provide some real-world therapeutic and economic benefits. The current study was designed to test the hypothesis that baseline IGT scores would significantly predict future drug use in comorbid bipolar disorder with cocaine or methamphetamine dependence.

2. Methods

2.1. Study design and protocol

A longitudinal study was designed to determine if a single baseline assessment of decision-making using IGT scores could predict future drug use in those with comorbid bipolar disorder with cocaine or methamphetamine dependence (comorbid group) up to 20-weeks after task administration. Comparison studies among bipolar types (I versus II) and various mood states are well-documented as cited earlier. However, there are no investigations comparing decision-making between patients with comorbid bipolar and stimulant dependence to those with stimulant dependence without bipolar illness. To help test our hypothesis we thought it was important to obtain empirical data to better understand the potential range of IGT performance in the comorbid group as a function of their addiction. Thus, we recruited subjects meeting DSM-IV criteria for cocaine dependence without a mood disorder (cocaine control group) and compared their IGT scores to the comorbid group.

In accordance with the Declaration of Helsinki, university Institutional Review Board approval of this research protocol was obtained. A Confidentiality Certificate was issued by the National Institute of Mental Health. Prior to study enrollment, eligible volunteers provided written, informed consent to participate.

Those enrolled in the comorbid group attended weekly study visits for 20-weeks as part of a clinical pharmacotherapy trial reported in detail elsewhere (Nejtek et al., 2008). Every four weeks after study assessments were completed, comorbid subjects received a $40 gift card to a local discount retail store. As drug use in cocaine abusers is well-studied, the cocaine control group was not followed longitudinally as our focus was not to predict their drug use risk. Thus, subjects in the cocaine control group attended one study visit where demographic information was collected, the IGT was administered, and afterward controls received their gift card.

2.2. Inclusion/exclusion criteria

Volunteers for the comorbid bipolar and cocaine control groups of all race/ethnic origins were invited to participate and were recruited from clinician referrals at local mental health clinics and/or drug treatment centers. Eligibility for the comorbid group included meeting DSM-IV criteria for current bipolar I or II disorder plus current cocaine or methamphetamine dependence, 20–50 years old; English-speaking with a high school diploma or equivalent or a Shipley IQ test score of >85, and participated in weekly outpatient behavioral addiction treatment (i.e. Intensive Outpatient Classes, Alcoholic Anonymous, Narcotics Anonymous, Dual Recovery Anonymous, etc.). Demographic eligibility for the cocaine control group was the same as for the comorbid group, but excluded any current DSM-IV mood disorder, any substance dependence other than cocaine, and psychotropic medications.

Both comorbid and cocaine control group volunteers were excluded if they were hospital inpatients, persons undergoing detoxification, suffering acute withdrawal symptoms, or incarcerated inmates. In addition, those with a substance-induced mood disorder, those who had attempted suicide in the past 6 months, a history of special education, mental retardation, dementia, brain injury, a central nervous system disorder, HIV/AIDS, cataracts, glaucoma; currently using benzodiazepines, sedatives/narcotics, prescription stimulants, use of any antipsychotic medications, and those receiving polypharmacy (i.e. more than two psychotropic medications) were ineligible. As we were interested in examining an ecologically valid sample, subjects with positive urine drug tests at study entry were allowed to participate.

2.3. Study assessments

All subjects were evaluated with the Structured Clinical Interview for DSM-IV Clinician Version (SCID-IV-CV) to verify current and lifetime Axis I diagnoses for mood and substance use disorders (First et al., 1997) and the IGT. At the baseline visit both groups provided sociodemographic information, a urine drug sample was collected, and the IGT was administered. At baseline and at every weekly visit, the comorbid group was also evaluated with the Young Mania Rating Scale ($YMRS_{11}$; Young et al., 1978), Inventory of Depressive Symptomatology – Clinician-rated ($IDS\text{-}C_{30}$; Rush et al., 2000; Trivedi et al., 2004), and the 10-item Stimulant Craving Questionnaire (SCQ_{10}; Tiffany et al., 1993) to measure manic, depressive symptoms and stimulant (cocaine or methamphetamine) craving.

The $YMRS_{11}$ and the $IDS\text{-}C_{30}$ are widely used instruments used to measure current manic and depression mood states (Young et al., 1978; Rush et al., 2000; Trivedi et al., 2004). In this study, the $YMRS_{11}$ symptom severity cutoff scores used were ≤ 12=normal, 13–19=minimal, 20–25=mild, 26–37=moderate, ≥ 38=severe. The $IDS\text{-}C_{30}$ symptom severity cutoff scores range from ≤ 11=normal, 12–23=mild, 24–36=moderate, ≥ 37=severe. The SCQ_{10} is a simple modification of the Cocaine Craving Questionnaire (CCQ) used in our previous studies (Brown et al., 2002; Nejtek et al., 2002, 2004, 2008) to assess methamphetamine cravings in the same manner as cocaine. Factor analytic reliabilities of internal consistencies of this questionnaire range from 0.92 to 0.72 with raw scores ranging from 10 to 70 (Tiffany et al., 1993).

2.4. The Iowa Gambling Task, instructions, scoring

The IGT is a computerized assessment that features four card decks (e.g. A, B, C, D) shown on a color computer monitor (Bechara et al., 1994, 1999). Two decks (A+B) are considered 'high-risk' and contain some high dollar winning cards (e.g. $100–1000), a few cards with small dollar losses (e.g. $20–50), and several cards with substantial monetary losses (e.g. $500–1250). Two other decks (C+D) are considered 'low-risk' as they have many more low dollar winning cards (e.g. $75-50) but have lower monetary losses (e.g. $25) thereby yielding small, but consistent monetary gains. In the present study, each deck was programmed to contain 60 cards with a maximum of 100 selections set with an inter-trial interval of 3 s. During the task, subjects who may run out of cards from a given deck must continue choosing from the remaining decks. The task automatically shuts off after the 100 selections are made.

Thus, subjects have 100 chances to learn the strategy to lose less and win more money during five learning blocks that contain 20 cards each. Block 1 consists of cards 1–20, Block 2 cards 21–40, Block 3 cards 41–60, Block 4 cards 61–80 and Block 5 cards 81–100. Net total scores for the entire IGT assessment (all blocks included) are calculated as the accumulated low risk minus high risk card choices [(C+D)−(A+B)]. Scores of ≤ 0 infer cognitive deficits associated with prefrontal brain injury or atrophy, while healthy controls score >10 (Bechara et al. 1994, 1999, 2001). In addition to the net total score [(C+D)−(A+B)], we analyzed total A+B scores and total C+D scores separately, and also the net total scores [(C+D)−(A+B)], for each Block 1 through 5 (for detail see Bechara et al. (1994, 1999, 2001, 2002) and Bechara and Damasio (2000)).

Task instructions given to the subjects were that they would receive a fictional $2000 credit to start the game, that they should win as much money as they can, and that the card color does not determine how much they can win. In addition, subjects were told that some decks were worse than others and that no matter how much they lost they could still win if they stayed away from the worst decks. Subjects were instructed to treat the play money as if they were using their own real money, and that if they ran out of cards from any given deck, they were told to continue choosing from the remaining decks. To perform well, subjects need to learn to inhibit risky, reward-based decision-making and avoid choosing from the 'high-risk' card decks.

2.5. Drug use

In addition to the SCID-IV-CV life chart, self-report and case manager reports for each subject were used to determine the years of drug dependence and the

number of abstinent days subjects had at the time of study entry. A urine specimen was collected at baseline and at every weekly visit for the comorbid group, and at the one and only visit for the cocaine control group. Current drug use was determined using a six-panel urine drug screen to identify cocaine (benzoylecgonine, 300 ng/mL), methamphetamine (d-methamphetamine, 1000 ng/mL), phencyclidine (PCP, 25 ng/mL), cannabis (11-norΔ^9 THC-9 COOH, 50 ng/mL), opiate (morphine, 300 ng/mL), and benzodiazepine (oxazepam, 300 ng/mL) use.

2.6. Pharmacotherapy

As indicated in the exclusion criteria, those currently using antipsychotics, benzodiazepines, sedatives/narcotics, prescription stimulants, or receiving psychotropic polypharmacy at study entry were ineligible to participate. As described in Nejtek et al. (2008), after all baseline assessments those in the comorbid group were randomized to receive either quetiapine or risperidone. Eleven comorbid subjects entered the study with a mood stabilizer and 16 were receiving an antidepressant. After the baseline assessment, quetiapine or risperidone was added to these 27 subjects' existing treatment plan while 36 subjects received quetiapine or risperidone as monotherapy. Weekly dose adjustments of the atypical antipsychotic were titrated up or down in a 'treat-to-symptoms' standard level of care protocol while adjunctive medication adjustments were strictly proscribed throughout the study (Nejtek et al., 2008).

2.7. Data analyses

Data comparisons were computed between the cocaine control group ($n=28$) and those in the comorbid group who completed ≥4 study weeks ($n=63$). Sociodemographic data, years of chronic drug use, and IGT scores were compared between the comorbid and cocaine control groups using analysis of variance and chi-square tests, as appropriate.

The independent variables used to predict drug use in the comorbid group were IGT net total scores [(C+D)−(A+B)], total A+B scores, total C+D scores, and net total [(C+D)−(A+B)] scores for each Block (1–5). Variables added to statistical models were age, race, sex, education, bipolar type (I, II), drug diagnosis (cocaine, methamphetamine), years of chronic drug use, and years of mental illness. The dependent variable of drug use was quantified in two ways, (1) as the percentage of positive urine drug tests divided by the total number of study weeks attended and (2) the total number of drug positive urine drug screens for each subject during the 20-week study. We did not use a last observation carried forward technique for missing urine drug screens due to attrition, or count a missing urine drug screen as a positive drug test. Instead, we calculated the percentage of positive urine drug tests/study weeks as a precise measure of drug use with subjects serving as their own control in terms of study participation.

Secondary dependent variables to measure manic mood state ($YMRS_{11}$), depressed mood state ($IDS\text{-}C_{30}$), and craving (SCQ_{10}) were added to the statistical models. Mood state and craving, bipolar type (I, II) and drug diagnosis (cocaine, methamphetamine) were used as covariates and as grouping variables to determine the impact these factors may have had in decision-making and drug use.

Linear regression, generalized linear model analysis and Bonferroni corrections for multiple pairwise comparisons were employed (IBM SPSS 19). *Pearson* correlations were performed to identify relationships among IGT scores, drug use, clinical, and sociodemographic variables in the comorbid group. All analyses were conducted using a 99% confidence interval and a two-tailed alpha of 0.01 to determine statistical significance. We chose a conservative probability to provide stronger support for our hypotheses that decision-making using IGT scores would significantly predict future drug use in the comorbid group.

3. Results

3.1. Sociodemographic group comparisons

Table 1 illustrates group differences in sociodemographic information and drug use history between the bipolar and stimulant dependence (BP+SD) comorbid group and the cocaine control group (cocaine dependence only). There were no significant group differences in race, sex, age, or years of chronic drug use; however, the cocaine control group had significantly more education and number of days of abstinence at study entry.

3.2. Comorbid group clinical characteristics

In the comorbid group, there were 53 bipolar I and 10 bipolar II subjects with lifelong mental illness (mean years of illness = 24.65 ± 8.02 years). The mean number of study weeks attended was 12.0 ± 5.7 with 14 subjects completing all 20-weeks. A consensus method of determination used by the PI and study psychiatrists combined with cut score criteria for the YMRS and IDC-C indicated that 17 (27%) subjects were in a mixed state, 28 (44%) were in a mild depressed state, 12 (19%) were hypomanic, and six (10%) were in a minimal manic mood state at study entry. Although most subjects met diagnostic criteria for bipolar I, we found mild depression (44%, 28/63) was the dominate mood state while the remaining subjects experienced mixed, hypomanic (46%, 29/63) or minimal manic (9.5%, 6/63) states. Of those who were cocaine dependent ($n=41$), eight were Black women, 11 were Black men, nine were White women and 13 were White men, while 13 White women and nine White men were methamphetamine dependent ($n=22$).

3.3. Comorbid and cocaine control group drug use

Eighteen comorbid bipolar patients with cocaine dependence entered the study drug free and remained drug abstinent, four used drugs continuously, and 19 slipped or relapsed after abstinence during the 20-week study. Seventeen comorbid bipolar patients with methamphetamine dependence entered the study drug free and remained drug abstinent, two used drugs continuously, and three slipped or relapsed after abstinence. Twenty-one out of the 28 total comorbid patients that continuously used, slipped or relapsed entered the study drug positive. Thus, 44% (28/63) had problems maintaining sobriety. The number of weeks of abstinence recorded prior to slips or relapses ranged from 2- to 19-weeks. None of those in the cocaine control group tested drug positive at the baseline assessment, and the number of drug abstinent days at study entry showed this group met DSM-IV criteria for sustained partial remission.

3.4. IGT scores, demographic variables, and medication in the comorbid group

Prior to comparing IGT scores between the comorbid and cocaine control groups, we examined the comorbid group alone to identify if there were demographic variables that may have influenced IGT performance. As Table 2 shows, age, sex, race, education, years of drug dependence, and years of mental illness did not significantly influence IGT scores in those with bipolar disorder and stimulant dependence. Additionally, medication use (quetiapine or risperidone) did not influence IGT net scores ($R^2=0.025$, $F_{(1,62)}=1.64$, $\beta=-7.56$, $t=-1.28$, $p=0.205$).

3.5. Bipolar I versus II, drug use, mood, and IGT

We analyzed bipolar type as an independent grouping variable with Bonferroni pairwise comparisons. As illustrated in Table 3, these analyses indicate that with the exception of the YMRS, there were no significant differences in depression, drug use, craving, or IGT decision-making between those with bipolar I versus II. The difference we found in the YMRS is a logical and inherent characteristic in the distinction between bipolar I and II diagnostic criteria. Only one slight trend was noted in IGT Block 1 net scores suggesting those with bipolar I took a few higher risks than those with bipolar II. However, we expect the novelty of encountering an unknown computer task was the stimulating factor for the bipolar I group that elicited this non-significant variation.

3.6. Cocaine versus methamphetamine, drug use, mood, craving and IGT

As the comorbid group had a mix of those with either cocaine or methamphetamine dependence, we examined potential

Table 1
Sociodemographic and Drug Use Variables.

Sample characteristics	BP+SD *n* (%)	Cocaine *n* (%)	χ^2	*p*
Women	30 (47.6)	9 (32.1)	1.890	0.169
Men	33 (52.4)	19 (67.9)		
Black	19 (30.2)	14 (50.0)	3.300	0.069
White	44 (69.8)	14 (50.0)		
Quantifiable Variables	***M*** (*S.D.*)	***M*** (*S.D.*)	***F***	***p***
Age	36.4 (6.7)	37.9 (6.2)	0.972	0.327
Yrs of Education	13.2 (1.4)	14.3 (2.6)	8.080	0.006
Yrs of Dependence	11.2 (6.3)	14.1 (6.6)	2.310	0.133
Drug Abstinent Days at Study Entry	45.8 (75.6)	260.4 (513.1)	10.448	0.002

SD=stimulant dependence, (*S.D.*)=standard deviation.

Table 2
Relationships between IGT and demographic variables in the comorbid group.

Dependent Variable	Parameter	*β*	Std. Error	*t*	*p*	95% CI		Partial eta squared	Observed power
						Lower bound	Upper bound		
Iowa Gambling Task net total [(C+D)−(A+B)]	Intercept	−20.999	34.432	−0.610	0.544	−90.031	48.032	0.007	0.092
	Age	0.669	0.780	0.859	0.394	−0.894	2.232	0.013	0.135
	Yrs of education	1.601	2.310	0.693	0.491	−3.030	6.233	0.009	0.105
	Yrs of dependence	−0.859	0.631	−1.361	0.179	−2.124	0.406	0.033	0.267
	Yrs of mental illness	−0.450	0.598	−0.753	0.455	−1.649	0.748	0.010	0.115
	Race=1 Black	−9.598	9.440	−1.017	0.314	−28.523	9.328	0.019	0.170
	Race=2 White	0[a]	–	–	–	–	–	–	–
	Sex=0 Women	−3.856	7.424	−0.519	0.606	−18.741	11.029	0.005	0.080
	Sex=1 Men	0[a]	–	–	–	–	–	–	–
Iowa Gambling Task Total A+B	Intercept	57.205	17.835	3.207	0.002	21.447	92.962	0.160	0.883
	Age	−0.353	0.404	−0.875	0.385	−1.163	0.456	0.014	0.138
	Yrs of education	−0.635	1.197	−0.531	0.598	−3.035	1.764	0.005	0.082
	Yrs of dependence	0.416	0.327	1.274	0.208	−0.239	1.072	0.029	0.240
	Yrs of mental illness	0.257	0.310	0.829	0.411	−0.364	0.878	0.013	0.129
	Race=1 Black	5.744	4.890	1.175	0.245	−4.059	15.547	0.025	0.211
	Race=2 White	0[a]	–	–	–	–	–	–	–
	Sex=0 Women	2.945	3.846	0.766	0.447	−4.766	10.655	0.011	0.117
	Sex=1 Men	0[a]	–	–	–	–	–	–	–
Iowa Gambling Task Total C+D	Intercept	40.076	17.813	2.250	0.029	4.363	75.789	0.086	0.599
	Age	0.286	0.403	0.709	0.481	−0.522	1.095	0.009	0.107
	Yrs of education	0.770	1.195	0.644	0.522	−1.626	3.166	0.008	0.097
	Yrs of Dependence	−0.381	0.326	−1.167	0.248	−1.036	0.273	0.025	0.209
	Yrs of mental illness	−0.204	0.309	−0.659	0.513	−0.824	0.416	0.008	0.099
	Race=1 Black	−5.375	4.884	−1.101	0.276	−15.166	4.416	0.022	0.191
	Race=2 White	0[a]	–	–	–	–	–	–	–
	Sex=0 Women	−2.152	3.841	−0.560	0.578	-9.853	5.548	0.006	0.085
	Sex=1 Men	0[a]	–	–	–	–	–	–	–

[a] This parameter is set to zero as it is redundant.

differences as a function of drug diagnosis. Although cocaine abusers had a greater number and percentage of positive urine drug tests during the study than methamphetamine abusers, those differences did not reach statistical significance. Using Bonferroni pairwise comparisons, drug use, mood symptoms, craving, and IGT scores were not significantly different between those who were dependent on cocaine versus methamphetamine (Table 4). Thus, we collapsed these two drug groups and proceeded with comparison analyses with the cocaine control group to examine potential IGT differences.

3.7. IGT scores in comorbid and cocaine control Groups

Table 5 shows that there were no significant differences in IGT net total scores [(C+D)−(A+B)], high risk A+B card choices, low risk C+D card choices or differences in net total scores for Blocks 1 through 5 between the comorbid and cocaine control groups. As no group differences in IGT scores were found, no further analyses using the cocaine control group were conducted.

3.8. Comorbid group IGT scores, sociodemographic, and clinical correlations

Pearson correlations showed there were no relationships meeting our statistical criteria (≤0.01) among IGT scores, age, years of education, or years of mental illness (Table 6). Statistical trends between years of drug dependence and IGT net total scores were noted. The total number of positive urine drug tests collected throughout the 20-week study were significantly related to total IGT A+B high risk card choices, net total scores for Block 1 (cards 1–20), Block 4 (cards 61–80) and Block 5 (cards 81–100). The percentage of drug positive tests were significantly related to Block 3 (cards 41–60) and statistical trends were also found with the IGT net total, A+B deck net total, Block 1 (cards 1–20) and Block 2 (cards 21–40). Having found these significant relationships

Table 3
Pairwise Comparisons of Bipolar I vs. II, Drug Use, Mood, and IGT Scores.

Dependent variable	(I) bipolar I [Mean]	(J) bipolar II [Mean]	Mean difference (I−J)	Std. Error	p
Total # of drug positive tests during study	Bipolar I [2.79]	Bipolar II [2.82]	−0.035	1.635	0.983
Total drug positive tests÷study weeks=% positive	Bipolar I [27.77]	Bipolar II [20.06]	7.709	13.890	0.581
YMRS	Bipolar I [18.67]	Bipolar II [13.20]	5.479	1.702	**0.002**
IDS	Bipolar I [25.75]	Bipolar II [21.18]	4.569	3.309	0.173
SCQ	Bipolar I [50.33]	Bipolar II [45.03]	5.305	5.726	0.358
Iowa Gambling Task Scores					
Net Total [(C+D)−(A+B)]	Bipolar I [−0.726]	Bipolar II [10.85]	−11.573	8.996	0.204
Total A+B	Bipolar I [50.14]	Bipolar II [43.77]	6.364	4.655	0.177
Total C+D	Bipolar I [49.90]	Bipolar II [53.99]	−4.085	4.714	0.390
Block 1, 1–20, Net Total	Bipolar I [−3.37]	Bipolar II [1.26]	−4.627	2.041	0.027
Block 2, 21–40, Net Total	Bipolar I [0.494]	Bipolar II [0.584]	−0.090	1.783	0.960
Block 3, 41–60, Net Total	Bipolar I [−0.158]	Bipolar II [0.638]	−0.797	2.604	0.761
Block 4, 61–80, Net Total	Bipolar I [1.29]	Bipolar II [2.96]	−1.671	3.289	0.613
Block 5, 81–100, Net Total	Bipolar I [1.02]	Bipolar II [5.41]	−4.388	3.875	0.262

YMRS=Young Mania Rating Scale, IDS=Inventory for Depressive Symptomatology Clinician-rated, SCO=Stimulant Craving Questionnaire, Std. Error=Standard Error.

Table 4
Pairwise Comparisons of Drug Diagnosis, Drug Use, Mood, and IGT Scores.

Dependent Variable	(I) drug diagnosis [mean]	(J) drug diagnosis [mean]	Mean difference (I−J)	Std. Error	p[a]	99% CI	
						Lower bound	Upper bound
Total # of drug positive tests during the study	Meth [1.84]	Cocaine [3.21]	−1.363	1.326	0.308	−4.899	2.173
Total drug positive tests÷study weeks=% positive	Meth [21.12]	cocaine [23.55]	−2.430	11.707	0.836	−33.647	28.787
YMRS	Meth [15.78]	Cocaine [15.99]	−0.508	1.392	0.717	−4.220	3.205
IDS-C	Meth [21.96]	Cocaine [23.79]	−1.829	2.763	0.511	−9.196	5.537
SCQ	Meth [48.08]	Cocaine [47.08]	1.805	4.671	0.701	−10.651	14.260
Iowa Gambling Task Net Total Score [(C+D)−(A+B)]	Meth [13.59]	Cocaine [0.683]	12.910	7.316	0.083	−6.597	32.417
Total A+B	Meth [41.95]	Cocaine [49.49]	−7.540	3.752	0.049	−17.545	2.466
Total C+D	Meth [56.27]	Cocaine [49.73]	6.538	3.824	0.093	−3.659	16.736
Block 1, 1–20, Net Total	Meth [0.332]	Cocaine [−2.06]	2.391	1.891	0.211	−2.650	7.433
Block 2, 21–40, Net Total	Meth [1.80]	Cocaine [−0.207]	2.004	1.421	0.164	−1.784	5.792
Block 3, 41–60, Net Total	Meth [1.82]	Cocaine [−0.258]	2.081	2.147	0.337	−3.644	7.805
Block 4, 61–80, Net Total	Meth [4.03]	Cocaine [1.06]	2.968	2.636	0.265	−4.062	9.998
Block 5, 81–100, Net Total	Meth [5.61]	Cocaine [2.15]	3.466	3.276	0.295	−5.270	12.202

[a] Adjustment for Multiple Comparisions; YMRS=Young Mania Rating Scale, IDS=Inventory for Depressive Symptomatology-Clinician Version, SCQ=Stimulant Craving Questionnaire.

Table 5
IGT Scores in Comorbid vs. Cocaine Control Groups.

Iowa Gambling Task	Bipolar+SD		Cocaine		F	p
	Mean	(S.D.)	Mean	(S.D.)		
Net Total [(C+D)−(A+B)]	1.53	23.76	7.86	27.80	1.243	0.268
Total A+B	48.92	12.33	46.07	13.90	0.963	0.329
Total C+D	50.77	12.19	53.93	13.90	1.202	0.276
Block 1, 1–20, Net Total	−2.28	6.30	−1.57	5.12	0.275	0.601
Block 2, 21–40, Net Total	0.47	4.76	0.86	6.85	0.098	0.755
Block 3, 41–60, Net Total	−0.16	6.57	2.14	7.20	2.248	0.137
Block 4, 61–80, Net Total	1.50	8.26	2.86	9.71	0.472	0.494
Block 5, 81–100, Net Total	2.00	10.10	3.57	8.97	0.504	0.480

SD=stimulant dependence, (S.D.)=standard deviation.

and trends, we then used regression analyses to examine the value of IGT scores predicting future drug use during the study.

3.9. Baseline IGT scores predict future drug use in comorbid bipolar outpatients

In support of our hypotheses, Table 7 shows that point estimates and the corresponding *p*-values for IGT A+B 'high-risk' card choices significantly predicted drug use and explained a significant proportion of the variance in the comorbid group. A trend noted in less risky IGT card choices (C+D cards) predicted a greater number of negative urine drug tests during the study. Using the net total scores [(C+D)−(A+B)] from each of the five blocks, we also found Blocks 1, 4, and 5 significantly predicted drug use and explained a significant proportion of the variance, while a trend was noted in Block 3. In terms of the percent of positive urine drug screens as a function of study weeks attended, we found Block 3 significantly predicted drug use and trends were also noted in Blocks 1 and 2 as well as net total scores for A+B and C+D cards. Taken together, these data suggest that IGT scores are clearly a valuable predictor of future drug use in this study patient population.

4. Discussion

This is the first longitudinal study to show that IGT scores obtained at a single baseline assessment predicts future objective drug use in comorbid bipolar disorder outpatients with cocaine or methamphetamine dependence. Our finding that IGT performance was not significantly influenced by bipolar type or mood state aligns with the available data in the literature (Clark et al., 2001, 2002; Frangou et al., 2008; Yechiam et al., 2008; Adida et al., 2011;

Table 6
Pearson Correlations in Comorbid Group.

Variables	Age	Years of education	Years of drug dependence	Years of mental illness	Total # drug positive tests during study	Drug positive tests / study weeks = %
Total # of drug positive tests during study	0.164 0.194	0.164 0.195	0.145 0.252	0.183 0.149	1.000 –	0.598 0.000
Total drug positive tests ÷ study weeks = % Positive	0.223 0.076	0.216 0.087	0.105 0.409	0.313 **0.012**	0.598 0.000	1.000
IGT Net Total [(C+D)−(A+B)]	−0.097 0.446	0.149 0.241	−0.274 0.028	−0.159 0.209	−0.282 0.024	−0.230 0.067
Total A+B	0.099 0.435	−0.131 0.302	0.269 0.032	0.168 0.183	0.304 **0.015**	0.241 0.055
Total C+D	−0.094 0.458	0.135 0.286	−0.247 0.049	−0.149 0.241	−0.275 0.028	−0.224 0.075
Block 1, 1–20, Net Total	−0.019 0.855	0.064 0.547	−0.229 0.045	0.068 0.595	0.322 **0.009**	0.267 0.033
Block 2, 21–40, Net Total	−0.118 0.261	0.251 0.016	−0.150 0.193	−0.122 0.337	−0.083 0.513	−0.282 0.024
Block 3, 41–60, Net Total	−0.144 0.172	0.203 0.052	−0.110 0.339	−0.232 0.066	−0.275 0.028	−0.375 **0.002**
Block 4, 61–80, Net Total	−0.059 0.574	0.133 0.205	−0.191 0.096	−0.073 0.569	−0.401 **0.001**	−0.182 0.150
Block 5, 81–100, Net Total	−0.049 0.643	0.196 0.061	−0.194 0.091	−0.149 0.239	−0.320 **0.010**	−0.182 0.151

Table 7
Some IGT Scores in Comorbid Group Predict Future Drug Use During Study.

Predictor	R^2	*F*	β	*t*	*p-Value*
Total Number of Drug Positive Urine Tests Collected During Study					
IGT Net Total [(A+B)−(C+D)]	0.080	5.370	−0.006	−2.317	0.024
IGT A+B Total	0.104	7.050	8.030	2.660	**0.010**
IGT C+D Total	0.076	5.070	−0.011	−2.250	0.028
IGT Block 1 Net total	0.104	7.190	0.025	2.680	**0.009**
IGT Block 2 Net total	0.007	0.432	−0.009	−0.657	0.513
IGT Block 3 Net total	0.075	5.050	−0.021	−2.250	0.028
IGT Block 4 Net total	0.161	11.850	−0.024	−3.440	**0.001**
IGT Block 5 Net total	0.102	7.060	−0.016	−2.660	**0.010**
Total Number of Drug Positive Tests ÷ Total Study Weeks Attended = % Positive					
IGT Net Total [(A+B)−(C+D)]	0.053	3.470	−0.230	−1.860	0.067
IGT A+B Total	0.058	3.826	0.241	1.956	0.055
IGT C+D Total	0.050	3.280	−0.224	−1.810	0.075
IGT Block 1 Net total	0.071	4.750	0.267	2.180	0.033
IGT Block 2 Net total	0.080	5.370	−0.282	−2.320	0.024
IGT Block 3 Net total	0.141	10.200	−0.375	−3.190	**0.002**
IGT Block 4 Net total	0.033	2.130	−1.820	−1.460	0.150
IGT Block 5 Net total	0.033	2.110	−0.182	−1.454	0.151

Martino et al., 2011). It is also worth mentioning that there were no medication effects influencing IGT decision-making or drug use. Although the comorbid group received the standard level of care for their bipolar illness in the parent trial and showed mood improvement over time (Nejtek et al. 2008), 44% of the subjects slipped or relapsed during the study. In fact, several study patients received their 60-day 'chip' for sobriety and then slipped or relapsed soon after celebrating this abstinence milestone. While evidence-based behavioral and pharmacotherapy treatments for bipolar illness may lead to illness recovery, these therapies did not ensure successful addiction recovery in this sample.

This study was not designed to explain decision-making results or drug use as an artifact of impulsivity – a construct which is broadly defined as involving cognition, personality traits, motivations, and disinhibition processes (Nigg, 2000; Miller et al., 2004). Moreover, whether impulsivity and risk-taking are synonymous is debatable as neuroimaging data suggest that these constructs arise from distinctly different brain areas and activate different cognitive systems (Evenden, 1999; Whiteside and Lynam, 2001; Dalley et al., 2011). The IGT taps into brain areas that are anatomically specific to risky 'value-based' decision-making such as the left ventral medial prefrontal cortex and the right dorsal anterior

prefrontal cortex that are not activated during tests of 'impulsive' decision-making (Gläscher et al., 2012). Along the lines of Holmes et al. (2009) who reported the bipolar phenotype has dissociable impulsive and risk-taking cognitive characteristics, we propose that IGT-decision-making in our comorbid bipolar patients may reflect real-world risk-taking elicited from value-based 'hedonic wanting.'

The comorbid and cocaine control groups had similar years of stimulant addiction and performed the IGT similarly, yet, differed in drug use status (current versus sustained partial remission). These data shed further light on the negative impact that long-term stimulant dependence has on decision-making abilities even after 8-months or more of abstinence (e.g. cocaine control group). Like our findings, Barry and Petry (2008) examined IGT scores among alcohol, cocaine, heroin, polydrug abusers and found no significant differences as a function of substance diagnosis, current use versus abstinence, or length of chronic use.

Rather than make the argument that the comorbid group should have poorer decision-making abilities due to their mental illness, these data suggest that lifelong stimulant dependence appears to permanently impair strategic decision-making regardless of having bipolar illness or not. These data also show that the IGT is a specific measure of risky decision-making in relation to the addiction disease rather than mental illness. Had we not compared IGT performance between the comorbid group and cocaine controls, we would not have this level of understanding about decision-making in relation to future drug use in those with comorbid bipolar disorder.

With regard to predicting future drug use, hedonic wanting may be the driving force perpetuating the persistent drug use we found in our comorbid group. Taken together, our results along with Holmes et al. (2009) and Gläscher et al. (2012) show a neurocognitive outcome of comorbid bipolar patients who seem to have great difficulty in resisting cocaine or methamphetamines once they have experienced years of addiction. Moreover, the strength of this study is finding that the IGT uncovers a cognitive value system that is a important predictor of future drug use in a complex and challenging-to-treat comorbid bipolar population.

The ability to predict drug use in a treatment-seeking group of comorbid bipolar outpatients is noteworthy for a number of reasons. First, in a real-world treatment setting, general psychiatrists are more likely to recognize mood symptoms leading to psychiatric relapse and much less likely to identify symptoms that will precipitate drug relapse in their comorbid patients. Obviously, those with comorbid bipolar disorder and cocaine or methamphetamine dependence have complicated treatment challenges. Thus, it is clinically relevant to determine critical windows of opportunity to help avert mental decompensation possibly triggered by drug slips or relapses. Although preliminary, these data show that a clinician will no longer have to spend valuable clinic time parsing out the contribution of mood state that might trigger drug use. Instead, assessing decision-making with the IGT should help clinicians quickly identify future drug use risks in their patients, at least within a 5-month period.

Second, other studies report that IGT 'high risk' scores predict substance use, but the methodology used in these studies has resulted in some confusion. For instance, the available data show drug use is quantified as self-reported abstinence in polysubstance-dependent alcoholics (De Wilde et al., 2013), self-reported alcohol relapse in alcohol dependent patients (Bowden-Jones et al., 2005), subjective alcohol use in college age men (Goudriaan et al., 2011), and the self-reported 'likelihood' of future ecstasy use (Schilt et al., 2009) in subjects *without* comorbid mood disorders. While important, these studies' focus was not to employ prediction models using longitudinal objective measures to predict drug use. Thus, our results help further clarify the use of IGT decision-making as a specific longitudinal predictor of objective, quantifiable drug use in a comorbid bipolar patient population.

Third, with regard to recovery, Schmitz et al. (2009) reported that IGT scores did not predict treatment retention in those with cocaine dependence receiving both behavioral and medication therapy. As the IGT was first developed to identify abnormal risk-taking and decision-making in neurologically impaired patients (Bechara et al., 1994), it is logical that the IGT would be more appropriate in predicting a negative outcome (i.e. substance use) rather than a positive outcome (i.e. treatment retention). Indeed, we found that the high risk A+B decks had more predictive value of drug use than the low risk C+D cards. Taken together, the IGT seems to be a better predictor of future slips or relapse, but not one of potential recovery.

Although the comorbid group attended weekly visits, received pharmacotherapy for their mental illness (through the parent clinical trial), and were undergoing weekly behavioral treatment, these intervention efforts seemed to have little influence on the subjects who used drugs during the study. However, any further explanation of our data other than to support a clinically relevant prediction of future use in a comorbid bipolar and stimulant dependence sample is beyond the scope of this investigation with the current dataset. To our credit, we have crossed a methodological obstacle shunned by most researchers who typically exclude drug-using comorbid bipolar patient populations from cognitive research. In addition, we have provided data that help support the ecological validity of the IGT to predict future drug use in a challenging sample of bipolar disorder outpatients with stimulant dependence.

The cognitive literature is replete with test battery comparisons between healthy controls and patients with bipolar disorder and/or comorbid bipolar. To date, this knowledge has initiated few therapeutic changes in treating comorbid bipolar illness in the real world. In contrast, our data are new and clearly augment our understanding of decision-making in those with comorbid bipolar disorder with stimulant dependence in comparison to cocaine controls. Going forward, our results suggest that a shift in treatment strategies for this specific patient population may be warranted. For example, (1) integrating a cognitive restructuring component together with any pharmacotherapy is crucial, (2) initiating and regularly updating a contractual sobriety agreement at each visit, (3) adding ongoing relapse prevention therapy to help patients develop self-control strategies, and (4) introducing a contingency management program to help simultaneously avert both psychiatric deterioration and drug relapse seem critically important.

4.1. Limitations and strengths

Limitations of the present research include the use of a comorbid sample enrolled in a clinical trial who received antipsychotic study medication, lack of a bipolar control group, modest sample size, and the use of only one decision-making test. However, our data clearly augments the extant literature in a number of ways. First, there are no longitudinal studies examining IGT decision-making as a predictor of future drug use in comorbid bipolar disorder with cocaine or methamphetamine dependence. In contrast to those using IGT scores to *predict* self-reported drug use in subjects without mood disorders (Bowden-Jones et al., 2005; Schilt et al., 2009; Goudriaan et al., 2011; De Wilde et al., 2013), our study utilized appropriate regression analyses to empirically predict objective drug use indices over time. Thus, our results help close a methodological gap in our knowledge about recognizing and predicting future risks for drug relapse in this vulnerable comorbid patient population.

Second, patients receiving an antipsychotic were excluded from study enrollment as part of the inclusion/exclusion criteria for the parent trial (Nejtek et al., 2008). After the baseline assessments, study patients in the comorbid group were randomized to receive one of two FDA-approved atypical antipsychotics. At first blush, this might be considered a limitation introducing an external validity bias; however, almost half of the subjects (44%) did not remain consistently drug free during the study. If anything, one might suspect that the medication would prevent subjects from using drugs based on the self-medication hypothesis (Khantzian, 1985). As the self-medication hypothesis states that those with mood disorders use drugs to alleviate untreated symptomatology (Khantzian, 1985), we did not find the medication reduced drug use. Importantly, we found neither medication nor mood state influenced IGT decision-making or future drug use. Thus, our data do not indicate that medication use biased the results one way or another.

Third, we purposely chose to examine a cocaine control group rather than a bipolar control group to better determine potential relationships among stimulant use, decision-making, and clinical indices in those with comorbid bipolar disorder. In doing so, the data suggests that the addiction was a more robust factor influencing decisions concerning future drug use rather than the mood disorder. This is evident as the comorbid group received the standard level of care in the parent clinical trial (Nejtek et al. 2008), and although mood symptoms improved, drug use was prevalent.

Fourth, the modest sample size may reflect our exclusion of those with a substance-induced mood disorder or polysubstance abuse. The estimated rate of 34% of stimulant use disorders in bipolar disorder is higher than in any other psychiatric illness (Regier et al., 1990; Goldberg et al., 1999; Strakowski and DelBello, 2000; Strakowski et al., 2000; Cassidy et al., 2001). Thus, we sought patients with a current diagnosis of bipolar disorder with cocaine or methamphetamine dependence as a clinically challenging and worthwhile population to study in a typical community-based clinic setting. Importantly, our sample size is substantially larger than most currently available studies examining IGT decision-making in bipolar disorder (Clark et al., 2001, 2002; Christodoulou et al., 2006; Yechiam et al. 2008; Frangou et al., 2008).

Finally, the IGT was the only decision-making task used to predict drug use. However, as multiple tests often stress a bipolar patient's physical and mental endurance, we chose the IGT as a relatively short, simple, and no-cost assessment that is well-known in the addiction field to test our hypothesis. Examining only the IGT allowed us to focus on the benefits of using the IGT in a real-world clinic setting to help clinicians prevent drug use in their comorbid bipolar patients. Using a neurocognitive test battery would not have been helpful to clinicians in the field as they could not easily replicate an extensive test battery in a real-world clinic.

5. Conclusion

Until now, there are no longitudinal studies examining the relationships among clinical indices, decision-making and drug use in comorbid bipolar patients. The evidence supports the use of the IGT at the beginning of treatment to help clinicians predict future drug use, slips, or relapses in their most vulnerable comorbid bipolar patients. In doing so, clinicians will have valuable insight about the trajectory of their patient's future drug use and the need to employ relapse prevention therapy. Armed with this information, clinicians will have *a priori* knowledge to help them decide which patients they should monitor more closely and identify those who might benefit from adjunctive cognitive restructuring to prevent drug slips and relapses. Moreover, clinicians should realize that decisions to use drugs may not be influenced by pharmacotherapy, mood state, bipolar type, or drug diagnosis. While this study provides preliminary evidence supporting the ecological validity of the IGT, the data should be viewed with caution. More research is needed to confirm these findings and further define drug use trajectories in those with comorbid bipolar disorder with cocaine or methamphetamine dependence.

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