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Nehal P. Vadhan, Catherine E. Myers, Elysia Benedict, Eric Rubin, Richard W. Foltin, and Mark A. Gluck

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Nehal P. Vadhan
Columbia University College of Physicians and
Surgeons and New York State Psychiatric Institute

Catherine E. Myers
VA New Jersey Health Care System, East Orange, New Jersey,
and New Jersey Medical School, Rutgers University of
Medicine and Dentistry of New Jersey

Elysia Benedict
Columbia University College of Physicians and Surgeons, New
York State Psychiatric Institute, and Long Island University

Eric Rubin and Richard W. Foltin
Columbia University College of Physicians and Surgeons and
New York State Psychiatric Institute

Mark A. Gluck
Rutgers University

Aspects of stimulus-response (S-R) learning, mediated by striatal dopamine signaling, have been found to be altered in cocaine users relative to healthy controls. However, the influence of cocaine users' marijuana and alcohol use has not been accounted for. This study evaluated S-R learning and other neurocognitive functions in cocaine users while controlling for the relative influences of marijuana and alcohol use. Twenty-five long-term cocaine users and 2 control groups (25 moderate marijuana and alcohol users and 23 healthy controls) completed a computerized assessment of probabilistic category learning (the Weather Prediction task), as well as measures of equivalence learning, declarative learning, and executive, attentional, and motor function. Cocaine users exhibited decreased performance on the Weather Prediction task, as well as measures of declarative learning, attention, and motor function ($p < 0.05$), relative to both control groups. Cocaine users exhibited decrements in probabilistic category learning, declarative recall, and attentional and motor function, compared with both marijuana and alcohol users and nondrug users. Therefore, these decrements appear to be specifically related to the cocaine use, but not the moderate marijuana and alcohol use, of long-term cocaine users.

Keywords: cocaine, stimulus-response learning, habit learning, striatum, neuropsychological, cognitive

Learning and memory functions contribute to the development and maintenance of cocaine dependence (Di Chiara, 1999; Hyman, 2005), and continued use of cocaine may alter these functions (Everitt & Robbins, 2005; Garavan & Stout, 2005). Stimulus-response (S-R) learning refers to the incremental learning of re-sponses to stimuli based on feedback, which may be instrumental in the development of reactivity to cocaine-related cues. Errors in S-R learning may interfere with responding to the changing consequences of behavior and thus have particular relevance for the acquisition or maintenance of "habits." Moreover, they could

plausibly interfere with learning new, adaptive S-R associations during drug treatment.

S-R learning is mediated primarily by dopaminergic mechanisms in the basal ganglia (Packard & Knowlton, 2002), and decreased dopamine receptor availability and transmission in the striatum has been found in long-term cocaine users, relative to healthy control participants (Martinez et al., 2004; Martinez et al., 2007). Additionally, a lack of the typical age-associated changes in striatal gray matter (Ersche, Jones, Williams, & Bullmore, 2013) and reduced dopamine transporter availability (Wang et al., 1997) have been reported in long-term cocaine users, relative to healthy controls. Finally, decreased dopamine transmission in the striatum has been found to be prospectively associated with indicators of cocaine-taking in the human laboratory (Martinez et al., 2007) and clinic (Martinez et al., 2011). Thus, the relationship between decreased striatal dopamine function and cocaine use may be in part mediated by S-R learning, particularly as dependence progresses (Everitt & Robbins, 2005).

Two forms of S-R learning are probabilistic category learning and equivalence learning. Probabilistic category learning refers to the successful prediction of dichotomous outcomes from different stimulus compounds, when each stimulus is only a partially accurate predictor of the outcome. Equivalence learning refers to two superficially distinct stimuli coming to be regarded as equivalent as a function of both being repeatedly associated with the same response. Performance on two tasks that measure these functions (i.e., the Weather Prediction task; Gluck, Shohamy, & Myers, 2002; and the Acquired Equivalence task; Myers et al., 2003) has been related to dopamine function in the basal ganglia, with contributions from the medial-temporal lobe (Moustafa, Keri, Herzallah, Myers, & Gluck, 2010; Myers et al., 2003; Myers et al., 2008; Poldrack, Prabhakaran, Seger, & Gabrieli, 1999; Shohamy, Myers, Onlaor, & Gluck, 2004).

These hypothesized neural bases are distinct from the prefrontal cortex regions that are primarily associated with more commonly used tasks that incorporate incremental learning, such as the Wisconsin Card-Sorting Task (e.g., Lie, Specht, Marshall, & Fink, 2006) and the Iowa Gambling task (e.g., Bolla et al., 2003). Further, the S-R tasks incorporate complex features of learning such as multiple/probabilistic relationships between stimuli and outcome, that may better relate to the complex relationships between cocaine cues in the natural environment and cocaine taking behavior. Given these features, it is relevant to examine S-R learning effects in cocaine- dependent individuals.

In a previous study (Vadhan et al., 2008), we found that long-term active cocaine users made more errors on the Acquired Equivalence task than healthy controls (group $n = 18$) on the trials that required learning of new discriminations while maintaining the previously learned discriminations. Thus, cocaine users' learning of stimulus discriminations under conflicting response demands was decreased, a finding that is consistent with cocaine users' difficulty in acquiring new behavioral responses to cocaine cues while established responses are concurrently reinforced (i.e., during periods of regular cocaine use). However, many of the cocaine users in this study also used marijuana and alcohol, substances that could have influenced the neurocognitive results, either independently (e.g., Bates, Bowden, & Barry, 2002; Solowij & Battisti, 2008) or in interaction with cocaine or each other (e.g., Moreno-López et al., 2012). Further, the measurement of other

relevant neurocognitive functions was minimal, limiting conclusions about the breadth of cognitive dysfunction in cocaine users.

The purpose of the current study was to address these issues via a comparison of performance on the Weather Prediction and Acquired Equivalence tasks, as well as other neurocognitive tasks, between long-term cocaine users, controls with similar marijuana and alcohol use, and controls with no illicit substance use. Our primary hypothesis was that the cocaine users would exhibit decreased performance on the Acquisition phase of the Acquired Equivalence task relative to both control groups.

Method

Participants

Recruitment and screening procedures have been detailed elsewhere for an independent sample of participants (Vadhan et al., 2008) and are presented briefly here. Participants were all adults (18–60 years old) who were not seeking drug treatment, and their patterns of illicit substance use and nonuse were confirmed by urine toxicology tests during outpatient screening and testing. No participant met *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (*DSM–IV*) criteria for a lifetime psychotic or bipolar disorder, nor for any current Axis I psychiatric disorder, as assessed by the Structured Clinical Interview for *DSM–IV* (SCID; First, Spitzer, Gibbon, & Williams, 1995). All denied currently taking psychoactive medications. No participant met *DSM–IV* criteria for any current substance use disorder, except cocaine dependence for the cocaine users. All participants denied any history of HIV/AIDS. All participants signed a consent form that was approved by the New York State Psychiatric Institute's Institutional Review Board.

Cocaine Users

Twenty-five long-term cocaine users (COC) participated in this study. All met minimum criteria for self-reported cocaine use patterns (> 10 years of use, and currently using twice/week, $70/wk, via the smoked route) and met *DSM–IV* criteria for current cocaine dependence. All also denied current use of any psychoactive substance besides cocaine, alcohol, marijuana, nicotine, and caffeine. On the day of screening, all participants in this group tested positive for cocaine metabolites, all participants in this group who reported marijuana use tested positive for Δ^9-THC metabolites, and none tested positive for any other psychoactive substance. These results were replicated on the day of testing, except that only 60% of the marijuana-using cocaine users tested positive for Δ^9-THC metabolites.

Marijuana- and Alcohol-Using Control Participants

Twenty-five moderate marijuana and alcohol users (MJ/Alc) participated in this study. All denied current use of any psychoactive substance besides alcohol, marijuana, nicotine, and caffeine. Minimal reported lifetime cocaine exposure ($\leq$10 times) was allowed as long as no cocaine use had been reported for the past year. On the day of screening, all marijuana users in this group tested positive for Δ^9-THC metabolites, and no participant in this

group tested positive for any other psychoactive substance. These findings were replicated on the day of testing.

Healthy Control Participants

Twenty-three healthy controls (HC) participated in this study. All denied current use of any psychoactive substance besides minimal alcohol, nicotine, and caffeine. Minimal lifetime exposure to marijuana (≤10 times) and other illicit substances (≤2 times) except cocaine was allowed, as long as no use of these substances had been reported for the past year. No participant in this group tested positive for any psychoactive substance on screening or testing days.

Group Differences

Demographic and clinical characteristics for all groups are presented in Table 1. Continuous variables were analyzed with two-tailed Analyses of Variance (ANOVA) and categorical variables were analyzed with chi-square tests, with individual pairwise tests to probe significant overall findings ($p < 0.05$). The MJ/Alc group was younger than the other groups ($p < 0.05$). The COC group had minimally higher scores on the Beck Depression Inventory (BDI-II; Beck, Steer, & Brown, 1996) than the control groups ($p < 0.05$), but all Group BDI-II scores were in the normal range. The COC group also had a higher proportion of black participants than the MJ/Alc group ($p < 0.05$), but not more than the HC group ($p > 0.05$). No significant group differences were found on education, self-reported impulsivity (Eysenck & Eysenck, 1978) or sex ratio ($p > 0.05$).

Self-reported substance use characteristics for all participants are presented in Table 2. As expected, the COC and MJ/Alc groups reported greater alcohol use than the HC group ($p < 0.05$). The MJ/Alc group reported a greater weekly frequency of marijuana use than the COC group, but the reported weekly amount of marijuana consumption was similar ($p > 0.05$).

Regarding lifetime substance use disorders, 40% ($n = 10$) of the COC group met criteria for a past alcohol use disorder, 28% ($n = 7$) met criteria for a past marijuana use disorder, and 4% ($n = 1$) met criteria for a past stimulant (other than cocaine) use disorder; 8% ($n = 2$) of the MJ/Alc group met criteria for a past alcohol use disorder and 4% ($n = 1$) met criteria for a past marijuana use disorder. No HC participant met criteria for any lifetime substance use disorder.

Materials

Testing procedures and the computerized S-R tasks have been detailed elsewhere (Knowlton et al., 1994; Myers et al., 2003; Vadhan et al., 2008). An additional battery of tasks was administered to capture other cognitive functions of the basal ganglia and the medial-temporal lobe, as well as the prefrontal cortex (i.e., motor function, declarative learning and recall, and attention/executive functions; Lezak, Howieson, Bigler, & Tranel, 2012). All tasks were counterbalanced for order across participants.

Weather Prediction Task (Knowlton et al., 1994). This task used the modified probabilities of Gluck et al. (2002). On each of 200 trials, between 1 and 3 tarot cards were dealt (see Figure 1), and participants were instructed to predict the weather ("sun" or "rain") based on these cards. Participants entered their prediction by key response and were given accuracy feedback consisting of a smiley/frown face and upward/ downward movement on the score bar.

All possible combinations of 1, 2, or 3 cards were used. Each card was associated with each outcome with a fixed probability; thus, card 1 was associated with sun on 80% of the trials on which it appeared and with rain on 20% of the trials on which it appeared; similarly cards 2, 3, and 4 were associated with sun on 60%, 40%, and 20% of trials, respectively. Cards could appear in any spatial order, trials were presented in a random but fixed order for all participants, and the outcomes sun and rain appeared equally often (Gluck et al. 2002). The dependent measure was percent optimal

Table 1
Demographic and Clinical Characteristics

	Cocaine users		Marijuana and alcohol users		Healthy controls		Test value	p value[a]	Group comparisons[a, b, c, d]
	M	SD	M	SD	M	SD			
Age (yrs)	**42.7**	**4.5**	**31.2**	**6.4**	**39.8**	**7.9**	**$F(2, 70) = 22.0$**	**< 0.001**	**MJ/Alc < COC, HC**
Education completed (yrs)	13.5	1.4	14.3	2.1	14.9	2.3	$F(2, 70) = 2.8$	0.07	
BDI-II total score	**6.3**	**7.3**	**2.8**	**4.8**	**2.1**	**3.1**	**$F(2, 70) = 4.3$**	**< 0.05**	**COC > MJ/Alc, HC**
Impulsivity Questionnaire total score	26.7	7.4	25.1	5.4	23.4	3.7	$F(2, 70) = 1.8$	0.20	
	%	n	%	n	%	n			
Sex[e]									
Male	72.0	18	60.0	15	78.3	18	$\chi^2(2) = 2.0$	0.37	
Female	28.0	7	40.0	10	21.7	5			
Race[f]									
Black	**80.0**	**20**	**44.0**	**11**	**56.5**	**13**	**$\chi^2(2) = 7.7$**	**< 0.05**	**COC > MJ/Alc**
White	12.0	3	40.0	10	30.4	7			
Hispanic	8.0	2	12.0	3	8.7	2			
Other	0.0	0	4.0	1	4.3	1			

[a] Bold indicates overall group difference ($p < .05$). [b] Only conducted when omnibus ANOVA was significant. [c] $p < .05$. [d] COC = cocaine users, MJ/Alc = marijuana and alcohol users; HC = healthy controls. [e] Comparison based on Male vs. not Male. [f] Comparison based on Black vs. not Black.

Table 2
Substance Use Characteristics

	Cocaine users		Marijuana and alcohol users		Healthy controls		Test value	p value[a]	Group comparisons[b, c, d]
	M	SD	M	SD	M	SD			
Cocaine									
Duration of regular use (yrs)	20.0	3.8							
Amount ($/wk)	290.5	278.1							
Most recent use (hrs before testing)	37.4	29.7							
Most recent use ($)	100.9	90.6							
Marijuana[e]									
Frequency (days/wk)	**1.9**	**1.9**	**3.4**	**2.0**			**$F(1, 31) = 4.4$**	**<0.05**	**MJ/Alc > COC**
Amount ($/wk)	24.3	40.5	27.2	24.1			$F(1, 31) = 0.1$	0.80	
Most recent use (hrs before testing)	127.9	201.9	112.6	59.7			$F(1, 31) = 0.1$	0.80	
Most recent use ($)	11.6	14.4	6.9	5.3			$F(1, 31) = 1.9$	0.18	
Alcohol									
Frequency (days/wk)	**2.8**	**2.5**	**2.4**	**1.1**	**1.2**	**1.0**	**$F(2, 52) = 4.7$**	**<0.05**	**COC, MJ/Alc > HC**
Amount (SDUs/wk)	**10.7**	**13.1**	**7.7**	**5.6**	**2.4**	**1.8**	**$F(2, 52) = 3.4$**	**<0.05**	**COC > HC**
Most recent use (hrs before testing)	67.4	74.7	116.8	127.9	157.3	166.8	$F(2, 52) = 2.1$	0.14	
Most recent use (SDUs)	3.6	3.6	2.7	1.8	1.8	0.8	$F(2, 52) = 1.6$	0.20	

[a] Bold indicates overall group difference ($p < .05$). [b] Only conducted when omnibus ANOVA was significant. [c] $p < .05$. [d] COC = cocaine users, MJ/Alc = marijuana and alcohol users; HC = healthy controls. [e] Comparison only conducted between COC and MJ/Alc groups.

responding; that is, choosing the outcome that was most associated with each particular stimulus configuration over the course of the task (see Shohamy et al., 2004).

Acquired Equivalence Task (Myers et al., 2003). On each trial, the screen showed 1 of 4 distinct cartoon faces as an antecedent (A1, A2, B1, or B2) and 2 of 4 distinct cartoon fish as the consequents (X1, X2, Y1, or Y2). The participant decided which fish belonged to the person (at first by guessing) with a key response and received accuracy feedback. In Acquisition stage 1 (shaping), two antecedents were each associated with a different consequent (e.g., A1→X1, B1→Y1); in Acquisition stage 2 (equivalence training) the remaining two antecedents were each associated with a stage 1 consequent (A2→X1, B2→Y1). Acquisition stage 3 (novel consequents) consisted of two antecedents trained with novel consequents (A1→X2, B1→Y2). During the Transfer phase, participants were tested (with no feedback) on all six previously trained face-fish pairs as well as two novel (untrained) pairs (A2→X2, B2→Y2). The dependent measure for

Acquisition stages 1–3 was errors to criterion, and the dependent measures for the Transfer phase was the percent of total errors made on trials that tested novel and previously learned pairs.

The Repeatable Battery for Assessment of Neuropsychological Status (RBANS; Randolph, Tierney, Mohr, & Chase, 1998). In the List-Learning task, participants learn a list of 10 words over 4 trials of oral presentation by the examiner, and recall them without presentation or cues after a 15-min interrupted delay (verbal learning and recall). The dependent measure was the total number of words produced during the learning and recall trials. In the Figure Copy task, participants copy a complex geometric figure and reproduce it from memory after a 15-min interrupted delay (visuospatial construction and recall). The dependent measures were the total scores, based on accuracy, on the copy and recall trials. In the Digit Span task, participants orally reproduce increasingly long strings of numbers presented to them by the examiner (immediate memory and attention). The dependent measure was the total number of strings reproduced accurately.

Stroop Color-Word Task (Golden, 1978). In the Word condition, participants read a list consisting of the names of three colors ("RED," "GREEN" AND "BLUE"). In the Color condition, participants name the ink colors (red, green and blue) of a list of strings of Xs. In the Color-Word condition (conflict condition) participants name the ink colors (red, green and blue) of a list of the color names when these characteristics are mismatched (selective attention and response inhibition). Each condition consisted of 100 items and the dependent measure was the number of items completed in 45 sec for each condition.

Trailmaking Test (Reitan & Wolfson, 1985). On Part A, participants connect a series of 25 encircled numbers in ascending order (psychomotor speed). On Part B, participants connect a series of 25 encircled numbers and letters in ascending order, alternating between numbers and letters (alternating attention and cognitive flexibility). The primary dependent measure was the completion time for each part (sec).
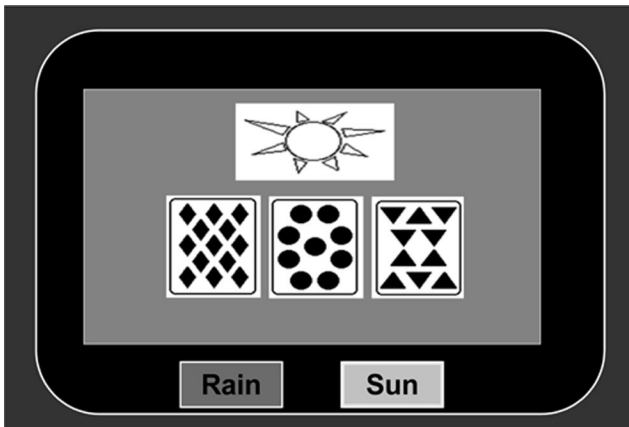

Figure 1. Weather prediction task stimuli.

Grooved Pegboard Test (Heaton, Grant, & Matthews, 1991). Participants place 25 grooved pegs into a series of matching holes one at a time (fine motor control and speed), and the primary dependent measure was the completion time for dominant and nondominant hands.

Procedure

All participants were instructed not to use any psychoactive substance on the morning of testing, except regular caffeine and nicotine; consistent with this requirement, no participant reported such use when queried. Before testing, all participants passed an alcohol breathalyzer test, and spent 30–45 min completing urine toxicology tests and self-report instruments. Additionally, no behavioral signs of intoxication were noted by the experimenter. Thus, it is unlikely that any participant was intoxicated during testing. Although nicotine use was not allowed during the session, a single caffeinated drink was permitted during the participants' lunch break.

Data Analyses

Weather Prediction Task. Only data from participants who completed all 200 trials were analyzed. Mixed (block × group) repeated-measures ANOVAs were used to examine group differences on mean percent of optimal responses on the following: 1) all 200 trials (4 blocks of 50 trials) and 2) the first 50 trials (5 blocks of 10 trials).

Acquired Equivalence Task. Only data from participants who completed Acquisition stage 3 within 96 trials were analyzed. Mixed-design repeated-measures ANOVAs were used to examine group differences on errors made during the following: 1) Acquisition stages 1–3 (stage × group) and 2) Transfer phase (trial type × group).

RBANS tasks. Between-groups univariate ANOVAs were used to examine raw score group differences on initial learning of the word list and figure, and performance on the Digit Span subtest. A between-groups univariate Analysis of Covariance (ANCOVA) was used to examine raw score group differences on recall of the word list and figure (learning and copy scores were the covariates, respectively).

Stroop, Trailmaking, and Grooved Pegboard tasks Mixed (condition × group) repeated-measures ANOVAs were used to examine group differences on these tasks.

All significant main effects and interactions were probed by pairwise univariate ANOVAs on the estimated marginal means. ANCOVA was used to address the potential confounding influence of group demographic and clinical differences, and was restricted to the level of main effects and interactions. Variables that were significantly different between groups and correlated with performance on at least one neurocognitive test were entered as covariates (these were race, age, and BDI-II scores; $p < 0.05$).[1] Although there were no group differences in sex ratio, sex was included as an additional covariate given the interest in the field in exploring the influence of sex on substance use–related outcomes (Tuchman, 2010).

Although all covariates were entered for analyses of all dependent measures, only those that changed the patterns of significance for the ANOVAs were reported. All analyses were considered

significant at $p < 0.05$; trends ($0.05 \leq p < 0.10$) were reported only for main effects and interactions and not probed further.

Results

Weather Prediction Task

All participants completed the required 200 trials. There was a within-subject effect of block ($F_{3, 210} = 28.4$, $p < 0.001$), with participants making more optimal responses as the task progressed (4, 3, 2 > 1; $p < 0.05$). There was also a between-subjects effect of group ($F_{2, 70} = 4.9$, $p < 0.05$), with the COC group making about 7–9% fewer optimal responses overall than both control groups ($p < 0.05$), but there was no block × group interaction ($p > 0.10$). When performance on the first 50 trials was examined as five 10-block trials (raw data not presented), there was no within-subject effect of block ($p > 0.10$), but there was a between-subjects effect of group ($F_{2, 70} = 4.5$, $p < 0.05$). The COC group made about 5–7% fewer optimal responses overall than both control groups ($p < 0.05$). No block × group interaction was seen ($p > 0.10$). Thus, all groups improved their optimal responding over time at equivalent rates, but the cocaine users produced fewer initial and fewer total optimal responses than controls (see Figure 2).

Acquired Equivalence Task

The data from this task as well as the other neurocognitive tasks are presented in Table 3 unless otherwise noted.

Five COC, three MJ/ALC, and two HC participants did not meet the completion criterion for the Acquired Equivalence task; these frequencies did not differ by group (Fisher's exact test = 1.3, $p > 0.10$). Regarding the Acquisition phase, there was a within-subjects effect of stage ($p = .01$), with participants making more errors during stage 3 than stage 1 ($p = .001$). There was no between-subjects effect of group or stage × group interaction ($p > 0.10$), indicating that all groups acquired stimulus discriminations similarly.

Regarding the Transfer phase, there was a within-subjects effect of trial type ($p < 0.001$), with participants making a greater percentage of errors on the new (Transfer phase) discriminations than the old (Acquisition stage 1) discriminations. There was no between-subjects effect of group or stage × group interaction ($p > 0.10$). However the stage × group interaction reached significance ($F_{2, 59} = 3.9$, $p < 0.05$) after race was entered as a covariate, with a trend for COC participants to make a greater percentage of errors than HC participants on old trial types ($p = .05$).

RBANS List-Learning Task

There was no between-subjects effect of group on words produced on the learning trials ($p > 0.10$), but there was an effect of group for words produced on the recall trial ($p < 0.001$) with initial learning controlled for. The COC group recalled about 2

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[1] Marijuana and alcohol use variables were not entered as covariates because (1) the alcohol use of the cocaine users was already controlled for by the alcohol use of the MJ/Alc group, and (2) < 50% of the entire sample were marijuana users, which would significantly limit the ANCOVA's power.
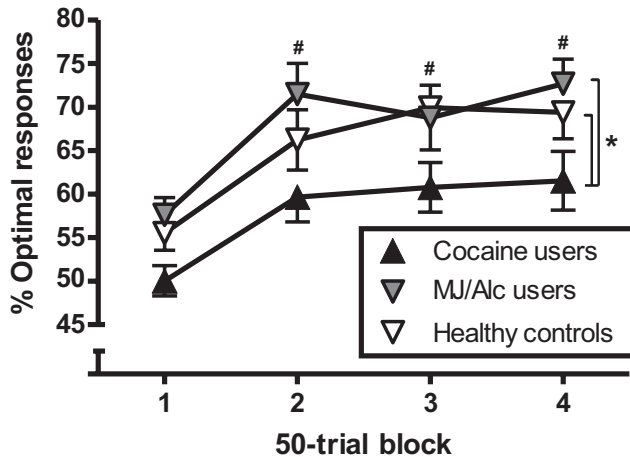
Figure 2. Weather prediction task performance; percent of optimal responses by blocks of trials in cocaine users and controls; each error bar represents one SEM; # indicates an overall within-subject difference from block 1 ($p < 0.05$); * indicates an overall between-group difference between the cocaine users and each control group ($p < 0.05$).

fewer words than both controls groups ($p < 0.05$). Thus, initial learning of words was similar among all groups, but the cocaine users exhibited poorer delayed recall than controls.

RBANS Figure Copy Task

There was a between-subjects effect of group on total score of the copy trial ($p < 0.05$), with the MJ/Alc group scoring about 2–2.5 more points than the COC and HC groups ($p < 0.05$). There was an effect of group for total score on the recall trial, controlling for the copy performance ($p < 0.01$), with the HC group scoring about 2–3 more points than the COC group ($p < 0.05$). Thus, the cocaine users copied the figure less accurately than the marijuana/alcohol users, and reproduced it less accurately after a delay than the healthy controls. The group effect on figure copy was lost after age was entered as a covariate ($p > 0.10$), but the effect on figure recall was preserved ($p < 0.05$).

RBANS Digit Span Task

There was a between-subjects effect of group on the total raw score ($p < 0.01$), with the COC group correctly reproducing about 2.5 strings fewer than both controls groups ($p < 0.01$), indicating decreased immediate memory and attention relative to controls.

Stroop Task

There were within-subject effects of condition ($p < 0.01$) for the Stroop, Trailmaking, and Grooved Pegboard tasks that were in the expected direction (e.g., Trails B > Trails A).

On the Stroop task, there was a between-subjects effect of group ($F_{2, 70} = 4.8$, $p < 0.05$), with the COC group performing less well on the task overall than MJ/Alc group, and there was also a condition $\times$ group interaction ($F_{4, 140} = 2.6$, $p < 0.05$). When each condition was analyzed separately, there were main effects of group for the Word and Color-Word conditions ($p < 0.05$). Pair-

wise comparisons revealed that the COC group completed more than 12 fewer items than the MJ/Alc group under the Word condition ($p < 0.01$), and about 6–10 fewer items than both control groups under the Color-Word condition ($p < 0.05$). Thus, the cocaine users experienced greater interference on the Stroop task than the controls. When race was entered as a covariate, the condition $\times$ group interaction was reduced to a trend ($p < 0.10$).

Trailmaking Test

There was a between-subjects effect of group ($p < 0.01$) on the Trailmaking test, with the COC group taking longer than both control groups ($p < 0.05$) to complete the task overall. There was also a condition $\times$ group interaction ($p < 0.01$). When each condition was analyzed separately, there was a group main effect for Part B ($p < 0.01$), with the COC group completing it about 18–21 sec slower than each control group ($p < 0.05$). Thus the cocaine users exhibited decreased alternating attention and cognitive flexibility (Part B) relative to controls, despite similar psychomotor speed (Part A). The initial group effect was reduced to a trend ($p < 0.10$) when race or age was entered as a covariate, but the interaction was preserved ($p < 0.05$; see Figure 3).

Grooved Pegboard Test

There was a between-subjects effect of group ($p < 0.01$), with the COC group taking about 14–19 sec longer to complete the task (averaged between dominant and nondominant hands) than both control groups ($p < 0.05$). There was no condition $\times$ group interaction ($p > 0.10$). Thus, the cocaine users exhibited decreased bilateral motor performance relative to controls.

There were no differences between the 2 control groups ($p > 0.10$) on any task. Inclusion of BDI-II scores or sex ratio as covariates did not change the significance patterns for any analyses.

Discussion

In this study, long-term active cocaine users exhibited less optimal learning of probabilistic categorical relationships (Weather Prediction task) than control participants who were similar in reported use of marijuana and alcohol, and control participants who did not use illicit substances. The cocaine users also exhibited decreased performance on measures of declarative recall (List and Figure Recall), attention (Trailmaking and Digit Span tasks), and motor function (Grooved Pegboard task), relative to both control groups. However, contrary to our hypothesis, no group differences were seen on equivalence learning (Acquired Equivalence task).

The Weather Prediction task results suggest that active cocaine users have greater difficulty than noncocaine users in learning to predict outcomes when the predictors are only probabilistically related to the outcome, a difficulty that was consistently apparent during performance. Problems in cognitively distilling probabilistic relationships may underlie difficulty with reducing cocaine use, because the negative consequences of cocaine use and the positive consequences of cocaine abstinence are typically uncertain. Although a decrement on the Weather Prediction task was not revealed in our previous study (Vadhan et al., 2008), the results of the current study do converge with the results of a study of

Table 3
Neurocognitive Test Performance

	Cocaine users		Marijuana and alcohol users		Healthy controls		ANOVA results[a, b]	Pairwise comparisons[a, c, d, e, f]
	M	*SD*	*M*	*SD*	*M*	*SD*		
Acquired Equivalence task[g]								
Acquisition Phase							**Stage: $F(2, 120) = 4.7$, $p = .01$; Group: $F(2, 60) = 2.1$, $p = .13$; Condition × group: $F(4, 120) = 1.4$, $p = .25$**	**Stage: 3 > 1**
Stage 1 (# errors)	2.1	2.0	1.6	1.7	1.1	1.5		
Stage 2 (# errors)	4.2	6.5	1.4	1.9	1.9	1.9		
Stage 3 (# errors)	3.5	3.0	4.1	5.1	2.9	3.9		
Transfer Phase							**Trial type: $F(1, 60) = 18.4$, $p < .001$; Group: $F(1, 60) = 0.7$, $p = .51$; Condition × group: $F(2, 60) = 1.7$, $p = .19$**	**Trial type: New > Old**
"Old" (% errors)	12.3	16.7	8.9	10.1	4.0	7.7		
"New" (% errors)	16.6	21.1	24.3	30.3	17.4	22.5		
RBANS List Learning								
Learning trials 1–4 (raw)	27.0	12.7	29.0	4.4	29.0	3.7	Group: $F(2, 70) = 0.5$, $p = .60$	
Recall (raw)[h]	**4.6**	**2.5**	**6.7**	**2.6**	**6.8**	**2.1**	**Group: $F(3, 69) = 9.1$, $p < .001$**	**COC < MJ/Alc, HC**
RBANS Figure Copy								
Copy (raw)	**14.6**	**4.1**	**16.7**	**3.0**	**14.2**	**2.9**	**Group: $F(2, 70) = 3.8$, $p = .03$**	**MJ/Alc > COC, HC**
Recall (raw)[h]	**9.2**	**4.6**	**12.5**	**4.6**	**11.5**	**3.2**	**Group: $F(3, 69) = 4.1$, $p < .01$**	**HC > COC**
RBANS Digit Span	**10.0**	**2.5**	**12.4**	**2.4**	**12.5**	**2.5**	**Group: $F(2, 70) = 8.5$, $p = .001$**	**COC < MJ/Alc, HC**
Stroop Color-Word task							**Condition: $F(2, 140) = 995.1$, $p < .001$; Group: $F(2, 70) = 4.9$, $p < .05$; Condition × group: $F(4, 140) = 2.6$, $p < .05$**	**Condition: W > C > CW; Group: MJ/Alc > COC; Condition × group: see below**
Word (items)	**91.8**	**16.7**	**104.4**	**13.8**	**99.5**	**13.9**	**Group: $F(2, 70) = 4.6$, $p < .05$**	**MJ/Alc > COC**
Color (items)	68.6	10.2	71.2	10.1	70.0	12.0	Group: $F(2, 70) = 0.4$, $p > .05$	
Color-Word (items)	**32.6**	**8.5**	**42.7**	**8.9**	**39.1**	**9.3**	**Group: $F(2, 70) = 8.3$, $p = .001$**	**COC < MJ/Alc, HC**
Grooved Pegboard test							**Condition: $F(1, 70) = 39.6$, $p < .001$; Group: $F(2, 70) = 7.9$, $p = .001$; Condition × group: $F(2, 70) = 1.3$, $p = .27$**	**Condition: ND > D; Group: COC > MJ/Alc, HC**
Dominant (sec)	85.6	21.9	66.9	10.5	71.0	12.3		
Nondominant (sec)	95.4	31.4	75.2	11.6	86.0	17.1		

[a] Analyses are uncorrected for race, age, sex or BDI-II scores. [b] Bold indicates overall group difference ($p < .05$). [c] Only conducted when omnibus ANOVA was significant. [d] $p < .05$. [e] COC = cocaine users; MJ/Alc = marijuana and alcohol users; HC = healthy controls. [f] W = Word; C = Color; CW = Color-Word; D = dominant hand; ND = nondominant hand. [g] Analyses only conducted for Stage 3 solvers. [h] Analyses are corrected for Learning/Copy trial performance.

decision-making (Verdejo-Garcia et al., 2007); this study found that cocaine users exhibited suboptimal choices on a simulated gambling task dependent on incremental learning, relative to near-daily marijuana smokers and healthy controls.

It is interesting to note, however, that the current study and all previous studies that have examined Weather Prediction task performance in cocaine users (Gonzalez et al., 2008; Vadhan et al., 2008) have shown increased learning over trials. This ability to learn from feedback during the task, albeit suboptimally, contrasts with the relative lack of learning on the Weather Prediction task shown by participants with Parkinson's disease (Knowlton, Mangels, & Squire, 1996) and Tourette's syndrome (Marsh et al., 2004). These two disorders, like cocaine dependence, are characterized by striatal dopamine dysregulation. However the degree of striatal pathophysiology and behavioral compulsion in these disorders is greater than that seen in cocaine dependence, which may be reflected in differing performance on this measure of habit learning.

The cocaine users' performance on the Acquisition Phase of the Acquired Equivalence task was similar to that of controls', indicating that their ability to form simple (i.e., nonprobabilistic) associations between discrete stimuli was largely intact. Although these data differ from our previous study (Vadhan et al., 2008), they do corroborate the conclusion from that study that impairment on the two S-R learning tasks is dissociated in cocaine users. The impaired transfer of old pairs in the cocaine groups, once group differences in racial composition were accounted for, may indicate mild difficulty with generalization of learning. This pattern mirrors that seen on the RBANS Figure and List-Learning tasks, for which cocaine users' initial learning was preserved, but delayed recall (which is also hippocampal-dependent) was decreased relative to the controls'.

The cocaine users also exhibited decreased performance on the Digit Span, Trailmaking Part B, and Grooved Pegboard tasks, relative to their control groups. Of note, performance on these tasks ranged from 1.3 to 1.5 *SD*s below the performance of
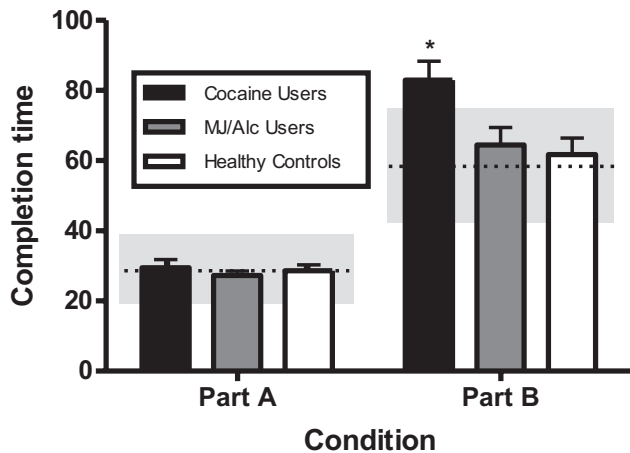
Figure 3. Trailmaking test performance; completion time (sec) by condition in cocaine users and controls; each error bar represents one SEM; * indicates a between-group difference between the cocaine users and each control group (*p* < 0.05); dotted lines and shaded areas represent the normative mean ± 1 *SD* for the task (Tombaugh, 2004).

independent normative samples (e.g., Tombaugh, 2004). Although prior findings from studies of cocaine users with these tasks are mixed (Gillen et al., 1998; Kalapatapu et al., 2011; Robinson, Heaton, & O'Malley, 1999; Smelson, Roy, Santana, & Engelhart, 1999; Toomey et al., 2003; Woicik et al., 2009), the Digit Span and Trailmaking data are consistent with a meta-analysis (Jovanovski, Erb, & Zakzanis, 2005) that highlighted attention as the most robustly decreased function in cocaine users. The clinical relevance of this observation is demonstrated by the prospective relationship between attentional performance and treatment outcome for cocaine abuse (Aharonovich, Nunes, & Hasin, 2003; Carpenter, Martinez, Vadhan, Barnes-Holmes, & Nunes, 2012). The burgeoning literature on habit learning in substance abusers may also point toward a significant role for S-R learning, which may be influenced by attentional decrements, in cocaine dependence.

Although no studies were found in which Grooved Pegboard task performance predicted treatment outcome for cocaine abuse, one study found that it may be related to employment outcomes in methamphetamine users (Weber et al., 2012). Further, performance on this task is considered a biomarker for dopamine dysfunction of the nigrostriatal pathway in Parkinson's patients (Bohnen, Kuwabara, Constantine, Mathis, Moore, 2007). Thus the Grooved Pegboard results from the current study are consistent with findings of dopamine depletion across the striatum in cocaine users (e.g., Martinez et al., 2007).

Regarding the other tasks, group differences were originally seen on the Figure Copy and Stroop tasks, but they did not survive correction for age or race. This highlights the importance of controlling for demographic differences in neurocognitive research in substance abusers (Bedi & Redman, 2008; Woicik et al., 2009), particularly if the investigators seek to associate neurocognitive decrements with the primary drug of abuse. Yet, despite the statistical corrections, the influence of these differences on the other results of the current study cannot be definitively ruled out.

Further, although the current marijuana and alcohol use of the cocaine users was fairly well-controlled for by the substance-using control group, the study was not designed to assess the specific influence of these substances (either past or present) within each group on neurocognitive performance. The study design may also have been underpowered to test for the various factor interactions. Finally, the influence of motivation on task performance (Vadhan, Hart, Haney, van Gorp, & Foltin, 2009) was not addressed in this study.

This study was the first, to our knowledge, to examine these S-R learning functions in cocaine users in comparison with both drug-using and nondrug-using controls. Additionally, all of the cocaine users were required to submit cocaine-positive urine samples on the day of testing. These methodological strengths address common limitations of neurocognitive studies of cocaine users, and allow the observed neurocognitive decrements to be more closely tied to the cocaine use of the participants. As such, the results of this study were not consistent with the suggestion that recent cocaine use may mask cognitive problems in cocaine users (Woicik et al., 2009).

In sum, this study demonstrated performance decrements in probabilistic category learning and other neurocognitive functions in long-term cocaine users, when compared with both healthy controls and moderate marijuana and alcohol users. These decrements may be related to the degree of frontostriatal DA alterations present in heavy cocaine users, but not moderate users of marijuana and alcohol, and may shed light on why cocaine users find it more difficult to initiate changes in their drug-related behavior. However, it remains unknown whether these decrements are the result of long-term cocaine use, or existed before the initiation of cocaine use, in human participants. Future studies may further clarify the relationships between cocaine use, dopamine, and S-R learning, by examining these functions in less-experienced cocaine users, and concurrently with neurobiological measures of frontostriatal dopamine function or in the context of acute cocaine intoxication.

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