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Learning functions in short-term cocaine users

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ABSTRACT

Objective: This study examined learning functions in short-term cocaine users and control participants.

Method: Seventeen active cocaine users (reporting 3.5 mean years of cocaine use) and seventeen non-cocaine-using controls (with similar reported levels of alcohol and marijuana use) were compared on tasks measuring different aspects of learning.

Results: The cocaine users performed more poorly on the Weather Prediction and List-Learning tasks, as well as supplementary executive and psychomotor function tasks, than controls.

Conclusions: Individuals with a relatively short duration of cocaine use exhibited moderate weaknesses in probabilistic category learning, verbal learning and psychomotor functions, relative to controls. These weaknesses may underpin difficulty in learning from the probabilistic consequences of behavior and hinder the ability to respond to cognitive-behavioral treatments.

1. Introduction

Changes in learning functions may be associated with cocaine use disorder from both etiological and consequential perspectives (Di Chiara, 1999; Garavan & Stout, 2005) and may impair treatment efforts (Cadet & Bisagno, 2016). Biases in stimulus-response (S-R) learning, defined as the feedback-based incremental learning of responses to stimuli that may be relevant to the learning of habits (Packard & Knowlton, 2002), have been observed in cocaine users (Strickland, Reynolds, & Stoops, 2016; Vadhan et al., 2008, 2014). This may be rooted in altered striatal dopamine signaling (e.g., Martinez et al., 2007; Porter-Stransky et al., 2011), which itself may change during extended cocaine exposure (Letchworth, Nader, Smith, Friedman, & Porrino, 2001).

Similar alterations are evident in primary users of other substances (e.g., Mátyássi et al., 2012; Myers et al., 2016, 2017; van de Giessen et al., 2016), potentially implicating cocaine users' use of these and

other substances as a confounding explanation for neural and cognitive alterations. Yet weaknesses in probabilistic category learning (i.e., S-R categorization of stimuli based on probabilistic feedback), verbal learning and visual recall, as well as executive, attention and motor functions, have been found in long-term cocaine users even after secondary alcohol or marijuana use has been accounted for (Vadhan et al., 2014). This is clinically-relevant in that the ability to learn, remember and execute responses accordingly is critical to acquiring (and changing) habitual behavior, and suggests that the secondary substance use of cocaine users does not play a critical role in this regard.

However, the population of cocaine users is heterogeneous, and subtypes (e.g., current vs. former users, treatment seekers vs. non-treatment seekers) have been found to exhibit distinct neurobehavioral characteristics (e.g., Castelluccio, Meda, Muska, Stevens, & Pearson, 2014; Moeller et al., 2018), highlighting the potential complexity of the relationship between cocaine use and cognitive function. For example, relatively older cocaine users (mean age: 56.8 yrs) exhibited worse

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performance on tests of attention and psychomotor speed, compared to younger cocaine users (mean age: 34.5 yrs) and age-similar controls (Kalapatapu et al., 2011).

One consistent factor among the subtypes of cocaine users in the studies cited above is the relatively long average duration of the participants' reported cocaine use (i.e., mean use: 10–21 yrs). As such, an open question is the extent to whether that amount of cocaine exposure is necessary for cognitive weaknesses (particularly those in learning) to be apparent, or that relatively shorter exposure is sufficient. Although cocaine users' neurocognition has been studied extensively (e.g., Frazer, Richards, & Keith, 2018), with potential confounding factors such as age and use of other substances accounted for in some studies (e.g., Kalapatapu et al., 2011; Vadhan et al., 2014), individuals specifically with relatively short-term (ST) cocaine exposure have not been explicitly studied to our knowledge. This is important, since individuals early in their cocaine-using trajectories may have less ingrained cocaine use patterns and are perceived to be more responsive to psychological interventions. An examination of learning task performance in such individuals would shed greater light on the cocaine exposure sufficiency question, habit learning and the capacity to respond to interventions.

Therefore, the purpose of the current study was to compare the performance of short-term cocaine users on tasks of S-R learning and declarative memory (i.e., explicit and intentional learning and recall of information), as well as related cognitive functions, to age-similar controls with similar alcohol and marijuana use. We hypothesized that the users would exhibit weaker performance on these tasks than non-cocaine users with similar marijuana and alcohol use.

2. Methods

This study was approved by the NYS Psychiatric Institute IRB, and all participants provided written informed consent. Participant recruitment and data collection methods were nearly identical to a previous study (Vadhan et al., 2014).

2.1. Participants

Participants were all nontreatment-seeking English-speaking adults (32.3% female) who were recruited primarily from 2010 to 2012 through local advertisements. Participants were excluded if they reported neurological or developmental disorders, met *DSM-IV* criteria for any current Axis I psychiatric disorders or lifetime psychotic or bipolar disorder, or were using other substances besides cocaine, marijuana, alcohol, nicotine, or caffeine. Urine toxicology tests were used to confirm participants' reported substance use and nonuse at screening and testing sessions.

2.2. Short-term (ST) cocaine users

Cocaine users ($n = 17$) were required to report that they had used cocaine for < 10 years¹ (observed range was 1–8 yrs) and that they were currently spending at least \$50 per week on cocaine. The proportion of reported primary routes of cocaine administration was as follows: smoked (58.8%; $n = 10$), intranasal (35.3%; $n = 6$), and intravenous (5.8%; $n = 1$). Twelve (70.6%) participants met *DSM-IV* criteria for a cocaine use disorder.

2.2.1. Control participants

Control participants ($n = 17$) were non-cocaine users (< 10 reported lifetime exposures to cocaine, none within the last year). Current

¹ This criterion was based on unpublished data in an independent sample of cocaine users from the laboratory indicating physiological differences ($p < 0.05$) between participants above and below this threshold.

alcohol and marijuana use was permitted, to control for the cocaine users' use of these substances. None of the control participants met *DSM-IV* criteria for any current or lifetime substance use disorder. 10 of these participants were newly recruited for this study; 7 were sampled from the previous study (Vadhan et al., 2014) based on demographic criteria (with neurocognitive data blinded), to enlarge the sample size.

Demographic, clinical and substance use characteristics for both groups are presented in Table 1, and were analyzed with two-tailed Analyses of Variance (ANOVA) or chi-square tests. Other than reported years of education (controls > cocaine users; $p < 0.05$), there were no significant group differences on these measures ($p > 0.05$).

2.3. Measures

Testing procedures, the computerized S-R tasks and the standard neuropsychological tests have been described elsewhere (Knowlton, Squire, & Gluck, 1994; Myers et al., 2003; Vadhan et al., 2008). All tasks were counterbalanced for order across participants, all participants were tested as outpatients, and standard measures were taken to rule out participant intoxication during testing. On average, the cocaine users' reported last use of cocaine was about 1 1/4 days prior to testing, and all tested positive for urine-cocaine metabolites on the day of testing.

2.3.1. S-R learning tasks

On the Acquired Equivalence Task (Myers et al., 2003), participants were asked to associate antecedent stimuli (cartoon faces) with consequent stimuli (cartoon fish), via accuracy feedback through three Acquisition stages (shaping, equivalence training, and novel consequents). During the test phase (Transfer) participants were tested (with no feedback) on previously-trained as well as novel stimulus pairs. The dependent measures for each phase were the number and percent of errors made, respectively.

On the Weather Prediction task (Knowlton et al., 1994), participants were instructed to predict probabilistic outcomes based on stimulus array of one to three tarot cards based on ongoing accuracy feedback, with performance measured by the percent of optimal responses across 200 trials.

2.4. Declarative memory tasks (RBANS; Randolph, Tierney, Mohr, & Chase, 1998)

The List-Learning and Figure Copy tasks were used to assess declarative memory. On the List-Learning task, participants learned a list of ten words over four trials and were asked to recall the words after a delay. On the Figure Copy task, participants were asked to copy and reproduce a complex geometrical figure.

2.4.1. Executive, attention and motor tasks

Several tests of executive function, attention, and motor control were administered as supplementary tasks, in parallel with the methodology of Vadhan et al. (2014). On the Stroop Color-Word task (Golden, 1978), participants were asked to name the colors of color names when they were mismatched, as well as complete word-reading and color-naming control conditions. The dependent measure was the number of items on each list completed within 45 s. On the Trail-making test (Reitan & Wolfson, 1985), participants were asked to connect a series of 25 encircled numbers (Part A) and a series of 25 encircled numbers and letters, alternating between the numbers and letters (Part B). The dependent measure was completion time. On the RBANS Digit Span task, participants were asked to reproduce long strings of numbers. The dependent measure was the raw accuracy score. On the Grooved Pegboard test (Heaton, Grant, & Matthews, 1986), participants were asked to place 25 grooved pegs into matching holes with both dominant and nondominant hands. The dependent measure was completion time.

Table 1
Demographic and clinical characteristics.

	Short-term cocaine users		Controls		Test value	P value ^a
	M	SD	M	SD		
Age (yrs)	35.6	9.5	34.3	10.1	t (32) = -0.4	0.50
Education completed (yrs)	12.6	1.7	14.1	2.3	t (32) = 2.2	0.04
BDI-II total score	4.9	7.0	3.6	5.2	t (32) = -0.6	0.56
Impulsivity Questionnaire total score	25.0 ^b	6.1	25.6 ^c	4.3	t (22) = 0.3	0.79
Sex	%	n	%	n		
Male	76.5	13	58.8	10	χ^2 (1) = 1.2	0.27
Female	23.5	4	41.1	7		
Race ^d						
Black	47.1	8	35.3	6	χ^2 (1) = 0.5	0.49
White	5.9	1	41.2	7		
Hispanic	35.3	6	17.6	3		
Other	11.8	2	5.9	1		
Cocaine	M	SD				
Duration of regular use (yrs)	3.5	2.5				
Frequency (days/wk)	4.4	1.7				
Amount (\$/wk)	194.1	157.0				
Most recent use (hrs prior to testing)	30.9	17.9				
Most recent use (\$)	54.3	45.9				
Alcohol	n = 13	76.5%	n = 13	76.5%	χ^2 (1) = 1.2	0.27
	M	SD	M	SD		
Frequency (days/wk)	1.8	2.4	2.2	1.2	t (24) = 0.5	0.61
Amount (SDUs/wk)	4.7	5.7	7.6	5.3	t (24) = 1.3	0.20
Marijuana	n = 4	23.5%	n = 7	41.1%	χ^2 (1) = 0.5	0.49
	M	SD	M	SD		
Frequency (days/wk)	1.9	1.6	2.4	1.5	t (9) = 0.6	0.57
Amount (\$/wk)	12.8	16.6	29.4	34.1	t (9) = 0.9	0.39
Both marijuana and alcohol	n = 3	17.6%	n = 7	41.2%	χ^2 (1) = 2.3	0.13

^a Bold indicates overall group difference ($p < 0.05$).

^b $n = 14$.

^c $n = 10$.

^d Comparison based on Black vs. not Black.

2.5. Data analyses

As in the Vadhan et al. (2014) study, the Acquired Equivalence, Weather Prediction, Stroop, Trailmaking and Pegboard tasks were analyzed using mixed repeated measures ANOVAs. Significant condition \times group interactions were probed with t -tests. The List-Learning, Figure Copy, and Digit Span tests were analyzed with between-group univariate tests (ANOVAs for initial learning trials, and for List-Learning and Figure Copy, Analyses of Covariance [ANCOVA] for recall trials [with initial learning trials serving as the covariates]). Additionally, since level of education differed between groups, and was (only) correlated with List-learning performance, it was entered as an additional covariate for the List-learning analysis.

3. Results

See Table 2 for raw data and full statistical results.

3.1. Weather prediction task (Fig. 1)

All participants completed the required 200 trials. There was an effect of block ($F_{3, 96} = 15.5$, $p < 0.01$), with participants overall making more optimal responses after the first block (4, 3, 2 > 1; all $p < 0.01$). There was also an effect of group ($F_{1, 32} = 5.0$, $p < 0.05$), with the ST cocaine group exhibiting about 9% fewer optimal responses than the control group overall. There was no block \times group interaction ($p > 0.10$). Thus, the ST cocaine group exhibited weaker probabilistic category learning than the control group.

3.2. Acquired equivalence task²

In the Acquisition phase, there was a trend effect for errors to increase across stages ($F_{2, 54} = 2.6$, $0.05 < p < 0.10$). There was no effect of group ($p > 0.10$) nor a stage \times group interaction ($p > 0.10$). In the transfer phase, there was an effect of trial type ($F_{1, 27} = 9.4$, $p < 0.01$), with participants overall making more errors on the new stimulus pairs than the old pairs overall. There was no effect of group ($p > 0.10$) nor a trial type \times group interaction ($p > 0.10$).

3.3. List-learning task

There was an effect of group ($F_{1, 32} = 6.6$, $p < 0.05$) on the learning trials, with the control group scoring about 3.5 points higher on the learning trials than the ST cocaine group. There was no effect of group (with learning performance as a covariate) on the recall trials ($p > 0.10$), and this did not change after education was entered as a covariate. Thus, the ST cocaine group learned fewer words than the control group initially, but after accounting for this learning difference (and differential educational level), the ST cocaine group did not exhibit weaker recall performance.

3.4. Figure copy task

There was no effect of group on the copy trial ($p > 0.10$), but there

² Only data from participants who completed Acquisition stage 3 within 96 trials were analyzed.

Table 2
Neurocognitive test performance.

	Cocaine users		Healthy controls		ANOVA results ^a	Pairwise comparisons ^{a,b,c,d}
	M	SD	M	SD		
Acquired equivalence task^e						
Acquisition phase						
Stage 1 (# errors)	1.5	2.5	1.7	1.7	Stage: $F(2,54) = 2.6, p = 0.08$; Group: $F(1,27) = 0.1, p = 0.71$; Condition \times group: $F(2,54) = 0.6, p = 0.58$	
Stage 2 (# errors)	2.1	3.9	1.7	2.1		
Stage 3 (# errors)	3.7	6.1	2.5	3.4		
Transfer phase						
“Old” (% errors)	5.6	6.2	6.8	10.4	Trial type: $F(1,27) = 9.4, p < 0.01$; Group: $F(1,60) = 0.7, p = 0.51$; Condition \times group: $F(1,27) = 0.1, p = 0.74$	Trial type: New > Old
“New” (% errors)	14.9	18.7	14.3	18.7		
RBANS list learning^f						
Learning trials 1–4 (raw)	26.4	3.9	29.9	4.1	Group: $F(1,32) = 6.6, p = 0.02$	
Recall (raw) ^g	5.7	2.3	7.2	1.9	Group: $F(1,31) = 0.5, p = 0.50$	
RBANS figure copy						
Copy (raw)	16.4	3.0	15.8	3.4	Group: $F(1,32) = 0.2, p = 0.64$	
Recall (raw) ^g	10.7	3.6	12.2	4.3	Group: $F(1,31) = 3.5, p = 0.07$	
RBANS digit span						
Digit span	10.5	2.7	11.5	2.2	Group: $F(1,32) = 1.4, p = 0.24$	
Stroop Color-Word task						
Word (items)	95.3	13.8	104.5	10.4	Condition: $F(2,64) = 471.2, p < 0.001$; Group: $F(1,32) = 6.1, p = 0.02$; Condition \times group: $F(2,64) = 0.3, p = 0.73$	Condition: W > C > CW; Group: CONT > COC
Color (items)	68.6	10.5	74.8	11.8		
Color-word (items)	37.6	8.5	44.7	10.0		
Trailmaking test						
Part A (sec)	30.7	9.4	27.1	7.2	Condition: $F(1,32) = 115.9, p < 0.001$ (B > A) ; Group: $F(1,32) = 7.8, p < 0.01$ (COC > CONT); Condition \times group: $F(1,32) = 8.3, p < 0.01$	Condition: B > A; Group: COC > CONT
Part B (sec)	80.3	27.0	55.7	14.5		
Grooved Pegboard test						
Dominant (sec)	74.2	9.7	64.7	5.2	Condition: $F(1,32) = 48.7, p < 0.001$ (ND > D) ; Group: $F(1,32) = 5.7, p = 0.02$; Condition \times group: $F(1,32) = 3.7, p = 0.06$	Condition: D > ND; Group: COC > CONT
Nondominant (sec)	82.4	8.3	79.2	11.8		

^a Bold indicates significant difference ($p < 0.05$)

^b Only conducted when omnibus ANOVA was significant.

^c COC = cocaine users, CONT = controls.

^d W = Word, C = Color, CW = Color-Word, A = Part A, B = Part B, AD = dominant hand, ND = nondominant hand.

^e Analyses only conducted for Stage 3 solvers.

^f Data and analyses are presented as uncorrected for educational level.

^g Analyses are corrected for Learning/Copy trial performance.

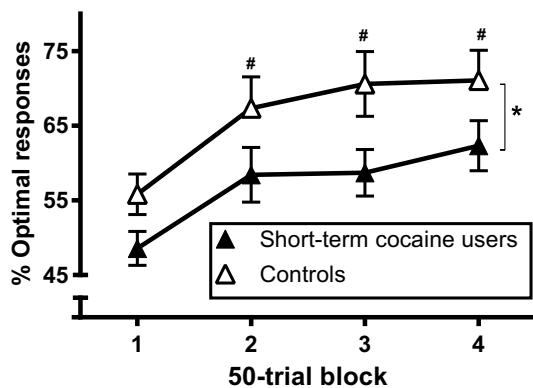


Fig. 1. Percent of optimal responses by blocks of trials in cocaine users and controls on the Weather Prediction Task. Each error bar represents one SEM; # indicates an overall within-subject difference from block 1 ($p < 0.05$); * indicates an overall between-group difference ($p < 0.05$).

was a trend for the ST cocaine group to perform worse (with copy performance as a covariate) on the recall trial ($0.05 < p < 0.10$) than the control group.

3.5. Digit span task

There was no effect of group on total scores ($p > 0.10$).

3.6. 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 an effect of group ($F_{1, 32} = 6.1, p < 0.05$), with the ST cocaine group completing fewer items across conditions than the control group. There was no significant condition \times group interaction ($p > 0.10$). Thus, the ST cocaine group exhibited weaker psychomotor function, including on a trial measuring cognitive control, on the Stroop task than the control group.

3.7. Trailmaking test

There was an effect of group ($F_{1, 32} = 7.7, p < 0.01$), with the ST cocaine group exhibiting slower completion times overall than the control group. There was also a condition \times group interaction ($F_{1, 32} = 8.3, p < 0.01$), with the ST cocaine group exhibiting slower completion times (about a 24-s difference) than the control group on Part B ($p < 0.01$), but not Part A ($p > 0.10$). Thus, the ST cocaine

group exhibited weaker psychomotor function and cognitive flexibility than the control group.

3.8. Grooved pegboard test

There was an effect of group ($F_{1, 32} = 5.7, p < 0.05$), with the ST cocaine group exhibiting slower completion times than the control group. There was a trend condition \times group interaction ($0.05 < p < 0.10$) for a greater group difference with the dominant hand than the nondominant. Thus, the ST cocaine group exhibited weaker overall fine motor skill than the control group.

4. Discussion

This study was the first (to our knowledge) to explicitly compare individuals who had been using cocaine for a relatively short duration (mean of 3.5 yrs) to controls on performance of learning and other cognitive tasks. Consistent with our hypotheses, the short-term (ST) cocaine users exhibited decreased performance on the Weather Prediction, List-Learning, Stroop, Trailmaking, and Grooved Pegboard tasks. These results indicate that certain learning, executive and psychomotor functions of the ST cocaine users were moderately weaker than controls who were similar on reported alcohol and marijuana use and most demographic characteristics.

Thus, the results are consistent with our previous study (Vadhan et al., 2014), where a group of long-term (LT) cocaine users (mean duration: 20.0 yrs; mean age: 42.7 yrs) also performed more poorly on those same tasks than groups of controls who were similar either on age (mean of 39.8 yrs) or reported marijuana and alcohol use. This suggests that even relatively short-term cocaine exposure is sufficient for cognitive weaknesses to be present, which in this case consists of moderate difficulty with learning incremental responses probabilistically and intentionally learning verbal information, as well as controlling automatic responses, shifting between cognitive sets and controlling motor behavior. These functions may underpin aspects of habit learning that are related to substance use disorders.

However, the ST cocaine users did not exhibit weaker performance on measures of S-R equivalence learning (i.e., learning equivalence between 2 stimuli via their associations with other stimuli; Acquired Equivalence task), visual learning (Figure Copy) or auditory attention (Digit Span), relative to controls. Aside from the equivalence learning finding, these results suggest a narrower pattern of cognitive problems than the LT cocaine users. Still, it is important for clinicians to be aware of any potential cognitive problems, as well as distinctions between cocaine user subtypes, and perhaps adjust their perception and approach accordingly when working with such individuals (Aharonovich et al., 2018).

The limitations of this study include a relatively small sample size, reliance on self-report for duration of cocaine use, and a relatively broad definition of short-term cocaine use. We note that it was difficult to find ST cocaine users (particularly true cocaine initiates), resulting in slow recruitment and necessitating a relatively broad inclusion criterion. Two strengths of the study were the novelty of the ST cocaine-using sample, and that the groups were similar on many demographic and clinical characteristics (other than cocaine use histories and educational level) to each other, facilitating interpretations regarding short-term cocaine exposure.

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Contributors

All authors significantly contributed to and have read and approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

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