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Short communication

## Drug fluency: A potential marker for cocaine use disorders

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### Abstract

The goal of the current study was to tailor semantic fluency to increase its sensitivity and ecological validity in the study of drug use disorders. On a newly modified “drug” fluency task, individuals with cocaine use disorders who tested positive for cocaine at study day named more drug-related words than control subjects. The number of words provided on the classical semantic fluency task (animals and fruits/vegetables) did not differ between the groups. While the individuals with cocaine use disorders who tested negative for cocaine at study day did not differ from the control subjects in total words named on this task, a qualitative analysis indicated that both cocaine subgroups provided significantly more words pertaining to the experience of using drugs (paraphernalia, administration) than the matched control subjects. These results demonstrate that compared to classical neurocognitive assessment tools, newly tailored measures may be more sensitive to cocaine use disorders, psychopathologies that are often characterized by mild neuropsychological deficits but a well-circumscribed attentional bias to drug-related cues. Future studies are needed to probe the exact cognitive processes and neural circuitry underlying performance on this cue-sensitive 1-min measure.

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### 1. Introduction

Neuropsychological (NP) tests have emerged from the necessity to non-invasively identify a putative brain dysfunction mostly in individuals suffering from brain trauma or pronounced learning disabilities (Lezak, 1995). However, the development of sensitive neuroimaging techniques has been replacing this diagnostic need with a more descriptive role for NP tasks, such as the association of behavioral, cognitive and emotional function with a documented brain lesion. In recent years, this combined neurobehavioral functional mapping has extended to disorders where deficits at both the neural and cognitive levels may be relatively subtle (Franklin et al., 2002; Goldstein et al., 2004), yet predictive of clinical treatment outcomes (Aharonovich et al., 2006), such as in cocaine use disorders. However, a gap remains between the NP tools that continue to use a neutral

context when assessing cognition, and evidence that points to a core impact of emotion, or context-specificity, on cognition in this psychopathology. For example, cocaine-related cues reliably elicit self-reported craving and more objectively measured physiological reactions in individuals with cocaine use disorders (Carter and Tiffany, 1999) as induced by various cognitive-behavioral methods (e.g., imagery, Sinha et al., 2000).

The goal of the current study was therefore to adapt a neutral NP tool to incorporate a symptom-specific context with the goal of probing the effect of salient context/emotion on cognition in cocaine use disorders. A similar approach was previously used with a single NP task, the color-word Stroop (Hester et al., 2006), where subjects have to ignore the meaning of drug-related words or pictures to perform the task at hand (pressing for stimulus color); compared to non-drug using populations, active cocaine users display an attentional bias to cocaine-related cues on this drug Stroop task (Hester et al., 2006). We hypothesized that similarly to results on this drug Stroop task, a semantic fluency task tailored specifically to elicit drug-related responses would differentiate between individuals with cocaine use disorders from healthy control subjects.

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2. Methods

2.1. Participants

Individuals with cocaine use disorders ( $n = 42$ ) met DSM-IV diagnostic criteria for current cocaine dependence or abuse. Comparison subjects were 42 healthy individuals that were matched to the cocaine subjects on gender, race, age, and education (Table 1). Exclusion criteria for all subjects were history of head trauma >30 min, a lifetime diagnosis of depression and/or history of other psychiatric or neurological disorders (apart from cocaine abuse or dependence for the cocaine group). All subjects provided a urine sample before the NP testing. A triage urine panel for drugs of abuse (Biopsych™) tested for the presence of cocaine (and other drugs) and their metabolites. A positive result indicated that a subject had used cocaine within 72 h of testing ( $n = 30$ ). Negative results reflected longer-term abstinence from cocaine ( $n = 12$ ). Except for cocaine in the cocaine subjects, a positive result for any drugs was exclusionary (i.e., all control subjects had urine negative results). Group differences were noted in history of cigarette smoking, state depression and verbal intelligence (Table 1). To control for the possible confounding effects of these variables, covariate analyses were used if there were significant associations with the study's dependent variables (Stevens, 1992).

2.2. NP assessment: a drug verbal fluency task

Semantic fluency is a NP task that measures the ability to name as many words from a specified semantic category (e.g., animals, fruits or vegetables) for a discrete period of time (e.g., 1 min). This verbal fluency task relies on intact executive functions including initiation, working-memory, monitoring, and activation of search strategies based on previously formed associations as mediated by temporal, parietal and prefrontal brain regions (Lezak, 1995; Mitrushina, 2005). We integrated an emotional component within this cognitive-behavioral task by choosing a semantic category (drug-related) that would be more salient

to one study group (individuals with cocaine use disorders) than to another (control subjects). Thus, we asked subjects to “call to mind and name as many drug-related words as possible for 1 min”. These could be “names of drugs, people, places, or states of mind related to getting, using, or recovering from drugs”. The responses for all fluency categories were audio-recorded. Correct responses (excluding repetitions and errors, i.e., words clearly not related to the selected semantic category) were summed for each category. The neutral semantic fluency categories (animals, then fruits or vegetables) always preceded the drug category, and all fluency tasks were administered midway of a more extensive NP battery of tests administered to all subjects.

2.3. Statistical analysis

Chi-square tests (for categorical variables) or univariate analyses of variance (ANOVA) (for continuous variables) were conducted to assess differences between the three groups (comparison subjects versus individuals with cocaine use disorders who were positive versus negative for cocaine in urine on study day) on all demographic and fluency variables. Post-hoc analyses were Bonferroni-corrected pairwise comparisons. Associations between continuous variables (e.g., drug fluency and the continuous possibly confounding variables) were examined with Pearson correlations. Otherwise, *t*-tests were used.

3. Results

There were no differences between the three study groups on the total correct words named for the non-drug semantic categories, animals and fruits or vegetables (Table 2). In contrast, there was a group main effect for total correct words named for the drug fluency category, where the cocaine positive group outperformed the control group; the cocaine negative group did not differ from the other two groups (Table 2).

Table 1  
Sample descriptives

	Controls <sup>†</sup> ( $n = 42$ )	Cocaine positive <sup>††</sup> ( $n = 30$ )	Cocaine negative <sup>†††</sup> ( $n = 12$ )	$\chi^2$	
<b>A. Demographics</b>					
Group distribution					
Gender (male/female)	32/10	22/8	9/3	0.3	
Race (Caucasian/African American/other)	14/23/5	8/20/2	1/8/3	5.1	
First language (English/other)	41/1	29/1	10/2	4.4	
Nicotine smoking (smoker/non-smoker) <sup>a</sup>	10/30 <sup>†††</sup>	23/6 <sup>†</sup>	8/2 <sup>†</sup>	23.5 <sup>**</sup>	
		<i>M</i> ± S.D.	<i>M</i> ± S.D.	<i>F</i>	
Group mean differences					
Age (years)		40.9 ± 6.9	42.6 ± 6.1	42.0 ± 6.6	0.6
Years of education		13.6 ± 2.0	12.6 ± 2.6	13.2 ± 2.0	1.6
Handedness: laterality quotient (Oldfield, 1971)		0.6 ± 0.7	0.6 ± 0.8	0.9 ± 0.4	2.3
State depression (Beck et al., 1996)		5.6 ± 7.2 <sup>††</sup>	14.8 ± 10.6 <sup>†</sup>	9.4 ± 7.4	9.0 <sup>**</sup>
Verbal intelligence: reading scale—wide range achievement test III		101.1 ± 12.7 <sup>††</sup>	92.3 ± 15.0 <sup>†</sup>	95.3 ± 13.1	3.4 <sup>*</sup>
Non-verbal intelligence: matrix reasoning (Wechsler, 1999)		11.2 ± 3.0	10.3 ± 3.5	9.8 ± 3.4	1.3
					<i>t</i>
<b>B. History of cocaine use</b>					
Cocaine use in the past 30 days (days) <sup>b</sup>	–	14.9 ± 8.5	8.7 ± 8.9		2.0
Age of cocaine use onset <sup>c</sup>	–	21.4 ± 5.8	22.8 ± 6.0		–0.7
Duration of cocaine use <sup>c</sup>	–	18.7 ± 6.7	17.7 ± 5.7		0.4

Note: *M* = mean; S.D. = standard deviation. Symbols (<sup>†,††,†††</sup>) designate significant ( $p < .05$ ) between-group differences based on Bonferroni-corrected pairwise comparisons.

<sup>a</sup>  $n = 79$  (due to missing data).

<sup>b</sup>  $n = 39$  (due to missing data).

<sup>c</sup>  $n = 40$  (due to missing data).

\*  $p < .05$ .

\*\*  $p < .01$ .

Table 2  
ANOVA results for semantic fluency categories (values are  $M \pm S.D.$ )

Semantic task	Controls ( $n = 42$ )	Cocaine positive ( $n = 30$ )	Cocaine negative ( $n = 12$ )	$F$
<b>A. Semantic fluency</b>				
Animals: total number correct (1 min)	20.0 $\pm$ 5.7	21.8 $\pm$ 5.7	20.0 $\pm$ 4.0	.97
Fruits/vegetables: total number correct (1 min)	18.6 $\pm$ 5.8	20.1 $\pm$ 5.4	18.0 $\pm$ 3.5	.97
<b>B. Drug fluency</b>				
Drug-related words: total number correct (1 min)	13.5 $\pm$ 4.7 <sup>††</sup>	16.9 $\pm$ 5.9 <sup>†</sup>	14.3 $\pm$ 4.4	3.9*
<b>Drug qualitative categories</b>				
People associated with drug use (dealer, junkie)	3.0 $\pm$ 2.0	3.4 $\pm$ 2.6	3.4 $\pm$ 1.9	0.5
Paraphernalia (pipe, needles)	2.2 $\pm$ 1.6 <sup>††,†††</sup>	3.8 $\pm$ 3.4 <sup>†</sup>	4.3 $\pm$ 2.8 <sup>†</sup>	5.6**
Recovery (rehab, detox)	1.7 $\pm$ 1.2	2.6 $\pm$ 2.2	1.8 $\pm$ 1.4	2.6
Adverse consequences of use (jail, overdose)	1.9 $\pm$ 2.0	2.1 $\pm$ 1.6	1.9 $\pm$ 1.8	0.1
Cocaine (cocaine, crack)	1.5 $\pm$ 1.0	1.9 $\pm$ 1.8	1.9 $\pm$ 1.3	0.9
Places where drug use/sales occur (alleyways, clubs)	1.5 $\pm$ 1.3	1.8 $\pm$ 1.6	1.7 $\pm$ 1.4	0.6
Routes of drug administration (inhale, inject)	1.1 $\pm$ 0.9	1.4 $\pm$ 1.8	1.8 $\pm$ 1.2	1.2
Marijuana (weed, pot)	1.2 $\pm$ 1.2	1.1 $\pm$ 1.3	1.5 $\pm$ 1.1	0.4
Physiological drug responses (stoned, dizziness)	0.9 $\pm$ 1.3	1.4 $\pm$ 1.8	1.8 $\pm$ 1.9	1.7
Drug administration via smoking (rolling papers, inhale)	0.5 $\pm$ 0.7 <sup>††,†††</sup>	1.5 $\pm$ 2.0 <sup>†</sup>	2.0 $\pm$ 2.0 <sup>†</sup>	6.9**
Hallucinogens (LSD, acid)	0.8 $\pm$ 1.1	0.6 $\pm$ 1.1	0.5 $\pm$ 1.2	0.4
Opiates (smack, heroin)	0.6 $\pm$ 0.8	0.6 $\pm$ 0.7	0.8 $\pm$ 1.2	0.2
Drug acquisition (borrow, buy)	0.4 $\pm$ 0.9	0.9 $\pm$ 1.4	0.3 $\pm$ 0.7	2.0
Alcohol (beer, booze)	0.5 $\pm$ 1.0	0.6 $\pm$ 0.7	0.7 $\pm$ 0.7	0.3
Amphetamines (uppers, speed)	0.6 $\pm$ 0.8	0.3 $\pm$ 0.7	0.4 $\pm$ 0.7	1.0
Methamphetamine (crank, meth)	0.4 $\pm$ 0.7	0.5 $\pm$ 0.9	0.7 $\pm$ 1.2	0.4
Depressant/barbiturates (valium, sedatives)	0.5 $\pm$ 0.8	0.6 $\pm$ 1.0	0.2 $\pm$ 0.4	1.3
Non-addictive prescription drugs (depakote, xanax)	0.4 $\pm$ 0.8	0.2 $\pm$ 0.5	0.1 $\pm$ 0.3	2.0
Ecstasy (X, MDMA)	0.4 $\pm$ 0.6	0.2 $\pm$ 0.4	0.1 $\pm$ 0.3	1.6
Drug preparation methods (baked, cooked-up)	0.2 $\pm$ 0.4	0.6 $\pm$ 1.0	0.3 $\pm$ 0.6	2.8

Note: The 20-most frequently endorsed drug fluency categories are presented in the table.  $M$  = mean; S.D. = standard deviation; degrees of freedom = 2, 83. Symbols (<sup>†,††,†††</sup>) designate significant ( $p < .05$ ) between-group differences based on Bonferroni-corrected pairwise comparisons.

\*  $p < .05$ .

\*\*  $p < .01$ .

To qualitatively inspect responses on this new drug fluency task, all drug fluency responses were organized into 42 distinct semantic categories by two independent raters (inter-rater agreement was good,  $r = 0.8$ ); the 20 most frequently endorsed categories are presented in Table 2 in order of frequency. Compared to control subjects, both cocaine subgroups reported significantly more words related to paraphernalia and drug administration via smoking (Table 2; note that there were no statistically significant differences between the two cocaine subgroups on any of the dependent variables). There was also a similar trend for drug preparation methods ( $p < .07$ ). Compared to the combined cocaine group, control subjects reported more words related to non-addictive prescription drugs ( $t(82) = -2.1$ ,  $p < .05$ ).

There were no significant correlations between reading level (estimate of verbal intelligence) or state depression with the three drug fluency variables that differed between the study groups (Table 2), across all study subjects. Similarly, these three drug fluency dependent variables did not differ significantly by history of cigarette smoking. Thus, the three demographic variables that differed between the groups (Table 1) did not contribute to this study's results as further ascertained by covariate analyses. There were also no significant correlations between the three drug fluency variables and cocaine use history (Table 1).

#### 4. Discussion

The goal of the current study was to tailor a classical NP tool, verbal fluency, to possibly improve its sensitivity and ecological validity in an effort to advance research on addictive disorders. Indeed, compared to age- and education-matched control subjects, the cocaine subjects that tested positive for cocaine at study day named more drug-related words on this modified drug fluency task. Compared to the control subjects, both cocaine subgroups (with positive or negative urines for cocaine at study day) also provided more drug-related words that were from goal-directed categories (e.g., smoking the drug and instruments implemented to use drugs). In contrast, the control subjects provided more non-addictive drug names.

Overall, we interpret these findings to indicate greater attentional bias and responsivity to drug-related cues in individuals with cocaine use disorders similarly to that previously reported in abusers of alcohol (Duka and Townshend, 2004), nicotine (Mogg and Bradley, 2002), heroin (Franken et al., 2000), and cocaine (Hester et al., 2006; Carpenter et al., 2006) using the drug Stroop NP task. Note that although in our study there were no significant correlations between the current drug fluency task and drug use history, drug fluency output was highest in the cocaine subgroup that tested positive for cocaine at study day; these results are therefore consistent with prior results

showing that a similar automatic processing bias is related to cocaine craving (Copersino et al., 2004; Hester et al., 2006) and may also be predictive of treatment outcome (Cox et al., 2002).

Our current drug fluency task may have also tapped heightened (“fresher”) memory for drug-related stimuli in the individuals with cocaine use disorders (Lee et al., 2006). An additional differential NP process that may have been triggered by this task encompasses a compromised emotion regulation/suppression in a drug-related context in the individuals with cocaine use disorders as possibly modulated by the rostroventromedial prefrontal cortex (Goldstein et al., 2007). Nevertheless, the precise cognitive processes and neural circuits that underlie performance on this newly tailored task remain to be established.

Limitations of the current study include the following: (1) fixed order of administration of both the semantic and drug fluency tasks across all subjects (the drug fluency task always followed the semantic fluency tasks): a randomized order may have elicited somewhat differential responses from the study participants; (2) the reliability and reproducibility of this newly developed instrument remains to be tested in larger sample sizes and different drug use populations. It would be of particular interest to include a sample of healthy control individuals with a high familiarity of drug-related stimuli (e.g., family members of addicted individuals, staff in drug treatment facilities or other professionals in the drug addiction field) to further examine this task’s specificity and predictive value. One could postulate that only in the drug addicted individuals, but not those highly familiar with drug addiction, responses on the drug fluency task would be diagnostically and clinically useful; (3) the use of this drug fluency task together with other measures of cognition (e.g., attention bias/cue reactivity, memory) and emotion (e.g., regulation), especially inside functional neuroimaging environments, is needed to ascertain the exact neurocognitive processes evoked by this task in drug addiction and other psychopathology; and (4) the contribution to results of craving, other withdrawal symptoms, and severity of use needs to be explored with more sensitive tools (e.g., other tasks that actively elicit craving), in as much as these factors have been associated with greater cue-reactivity in drug addicted individuals (e.g., Childress et al., 1987).

## 5. Conclusion

Our findings suggest that the drug fluency task activates drug-specific semantic networks in individuals with cocaine use disorders and that these networks are mostly distinguished by stimuli and experiences related to getting and using the drug. Overall, these behavioral results, which are obtainable in *1 min*, indicate that the drug fluency task may be a useful neurocognitive probe for prefrontolimbic (e.g., recall facilitated by attribution of salience) and striatal (e.g., goal-directed networks) brain function in individuals with cocaine use disorders. It remains to be established whether this and similar other tailored classical NP tools may improve the ability to differentiate between subgroups within the drug addicted population, offer a better description of

the scope of the drug-related automatic neurocognitive processing bias and its potential impact on behavior (e.g., compulsion), and be better probes of the specific neural circuits implicated in drug addiction.

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