



**HAL**  
open science

## I can't get it off my mind: Attentional bias in former and current cocaine addiction

Pauline Smith, Karim N'diaye, Maeva Fortias, Luc Mallet, Florence Vorspan

### ► To cite this version:

Pauline Smith, Karim N'diaye, Maeva Fortias, Luc Mallet, Florence Vorspan. I can't get it off my mind: Attentional bias in former and current cocaine addiction. *Journal of Psychopharmacology*, 2020, 34 (11), pp.1218-1225. 10.1177/0269881120944161 . hal-03020174

**HAL Id: hal-03020174**

**<https://hal.sorbonne-universite.fr/hal-03020174>**

Submitted on 23 Nov 2020

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

1        **Abstract word count:** 247 words

2        **Text word count:** 4237 words

3

4        *Title:* I can't get it off my mind: attentional bias in former and current cocaine  
5        addiction

6

7        *Authors:* Pauline Smith (1), Karim N'Diaye (1), Maeva Fortias (2), Luc Mallet  
8        (1,3,4)\*, Florence Vorspan (2,5,6)\*

9        \* Drs Mallet and Vorspan contributed equally.

10       *Affiliations:*

11       (1) Sorbonne Universités, CNRS UMR 7225, Inserm U 1127, Institut du Cerveau et  
12       de la Moelle épinière (ICM), Paris, France

13       (2) Assistance Publique–Hôpitaux de Paris, département de psychiatrie et de  
14       médecine addictologique, hôpital Fernand Widal, AP-HP, 200, rue du Faubourg-  
15       Saint-Denis, 75010 Paris, France; INSERM UMRS-1144, 75006 Paris, France

16 (3) Assistance Publique-Hôpitaux de Paris, Pôle de psychiatrie, Hôpitaux  
17 Universitaires Henri Mondor - Albert Chenevier, Université Paris-Est Créteil,  
18 Créteil, France

19 (4) Department of Mental Health and Psychiatry, Global Health Institute,  
20 University of Geneva, Geneva, Switzerland

21 (5) Inserm, UMR-S 1144, Paris, F-75006, France

22 (6) Université Paris Diderot, Sorbonne Paris Cité, UMR-S 1144, Paris, F-75013,  
23 France

24

25 *Acknowledgements:* We wish to thank Kristel Piani for her help in recruiting  
26 patients.

27 *Financial support:* This work was supported by the *Investissements d'Avenir*  
28 program managed by the ANR (under reference ANR-11-IDEX-0004-02) and by a  
29 grant of the FondaMental Foundation. The programme QuitCoc received funding  
30 from the French Ministry of Health (PHRC National 2012 AOM12390) and from  
31 ERA-NET. It was promoted by the DRCD (Direction de la Recherche Clinique et du  
32 Developpement) of the Assistance Publique-Hôpitaux de Paris.

## 33 **Abstract**

### 34 **Background**

35 Cocaine addiction is a global health issue with limited therapeutic options and a  
36 high relapse rate. Attentional bias (AB) towards substance-related cues may be an  
37 important factor of relapse. However, it has never been compared in former and  
38 current cocaine-dependent patients.

### 39 **Methods**

40 AB towards cocaine-related words was assessed using an emotional Stroop task in  
41 cocaine-dependent patients (CD, N=40), long-term abstinent former cocaine-  
42 dependent patients (ExCD, N = 24; mean abstinence: 2 years) and control subjects  
43 (N = 28). Participants had to name the colour of cocaine-related words, neutral  
44 words, and colour names. We assessed response times using an automatic voice  
45 onset detection method we developed, and we measured AB as the difference in  
46 response times between cocaine-related and neutral conditions.

### 47 **Results**

48 There was an overall group effect on AB towards cocaine, but no group effect on  
49 the colour Stroop effect. Two-by-two comparison showed a difference in AB

50 between CD and controls, while ExCD were not different from either. While CD  
51 showed a significant AB, consistent with the literature, neither ExCD nor controls  
52 showed a significant AB towards cocaine related words. We found no link between  
53 AB size and either addiction severity or craving.

#### 54 **Conclusions**

55 Cocaine abstinence was associated with an absence of significant AB towards  
56 cocaine-related words which may be interpreted either as absence of AB  
57 predicting success in maintaining abstinence, or as AB being able to disappear with  
58 long-term cocaine abstinence. Further research is needed in order to distinguish  
59 the role of AB in maintaining abstinence.

60

61

62

## 63 1. Introduction

64 Cocaine addiction is a clinical condition characterised by an excessive intake of  
65 cocaine, and a relapsing cycle of intoxication, binging, withdrawal and craving.  
66 Cocaine is the second most used illegal drug in Europe (EMCDDA, 2017) and in  
67 France, and a high rate of occasional users fall into cocaine addiction. Cocaine  
68 addiction is characterised by the severity of its medical and social consequences  
69 (Whiteford et al., 2013). Indeed, cocaine-dependent patients have a standardised  
70 mortality rate 4 to 8 times higher than their group of age peers (Degenhardt et al.,  
71 2011). However, there is to date no available substitution treatment for cocaine  
72 addiction (Castells et al., 2016), and relapse rates are very high (Paliwal et al.,  
73 2008).

74 One important neurobiological process involved in cocaine addiction is  
75 dopaminergic arousal of corticostriatal circuits, and in particular the reward  
76 system, which leads to a motor preparation and hyperattentive state towards  
77 drug-related cues (Franken, 2003). This arousal could play a causal role in key  
78 features of addiction such as drug use despite negative consequences and relapse  
79 (Pascoli et al., 2015). Among the cognitive consequences of this arousal is the  
80 development of an attentional bias (AB) towards cocaine, which may play an

81 important role in the success or failure of cocaine abstinence. AB is hypothesised  
82 to interact with craving, the overwhelming urge to consume the substance,  
83 through a loop of mutual reinforcement: the drug cues that patients notice because  
84 of AB could heighten their craving, and craving heighten AB (Field and Cox, 2008).  
85 While the importance of this link has been called into question (Field et al., 2009),  
86 understanding the role of AB in abstinence maintenance would likely allow getting  
87 a better picture of the cognitive factors implicated in relapse.

88 Emotional Stroop tasks are widely used neuropsychological tools for the study of  
89 AB in addiction (Field et al., 2009). They are based on the classic colour Stroop task,  
90 which is used to measure selective attention (Wright, 2017). In classic Stroop tasks,  
91 participants are instructed to name the colour in which colour names are written.  
92 In the cases where a colour name is written in another colour (ie “blue” written in  
93 green), this incongruence is associated with a slowing of the colour naming  
94 response, which is thought to be caused by the interference between the automatic  
95 response (reading the word) and the correct response (naming the ink colour)  
96 (MacLeod, 1991).

97 In emotional Stroop tasks, the interference is caused by the presence of  
98 emotionally salient words, and the slowing is thus caused by the attention towards  
99 the semantic content of these words. The exact mechanisms underlying the

100 emotional Stroop effect are not yet fully understood (Cox et al., 2006) but the  
101 strength of this effect is considered a measure of AB towards a specific semantic  
102 category of stimuli, such as a substance in the case of addiction.

103 Cocaine-related Stroop tasks have shown that cocaine-dependent patients exhibit  
104 a higher AB towards cocaine-related stimuli than control participants (Copersino  
105 et al., 2004; Franken et al., 2000; Hester et al., 2006; Rosse et al., 1994).

106 Moreover, AB intensity has been linked to both addiction severity and abstinence  
107 maintenance in several substance addictions. Higher AB towards the substance is  
108 linked to quantity and frequency of substance use (Field and Cox, 2008), and a  
109 higher AB at entry of an inpatient care program has been linked to greater chances  
110 of relapse in prospective studies on heroin- (Marissen et al., 2006) and alcohol-  
111 dependent patients (Cox et al., 2002). Patients who have a documented abstinence  
112 for several weeks display lower AB towards heroin (Gardini et al., 2009), and  
113 alcohol (Flaudias et al., 2013) than current users. On the other hand, a similar  
114 protocol used to test AB towards smoking words in 24-hour abstinent smokers  
115 failed to show a significant difference with ad libitum smokers (Munafò et al.,  
116 2003).

117 However, very few controlled studies have investigated AB among cocaine users



118 and its changes with abstinence. A recent review paper identified only 2  
119 prospective studies on this subject (Zhang et al., 2018). The first one assessed AB  
120 change after 8 weeks of either computer-based cognitive behavioural therapy or  
121 counselling. AB was assessed using an emotional Stroop task (DeVito et al., 2018),  
122 and they found a significant AB towards cocaine-related words pre-treatment, and  
123 a drop in AB post-treatment. The second one (Mayer et al., 2016) assessed AB,  
124 craving and drug use change after 5 sessions of AB modification training (or sham  
125 training). AB was assessed through a visual priming task and they found a  
126 significant AB pre-treatment and no AB post treatment in both treatment groups.

127 Because AB is acquired at the onset of cocaine addiction (Field and Cox, 2008) and  
128 drops with short-term abstinence (DeVito et al., 2018), one could expect that, as  
129 previously demonstrated with heroin and alcohol dependent patients, AB would  
130 drop further or disappear in patients with cocaine dependence who maintain a  
131 long-term abstinence.

132 Thus, to further explore this hypothesis, we decided to assess AB towards cocaine-  
133 related stimuli with an emotional Stroop task involving cocaine-related words. We  
134 compared AB in currently cocaine-dependent patients as well as in formerly  
135 cocaine-dependent patients to AB in healthy controls. We recorded addiction  
136 severity at the beginning of the task, as it has been reported to influence AB as

137 assessed by the emotional Stroop. We also recorded craving intensity before and  
138 after the task.

139

## 140 **2. Methods**

### 141 **2.1. Participants**

142 We recruited 40 currently cocaine-dependent patients (CD), 24 formerly cocaine-  
143 dependent patients (ex-CD), and 28 healthy control participants.

144 Inclusion criteria common to all three groups were being 18 years old or older,  
145 being affiliated to the French social security system, and giving informed written  
146 consent to participate in the study. Exclusion criteria common to all three groups  
147 were colour vision deficit and non-fluency in written or spoken French. Colour  
148 vision was assessed based on performance on a training test before the task. All  
149 participants spoke and read French fluently.

150 Patients were recruited among outpatients at an outpatient addiction clinic who  
151 had been diagnosed with either current or past cocaine dependence according to  
152 the DSM-IV (American Psychiatric Association and Association, 2000). Diagnosis

153 had been established by their referent psychiatrist at the beginning of treatment  
154 through a non-structured clinical interview, and was confirmed by their  
155 psychiatrist at the time of the study.

156 Inclusion criteria for the CD group was current diagnosed cocaine dependence, and  
157 declared cocaine use within the past two weeks. Inclusion criteria for the ex-CD  
158 group were lifetime diagnosed cocaine dependence, and declared last time of  
159 cocaine use being over two months prior.

160 We chose to rely on self-report for assessing last cocaine use, as it is reliable and  
161 easy to implement (Brown et al., 1992; Darke, 1998). This self-report was  
162 confirmed by patients' referring psychiatrist.

163 The healthy controls (HC) were recruited through public advertisement on a  
164 mailing list of people who volunteer to participate in cognitive science experiments  
165 (Risc.cnrs.fr). We excluded participants who had a history of substance abuse  
166 (excepting tobacco), neurological or psychiatric disorders through an interview  
167 with a psychiatrist. We selected participants on their age, sex, and education level  
168 in order to match the patients groups as closely as possible, which somewhat  
169 limited us in the number of participants we were able to recruit.

170 CD and ex-CD were recruited within the framework of the Declaration of Helsinki

171 and the ethical guidelines of the Fernand-Widal hospital for the analysis of data  
172 already collected during routine care (authorisation 2014-067 given on 15  
173 January 2015 by the CPP (Comité de Protection des Personnes, French regional  
174 ethical research committee) and did not receive monetary compensation for their  
175 participation. HC were recruited through a physiopathology study (Ethics  
176 Committee approval 2012-A01460-43) and received 25€ as compensation for  
177 their participation.

178 They all completed the MoCA (Montreal Cognitive Assessment; Nasreddine et al.,  
179 2005), which allows screening for mild cognitive impairment.

180 Data describing the severity of the past or current cocaine use were recorded with  
181 an ad-hoc questionnaire (age of first use and last use, products used, usage route,  
182 dose per day, frequency of use, date of last use), as well as data regarding the  
183 lifetime use of other substances. Cocaine craving was assessed with two tools: the  
184 OCCS (Obsessive-Compulsive Cocaine Craving Scale ; Vorspan et al., 2012) was  
185 used to assess cocaine craving and its consequences on the life of the patients  
186 within the last two weeks, and a visual analogue instant scale was used to assess  
187 current subjective craving.

188 The entire process of participating in the study took place in the same day for

189 participants, and it typically lasted between one and two hours.

190 Two former cocaine addicts withdrew their consent during the task because they  
191 felt uncomfortable, although they did not express a rise in their subjective craving.

## 192 **2.2. Task Design**

193 The task was designed using E-Prime 2.0 Standard. We adapted the emotional  
194 Stroop test developed for addiction to alcohol by Flaudias et al. (2013).

195 This task consists of three consecutive blocks where participants are asked to  
196 name the font colour of words shown on a computer screen. Each block is a  
197 different condition: neutral words, colour names and cocaine-related words. We  
198 chose not to mix the three conditions but to display stimuli in three distinct,  
199 successive blocks, so as to prevent interference that could have been caused by the  
200 cocaine-related words (Cox et al., 2006).

201 We used two different sets of cocaine-related words, corresponding to the forms  
202 of cocaine (cocaine hydrochloride and crack cocaine). Patients were shown the set  
203 of words consistent with the form in which they used cocaine, and healthy controls  
204 were randomly shown cocaine hydrochloride words.

205 We chose to use a voice response rather than using button pressing as Flaudias and

206 Llorca (2014) recommend using a vocal response modality for a more natural  
207 response and a more pronounced Stroop effect.

208 Participants were sat about fifty centimetres from a computer screen, asked to  
209 focus on a fixation cross, and to name the colour of the words that appear on the  
210 screen, regardless of their meaning. All words were randomly displayed in either  
211 red, green blue or yellow.

212 The main variable of interest was the interference caused by the cocaine and  
213 colour Stroop effects. This interference was calculated as the difference in reaction  
214 times between cocaine and neutral words on the one hand, and colour and neutral  
215 words on the other hand.

216 For reaction times calculations, we considered as usable answers only the correct  
217 trials where the first word said by the participant was the correct answer. We  
218 therefore excluded from the reaction time calculation trials where participants  
219 corrected their answer or started by saying "uh". The number of excluded trials for  
220 each group and types of trials can be found in Supplementary Table 1.

221 For accuracy calculations, where delayed reaction time was not a problem, we  
222 included all trials where participants started by giving a correct answer, even if  
223 they hesitated before answering.

### 224 2.3. Choice of words

225 In order to choose cocaine-related words, we selected potential words with  
226 clinicians working with cocaine addicts at the Fernand-Widal hospital. We then  
227 showed these words to a group of four cocaine users seeking treatment and asked  
228 them to choose the most salient ones and to suggest other words that were not on  
229 the list.

230 The final set of words consisted of four words associated with crack cocaine:  
231 “fumer” (to smoke), “pipe”, “caillou” (rock) and “crack”, and four words associated  
232 with cocaine hydrochloride: “sniffer” (to snort), “rail”, “ligne” (line) and “coke”.

233 Word frequencies were matched between neutral words and cocaine-related  
234 words in order not to overestimate AB towards cocaine. We did so using the  
235 Lexique 3.80 lexical database (New et al., 2004). We selected: “presser” (to press),  
236 “fauteuil” (armchair), “pont” (bridge), “chemise” (shirt). There was no significant  
237 difference in frequency between neutral words and cocaine-related words  
238 (Kruskal-Wallis  $\chi^2= 2.58$ , p-value = 0.28). We were later able to confirm that there  
239 was no reaction-time variation between words of the same category (data not  
240 shown, available upon request).

241 **2.4. Procedure**

242 We did not ask participants to abstain from using cocaine or any other substance  
243 prior to the test.

244 The experiment took place in a quiet room. The task started with two blocks of  
245 training. In the first one, participants were presented a series of coloured X  
246 (XXXXX) instead of words, for a total of 10 trials.

247 In the second one, five neutral words were presented twice to participants:  
248 “voiture” (car), “livre” (book), “chaussure” (shoe), “route” (road), “chaise” (chair),  
249 amounting to 10 trials.

250 We used four colour names: “bleu” (blue), “rouge” (red), “jaune” (yellow) and  
251 “vert” (green), all shown in random, incongruent colours. Participants had three  
252 seconds to name each colour, and inter-trial duration was 500 ms.

253 After the training phase, there were three condition blocks: neutral words, colour  
254 names and cocaine-related words were presented in a randomised order. Each  
255 word was presented in three different colours, twice for each colour (24 words per  
256 condition). Each patient thus named the colour of 92 words during the experiment,  
257 including 20 training words.



258 Patients were shown either cocaine-related words or crack-related words,  
259 according to the route of administration that they used most. Healthy controls  
260 were shown cocaine-related words.

261 Patients, but not HC, were asked to rate their craving on a scale from 0 to 10 both  
262 just before and just after the task.

263

## 264 **2.5. Data analysis**

### 265 *2.5.1. Power calculation*

266 Gardini (2009) was the only prior study using a drug Stroop task in former and  
267 current cocaine users. Based on their effect size, we expected 30 participants in  
268 each group to be sufficient to detect the expected effect with a one-sided test.

269 We were limited in our recruitment by two factors. First, few former cocaine users  
270 continue to attend their visits at the addiction clinic. Second, we chose to select  
271 healthy controls of a sex, age, and education level similar to those of patients. We  
272 chose to perform analysis when we reached 80% of the recruitment goal for all  
273 groups.

274 *2.5.2. Accuracy assessment*

275 Responses were manually assessed by listening to the recorded answers. We made  
276 two assessments for each trial: whether the answer was correct (i.e. the participant  
277 names the correct colour), and whether it was usable for data analysis (i.e. the first  
278 word that the participant says is the correct colour).

279 *2.5.3. Reaction time calculation*

280 Reaction times were calculated from the voice response, using the Seewave  
281 package for R (Sueur et al., 2008). We defined reaction time as the first time when  
282 sound intensity was greater than 15% of the maximum sound intensity for the trial.  
283 We ignored sounds that lasted under 100 ms or over 600 ms. We eliminated trials  
284 where the detected response time was under 200 ms or over 2000 ms (4% of  
285 trials).

286 *2.5.4. Statistical analysis*

287 Because normality assumptions were not always met, we chose to use non-  
288 parametric tests.

289 Patient and HC characteristics are described with frequencies and percentages,  
290 mean and standard deviation or median and range, as appropriate. Difference  
291 between groups for these characteristics were assessed using Kruskal-Wallis

292 (variance comparison for independent samples), Wilcoxon rank sum (median  
293 comparison test for two independent samples), and chi-square tests as  
294 appropriate.

295 We calculated a raw accuracy score on the 72 trials (excluding training) for each  
296 participant and a separate accuracy score by condition (colour, neutral, and  
297 cocaine words).

298 Reaction times to accurate response are presented as means and standard  
299 deviation by condition.

300 Colour Stroop interference was calculated as the difference between the mean  
301 reaction time for colour words minus mean reaction time for neutral words.

302 Emotional Stroop interference was calculated as the difference between the mean  
303 reaction time for cocaine words minus reaction time for neutral words.

304 Both interferences were calculated using only response times for usable trials.

305 Those four measures were described as means and standard deviations and  
306 compared between groups. We used Kruskal-Wallis (variance comparison for  
307 independent samples), Wilcoxon rank sum (median comparison test for two  
308 independent samples) and Jonckheere-Terpstra (similar to Kruskal-Wallis, but the

309 alternative hypothesis assumes an order relation between distributions) tests. The  
310 association between clinical factors and those four measures was tested in the two  
311 groups of patients with Spearman's correlation or Wilcoxon's rank sum test as  
312 appropriate.

313 Significance threshold was set at  $p = .05$ .

314

## 315 **3. Results**

### 316 **3.1. Demographic characteristics**

317 The demographic data we collected in the different populations who took part in  
318 the experiment is summarised in Table 1. There was no difference between groups  
319 on age (Kruskal-Wallis  $\chi^2 = 3.6$ ,  $p = 0.2$ ), sex (Kruskal-Wallis  $\chi^2 = 5.0$ ,  $p = 0.08$ ), or  
320 cognitive functioning (Kruskal-Wallis  $\chi^2 = 1.1$ ,  $p = 0.9$ ).

321

322

323

Variable (median [range])	Healthy controls (HC)	Ex-CD patients (ExCD)	CD patients (CD)	P-value	
				Overall comparison	Group comparisons
					HC - CD
					HC - ExCD
ExCD - CD					
<b>N</b>	28	24	40		
<b>Age</b>	46 [24-74]	45 [24-71]	41 [26-68]	ns	
<b>% women</b>	36	46	20	ns	
<b>% with higher education</b>	64	50	38	ns	
<b>% with normal MoCA score (≥26)</b>	59	54	60	ns	
<b>% tobacco smokers</b>	14	88	95	p<10 <sup>-10</sup>	p<10 <sup>-10</sup>
					p<10 <sup>-6</sup>
					ns
<b>% current alcohol use disorder</b>	0	22	51	p<10 <sup>-5</sup>	p<10 <sup>-4</sup>
					p<0.05
					p<0.05
<b>Alcohol intake/day</b>	0.1 [0;2]	0.1 [0;6.4]	0.2 [0;30]	ns	

<b>(standard glasses)</b>					
<b>% current THC use disorder</b>	0	30	38	p<0.005	p<0.001
					p<0.01
					ns
<b>THC intake/day (number of joints)</b>	0 [0;0.2]	0 [0;3.6]	0 [0;15]	p<0.01	p<0.005
					p<0.05
					ns
<b>% current opioid use disorder</b>	0	9	26	p<0.01	p<0.05
					ns
					ns
<b>Median number of cocaine addiction years</b>	/	5.5 [2;27]	6 [1;33]	ns	
<b>Median time since last cocaine dose</b>	/	2 years [0.2;17]	6 days [0;17]	p<10 <sup>-10</sup>	
<b>Obsessive-Compulsive Cocaine Craving Score (OCCS)</b>	/	1.5 [0;21]	23.5 [1;40]	p<10 <sup>-8</sup>	

<b>(/40)</b>					
<b>Visual analogic instant craving scale (/10)</b>	/	0 [0;9]	2 [0;10]	p<0.005	
<b>% preferential crack users</b>	/	21	38	ns	
<b>% with current medication</b>	0	96	100	p<10 <sup>-15</sup>	p<10 <sup>-15</sup>
					p<10 <sup>-11</sup>
					ns
<b>% with current opioid maintenance treatment</b>	0	9	26	p<0.01	p<0.05
					ns
					ns
<b>Of these:</b>					
<b>% with methadone</b>	/	33	50	ns	
<b>% with buprenorphine</b>	/	67	50	ns	
<b>% with antipsychotics</b>	0	38	75	p<10 <sup>-8</sup>	p<10 <sup>-8</sup>
					p<0.05
					ns

% with sedatives (benzodiazepines and Z-drugs)	0	42	63	p<10 <sup>-5</sup>	p<10 <sup>-6</sup>
					0.001
					ns

324 **Table 1: Demographic and clinical data.**

325 **3.2. Main analysis**

326 Group comparison showed an overall significant effect on the cocaine interference  
327 (Jonckheere-Terpstra JT = 1223, p = 0.03, increasing), and we found a significant  
328 difference between CD and HC (Jonckheere-Terpstra JT = 485, p = 0.03, increasing).  
329 The ex-CD group was not significantly different from either CD or HC (Jonckheere-  
330 Terpstra JT < 447, p > 0.2).

331 The CD group showed a significant slowing in the cocaine condition compared to  
332 the neutral condition (Wilcoxon W = 565, p = 0.02), while neither ex-CD group  
333 (Wilcoxon W = 207, p = 0.1), nor the HC (Wilcoxon W = 334, p = 0.3) did.

334 All three groups showed a significant slowing in the colour condition compared to  
335 the neutral condition, which corresponds to the colour Stroop effect (for the  
336 control group: Wilcoxon W = 203, p = 0.002). Group had no significant effect on the  
337 colour interference (Jonckheere-Terpstra JT= 1040, p = 0.4, increasing), and there  
338 was no significant difference between any two groups on this colour Stroop

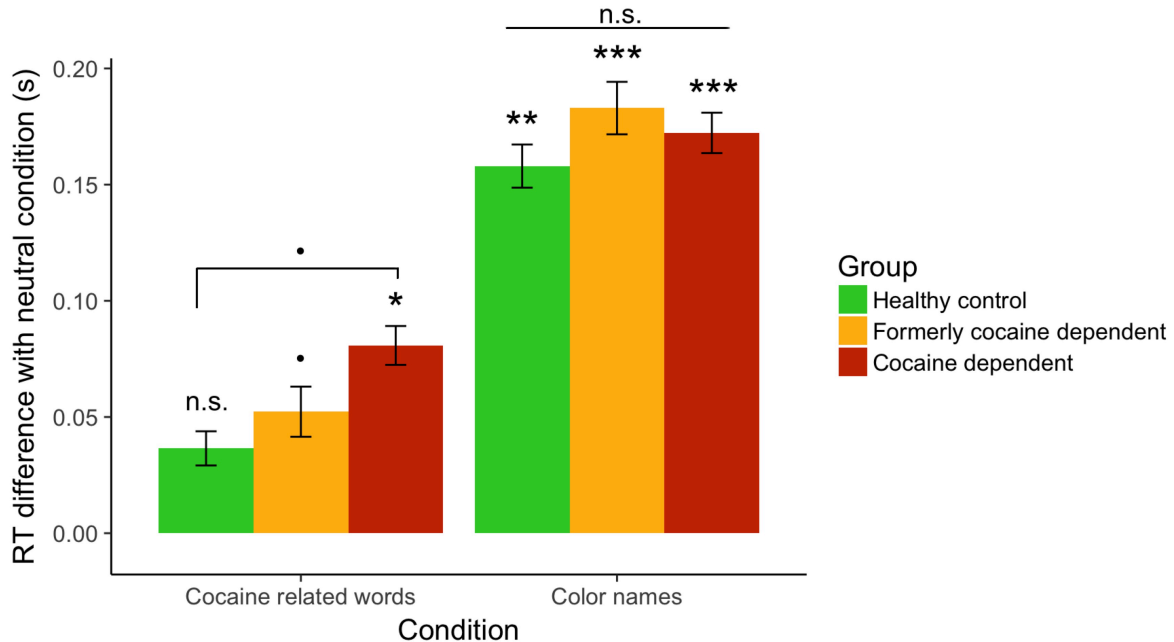




347 There was a significant group effect on overall accuracy (Kruskal-Wallis  $\chi^2 = 12.5$ ,  
348  $p = 0.002$ ): the two cocaine groups were not significantly different regarding  
349 overall accuracy (Wilcoxon  $W = 497$ ,  $p = 0.8$ ), but HC were significantly more  
350 accurate than the two other groups (Wilcoxon  $W > 473$ ,  $p < 0.005$ ).

351 Groups were also different in overall response time (Kruskal-Wallis  $\chi^2 = 12.0$ ,  $p =$   
352  $0.003$ ). Similarly, the cocaine groups were not significantly different regarding  
353 overall response times (Wilcoxon  $W = 409$ ,  $p = 0.3$ ), but HC were significantly faster  
354 when compared to either of the two cocaine groups (Wilcoxon  $W > 209$ ,  $p < 0.02$ ).

355 The colour and emotional Stroop effects for each group are plotted in Figure 1.



356 **Figure 1: Emotional (cocaine) Stroop effect and colour Stroop effect for the different groups. Stars above each**  
357 **bar denote significance level of the difference between interference sizes and zero; stars on dashes above**

358 groups of bars denote significance level of the difference between these bars. Notes: \*\*\*  $p < 0.001$ ; \*\*  $p < 0.01$ ; \*  
359  $p < 0.05$ ; <sup>ns</sup>  $p > 0.1$ .

360 We performed post-hoc analyses, which are reported in the supplementary  
361 material. We found no correlation between interferences and any clinical  
362 variables, including cocaine severity, and no effect of the task on cocaine craving.  
363 We did find an unexpected order effect for conditions, which is discussed in the  
364 supplementary material.

## 365 4. Discussion

366 The aim of our study was to investigate AB towards cocaine-related words in both  
367 currently (CD) and formerly (ex-CD) cocaine-dependent patients, using an  
368 emotional Stroop task. Our main hypothesis was that ex-CD would have a lower AB  
369 towards cocaine-related words than CD, or even show no AB towards cocaine.

370 As expected, we found that CD showed a larger AB towards cocaine than controls.  
371 Consistently with the literature, CD show a significant AB towards cocaine-related  
372 words, whereas, consistently with our hypothesis, ex-CD showed a non-significant  
373 AB, lower than that shown by CD. The control group, HC, shows no significant AB  
374 towards cocaine-related words. Additionally, as expected, all groups show a  
375 significant colour Stroop effect, and there is no difference between groups on the

376 size of the colour Stroop effect. Our study is the first one to our knowledge to assess  
377 cocaine-dependent patients and ex-patients through both a modified drug Stroop  
378 task and a colour Stroop task, allowing us to assert that the AB exhibited by  
379 participants is actually cocaine-specific, and not the consequence of a general  
380 attentional deficit.

381 The slowing of the CD group on cocaine-related words is coherent with the  
382 literature on AB towards various substances (Flaudias et al., 2013; Gardini et al.,  
383 2009). The 90 ms (i.e. 9%) slowing that we observed is on par with or stronger  
384 than other reports (e.g., 39 ms / 4%, from DeVito et al., 2018).

385 The absence of AB in ex-CD as measured by the cocaine-related Stroop effect is also  
386 coherent with the only published longitudinal study using a similar task in a  
387 prospective design, showing that an 8-week treatment (outpatient treatment,  
388 either counselling or cognitive behavioural therapy) was associated with a  
389 significant AB decrease in cocaine-dependent patients who maintain abstinence  
390 (DeVito et al., 2018).

391 However, unlike what has been reported with other substances (Field and Cox,  
392 2008), we found no link between addiction severity and AB size. As our sample size  
393 was limited, replication is necessary to confirm this result.

394 This AB difference could be explained by two different mechanisms, which cannot  
395 be distinguished by our experiment: either (1) cocaine-dependent patients with a  
396 lower to absent AB have an easier time maintaining abstinence, or (2) the process  
397 of maintaining abstinence causes a drop in AB. Hypothesis (1) is in line with  
398 findings that show that AB predicts relapse (Marissen et al., 2006) and that training  
399 to lower AB can lead to better treatment outcomes in addiction (Fadardi and Cox,  
400 2009; Schoenmakers et al., 2010) – though this effect is not consistent  
401 (Christiansen et al., 2015). However, the fact that maintaining abstinence is  
402 associated to a decrease in AB (DeVito et al., 2018) gives weight to hypothesis (2).

403 However, one possible bias in our result could be the presence of a general slowing  
404 or attentional deficit in CD and ex-CD: the slowing measured in cocaine-related  
405 words colour naming could actually not be specific to cocaine. But indeed,  
406 consistently with the literature (Hester et al., 2006), we found no difference  
407 between groups in the size of the colour Stroop effect: the measured difference in  
408 AB is thus not simply due to a general attentional processing difference. However,  
409 AB towards cocaine-related words in CD and ex-CD was also correlated with colour  
410 Stroop effect size in both the CD and ex-CD groups, which supports the idea,  
411 suggested in the literature (Compton et al., 2003), that colour and emotional  
412 Stroop effects could have some common basis, such as the involvement of the

413 medial and dorsolateral prefrontal cortex.

414 Our study is the first study comparing AB towards cocaine in control participants  
415 and both current cocaine-dependent patients and long-term abstinent patients,  
416 while eliminating the hypothesis of a non-specific attentional effect. It confirms  
417 that AB is lower in former- than in current cocaine-dependent patients. This study  
418 is a stepping-stone for the design of future prospective studies investigating the  
419 possible disappearance of AB with abstinence.

420 In order to start disentangling these two mechanisms, we are currently recruiting  
421 patients for a longitudinal study that will follow them during a 3-month abstinence  
422 attempt.

423 In addition to discussing results themselves, it is important to note that emotional  
424 Stroop tasks, despite their widespread use, have important limitations (Ataya et  
425 al., 2012a). Their reliability can drop below acceptable levels in some cases, and  
426 although we designed our task to minimise this issue by using vocal responses and  
427 separating conditions in successive blocks (Field and Christiansen, 2012),  
428 replication with other techniques such as eye-tracking (Marks et al., 2014) could  
429 be very useful.

430 The other issue with emotional Stroop task is their specificity: the interference

431 detected in drug Stroop tasks is likely to be influenced not only by attentional bias,  
432 but also by other factors such as inhibitory control or cue reactivity (Ataya et al.,  
433 2012b). Nevertheless, as Ataya et al. (2012b) point out, these various factors may  
434 all play a role in maintaining abstinence, and thus be interesting to measure when  
435 trying to understand the dynamics of treatment success.

436 Finally, Ex-CD reported lower craving than CD before the task, which is coherent  
437 with the fact that they successfully avoid using cocaine (Preston et al., 2009).  
438 Craving was non-significantly lower after the task in both groups: we can thus posit  
439 that our task does not heighten craving in participants. Several ex-CD participants  
440 were distressed by the task and made remarks about the fact that seeing cocaine-  
441 related words was unpleasant, and it was therefore important for us to make sure  
442 that our task did not have negative consequences on their craving. This distress  
443 was not captured by the craving scale, and could be an interesting object to explore  
444 in future research. One direction that could be particularly interesting would be  
445 the relationship between AB and the frequency of exposure to cocaine-related,  
446 although this frequency will be difficult to assess. Indeed, if these variables are  
447 negatively correlated, further research around exposure therapy such as the AB  
448 modification therapy discussed by Mayer et al. (Mayer et al., 2016) could help build  
449 a path for assisting cocaine-dependent patients in becoming abstinent.

450 The main limitation of our study is that the number of participants in the three  
451 groups is imbalanced, which is due to the difficulty of recruiting former cocaine  
452 users in a care setting, and to the difficulty of recruiting healthy controls matched  
453 in sex, age, and education level to patients. This may have reduced the power of the  
454 study and increased the risk of type 1 error. It is also important to note that women  
455 comprised a smaller percentage of the CD group than of either the Ex-CD or the HC  
456 group, and that the CD and Ex-CD groups were using psychotropic medications at  
457 a very high rate. These differences could contribute to or mask potential group  
458 differences.

459 We can also acknowledge that we did not control for the time of the last cocaine  
460 dose or medication or cigarette consumed by patients or healthy controls before  
461 the test. Neither did we record the possible withdrawal symptoms in the current  
462 cocaine users. Stricter laboratory conditions could be proposed for further studies.

## 463 **5. Conclusion**

464 Control participants and formerly cocaine-dependent patients do not have a  
465 significant AB towards cocaine, whereas current cocaine addicts display a specific  
466 interference effect when assessed with cocaine-related words. This is not a general  
467 interference effect, since the colour Stroop effect is observed with the same effect



468 size in all three groups.

469

## 470 6. References

471 American Psychiatric Association, Association, A.P., 2000. Diagnostic and statistical  
472 manual of mental disorders: DSM-IV-TR. N. Engl. J. Med. 4th, 943.  
473 <https://doi.org/10.1176/appi.books.9780890423349.5847>

474 Ataya, A.F., Adams, S., Mullings, E., Cooper, R.M., Attwood, A.S., Munafò, M.R.,  
475 2012a. Internal reliability of measures of substance-related cognitive bias. *Drug Alcohol*  
476 *Depend.* 121, 148–151. <https://doi.org/10.1016/j.drugalcdep.2011.08.023>

477 Ataya, A.F., Adams, S., Mullings, E., Cooper, R.M., Attwood, A.S., Munafò, M.R.,  
478 2012b. Methodological considerations in cognitive bias research: The next steps. *Drug*  
479 *Alcohol Depend.* 124, 191–192. <https://doi.org/10.1016/j.drugalcdep.2012.02.008>

480 Brown, J., Kranzler, H.R., Boca, F.K.D., 1992. Self-reports by alcohol and drug abuse  
481 inpatients: factors affecting reliability and validity. *Addiction* 87, 1013–1024.  
482 <https://doi.org/10.1111/j.1360-0443.1992.tb03118.x>

483 Castells, X., Cunill, R., Vidal, X., Capellà, D., 2016. Psychostimulant drugs for cocaine

484 dependence. Cochrane Database Syst. Rev. 4–7.  
485 <https://doi.org/10.1002/14651858.CD007380.pub4.www.cochranelibrary.com>

486 Christiansen, P., Schoenmakers, T.M., Field, M., 2015. Less than meets the eye:  
487 Reappraising the clinical relevance of attentional bias in addiction. *Addict. Behav.* 44,  
488 43–50. <https://doi.org/10.1016/j.addbeh.2014.10.005>

489 Compton, R.J., Banich, M.T., Mohanty, A., Milham, M.P., Herrington, J., Miller, G.A.,  
490 Scalf, P.E., Webb, A., Heller, W., 2003. Paying attention to emotion: An fMRI  
491 investigation of cognitive and emotional Stroop tasks. *Cogn. Affect. Behav. Neurosci.*  
492 3, 81–96. <https://doi.org/10.3758/CABN.3.2.81>

493 Copersino, M.L., Serper, M.R., Vadhan, N., Goldberg, B.R., Richarme, D., Chou,  
494 J.C.Y., Stitzer, M., Cancro, R., 2004. Cocaine craving and attentional bias in cocaine-  
495 dependent schizophrenic patients. *Psychiatry Res.* 128, 209–218.  
496 <https://doi.org/10.1016/j.psychres.2004.07.006>

497 Cox, W.M., Fadardi, J.S., Pothos, E.M., 2006. The addiction-stroop test: Theoretical  
498 considerations and procedural recommendations. *Psychol. Bull.* 132, 443–76.  
499 <https://doi.org/10.1037/0033-2909.132.3.443>

500 Cox, W.M., Hogan, L.M., Kristian, M.R., Race, J.H., 2002. Alcohol attentional bias as  
501 a predictor of alcohol abusers' treatment outcome. *Drug Alcohol Depend.* 68, 237–243.

502 [https://doi.org/10.1016/S0376-8716\(02\)00219-3](https://doi.org/10.1016/S0376-8716(02)00219-3)

503 Darke, S., 1998. Self-report among injecting drug users: A review. *Drug Alcohol*  
504 *Depend.* 51, 253–263. [https://doi.org/10.1016/S0376-8716\(98\)00028-3](https://doi.org/10.1016/S0376-8716(98)00028-3)

505 Degenhardt, L., Singleton, J., Calabria, B., McLaren, J., Kerr, T., Mehta, S., Kirk, G.,  
506 Hall, W.D., 2011. Mortality among cocaine users: A systematic review of cohort  
507 studies. *Drug Alcohol Depend.* 113, 88–95.  
508 <https://doi.org/10.1016/j.drugalcdep.2010.07.026>

509 DeVito, E.E., Kiluk, B.D., Nich, C., Mouratidis, M., Carroll, K.M., 2018. Drug Stroop:  
510 Mechanisms of response to computerized cognitive behavioral therapy for cocaine  
511 dependence in a randomized clinical trial. *Drug Alcohol Depend.* 183, 162–168.  
512 <https://doi.org/10.1016/j.drugalcdep.2017.10.022>

513 EMCDDA, 2017. *European Drug Report 2017: Trends and Developments.*  
514 <https://doi.org/10.2810/88175>

515 Fadardi, J.S., Cox, W.M., 2009. Reversing the sequence: Reducing alcohol consumption  
516 by overcoming alcohol attentional bias. *Drug Alcohol Depend.* 101, 137–145.  
517 <https://doi.org/10.1016/j.drugalcdep.2008.11.015>

518 Field, M., Christiansen, P., 2012. Commentary on Ataya et al. (2012), ‘Internal

519 reliability of measures of substance-related cognitive bias.' *Drug Alcohol Depend.* 124,  
520 189–190. <https://doi.org/10.1016/j.drugalcdep.2012.02.009>

521 Field, M., Cox, W.M., 2008. Attentional bias in addictive behaviors: A review of its  
522 development, causes, and consequences. *Drug Alcohol Depend.* 97, 1–20.  
523 <https://doi.org/10.1016/j.drugalcdep.2008.03.030>

524 Field, M., Munafò, M.R., Franken, I.H.A., 2009. A Meta-Analytic Investigation of the  
525 Relationship Between Attentional Bias and Subjective Craving in Substance Abuse.  
526 *Psychol. Bull.* 135, 589–607. <https://doi.org/10.1037/a0015843>

527 Flaudias, V., Brousse, G., de Chazeron, I., Planche, F., Brun, J., Llorca, P.-M., 2013.  
528 Treatment in hospital for alcohol-dependent patients decreases attentional bias.  
529 *Neuropsychiatr. Dis. Treat.* 9, 773–9. <https://doi.org/10.2147/NDT.S42556>

530 Flaudias, V., Llorca, P.-M., 2014. A brief review of three manipulations of the Stroop  
531 task focusing on the automaticity of semantic access. *Psychol. Belg.* 54, 199–221.

532 Franken, I.H.A., 2003. Drug craving and addiction: Integrating psychological and  
533 neuropsychopharmacological approaches. *Prog. Neuropsychopharmacol. Biol.*  
534 *Psychiatry* 27, 563–579. [https://doi.org/10.1016/S0278-5846\(03\)00081-2](https://doi.org/10.1016/S0278-5846(03)00081-2)

535 Franken, I.H.A., Kroon, L.Y., Weirs, R., Jansen, A., 2000. Selective cognitive

536 processing of drug cues in heroin dependence. *J. Psychopharmacol. (Oxf.)* 14, 395–400.  
537 <https://doi.org/10.1177/026988110001400408>

538 Gardini, S., Caffarra, P., Venneri, A., 2009. Decreased drug-cue-induced attentional  
539 bias in individuals with treated and untreated drug dependence. *Acta Neuropsychiatr.*  
540 21, 179–185. <https://doi.org/10.1111/j.1601-5215.2009.00389.x>

541 Hester, R., Dixon, V., Garavan, H., 2006. A consistent attentional bias for drug-related  
542 material in active cocaine users across word and picture versions of the emotional Stroop  
543 task. *Drug Alcohol Depend.* 81, 251–257.  
544 <https://doi.org/10.1016/j.drugalcdep.2005.07.002>

545 MacLeod, C.M., 1991. Half a century of research on the Stroop effect: an integrative  
546 review. *Psychol. Bull.* 109, 163–203.

547 Marissen, M.A.E., Franken, I.H.A., Waters, A.J., Blanken, P., Brink, W. Van Den,  
548 Hendriks, V.M., 2006. Attentional bias predicts heroin relapse following treatment.  
549 *Addiction* 101, 1306–1312.

550 Marks, K.R., Roberts, W., Stoops, W.W., Pike, E., Fillmore, M.T., Rush, C.R., 2014.  
551 Fixation time is a sensitive measure of cocaine cue attentional bias: Attentional bias and  
552 cocaine. *Addiction* 109, 1501–1508. <https://doi.org/10.1111/add.12635>

553 Mayer, A.R., Wilcox, C.E., Dodd, A.B., Klimaj, S.D., Dekonenko, C.J., Claus, E.D.,  
554 Bogenschutz, M., 2016. The efficacy of attention bias modification therapy in cocaine  
555 use disorders. *Am. J. Drug Alcohol Abuse* 42, 459–468.  
556 <https://doi.org/10.3109/00952990.2016.1151523>

557 Munafò, M., Mogg, K., Roberts, S., Bradley, B.P., Murphy, M., 2003. Selective  
558 processing of smoking-related cues in current smokers, ex-smokers and never-smokers  
559 on the modified Stroop task. *J. Psychopharmacol. Oxf. Engl.* 17, 310–316.  
560 <https://doi.org/10.1177/02698811030173013>

561 Nasreddine, Z.S., Phillips, N.A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin,  
562 I., Cummings, J.L., Chertkow, H., 2005. The Montreal Cognitive Assessment, MoCA:  
563 A brief screening tool for mild cognitive impairment. *J. Am. Geriatr. Soc.*  
564 <https://doi.org/10.1111/j.1532-5415.2005.53221.x>

565 New, B., Pallier, C., Brysbaert, M., Ferrand, L., 2004. Lexique 2: A new French lexical  
566 database. *Behav. Res. Methods ...* 36, 516–524.

567 Paliwal, P., Hyman, S.M., Sinha, R., 2008. Craving predicts time to cocaine relapse:  
568 Further validation of the Now and Brief versions of the cocaine craving questionnaire.  
569 *Drug Alcohol Depend.* 93, 252–259. <https://doi.org/10.1016/j.drugalcdep.2007.10.002>

570 Pascoli, V., Terrier, J., Lu, C., Lu, C., 2015. Sufficiency of Mesolimbic Dopamine

571 Neuron Stimulation for the Progression to Addiction Article Sufficiency of Mesolimbic  
572 Dopamine Neuron Stimulation for the Progression to Addiction. *Neuron* 88, 1054–1066.  
573 <https://doi.org/10.1016/j.neuron.2015.10.017>

574 Preston, K.L., Vahabzadeh, M., Schmittner, J., Lin, J.L., Gorelick, D.A., Epstein, D.H.,  
575 2009. Cocaine craving and use during daily life. *Psychopharmacology (Berl.)* 207, 291–  
576 301. <https://doi.org/10.1007/s00213-009-1655-8>

577 Rosse, R.B., McCarthy, M.F., Alim, T.N., Deutsch, S.I., 1994. Saccadic distractibility  
578 in cocaine dependent patients: A preliminary laboratory exploration of the cocaine-OCD  
579 hypothesis. *Drug Alcohol Depend.* 35, 25–30. [https://doi.org/10.1016/0376-](https://doi.org/10.1016/0376-8716(94)90106-6)  
580 [8716\(94\)90106-6](https://doi.org/10.1016/0376-8716(94)90106-6)

581 Schoenmakers, T.M., de Bruin, M., Lux, I.F.M., Goertz, A.G., Van Kerkhof, D.H.A.T.,  
582 Wiers, R.W., 2010. Clinical effectiveness of attentional bias modification training in  
583 abstinent alcoholic patients. *Drug Alcohol Depend.* 109, 30–36.  
584 <https://doi.org/10.1016/j.drugalcdep.2009.11.022>

585 Sueur, J., Aubin, T., Simonis, C., 2008. Equipment Review: Seewave , A Free Modular  
586 Tool for Sound Analysis and Synthesis. *Bioacoustics* 18, 213–226.

587 Vorspan, F., Bellais, L., Romo, L., Bloch, V., Neira, R., Lépine, J.-P., 2012. The  
588 Obsessive–Compulsive Cocaine Scale (OCCS): A Pilot Study of a New Questionnaire

589 for Assessing Cocaine Craving. *Am. J. Addict.* 21, 313–319.  
590 <https://doi.org/10.1111/j.1521-0391.2012.00248.x>

591 Whiteford, H.A., Degenhardt, L., Rehm, J., Baxter, A.J., Ferrari, A.J., Erskine, H.E.,  
592 Charlson, F.J., Norman, R.E., Flaxman, A.D., Johns, N., Burstein, R., Murray, C.J.L.,  
593 Vos, T., 2013. Global burden of disease attributable to mental and substance use  
594 disorders: Findings from the Global Burden of Disease Study 2010. *The Lancet* 382,  
595 1575–1586. [https://doi.org/10.1016/S0140-6736\(13\)61611-6](https://doi.org/10.1016/S0140-6736(13)61611-6)

596 Wright, B.C., 2017. What Stroop tasks can tell us about selective attention from  
597 childhood to adulthood. *Br. J. Psychol.* 108, 583–607.  
598 <https://doi.org/10.1111/bjop.12230>

599 Zhang, M., Ying, J., Wing, T., Song, G., Fung, D., Smith, H., 2018. A Systematic  
600 Review of Attention Biases in Opioid, Cannabis, Stimulant Use Disorders. *Int. J.*  
601 *Environ. Res. Public. Health* 15, 1138. <https://doi.org/10.3390/ijerph15061138>

602