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

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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 tasks 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					
N	28	24	40		
Age	46 [24-74]	45 [24-71]	41 [26-68]	ns	
% women	36	46	20	ns	
% with higher education	64	50	38	ns	
% with normal MoCA score (≥26)	59	54	60	ns	
% tobacco smokers	14	88	95	p<10 ⁻¹⁰	p<10 ⁻¹⁰
					p<10 ⁻⁶
					ns
% current alcohol use disorder	0	22	51	p<10 ⁻⁵	p<10 ⁻⁴
					p<0.05
					p<0.05
Alcohol intake/day	0.1 [0;2]	0.1 [0;6.4]	0.2 [0;30]	ns	

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

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

% with sedatives (benzodiazepines and Z-drugs)	0	42	63	p<10 ⁻⁵	p<10 ⁻⁶
					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).

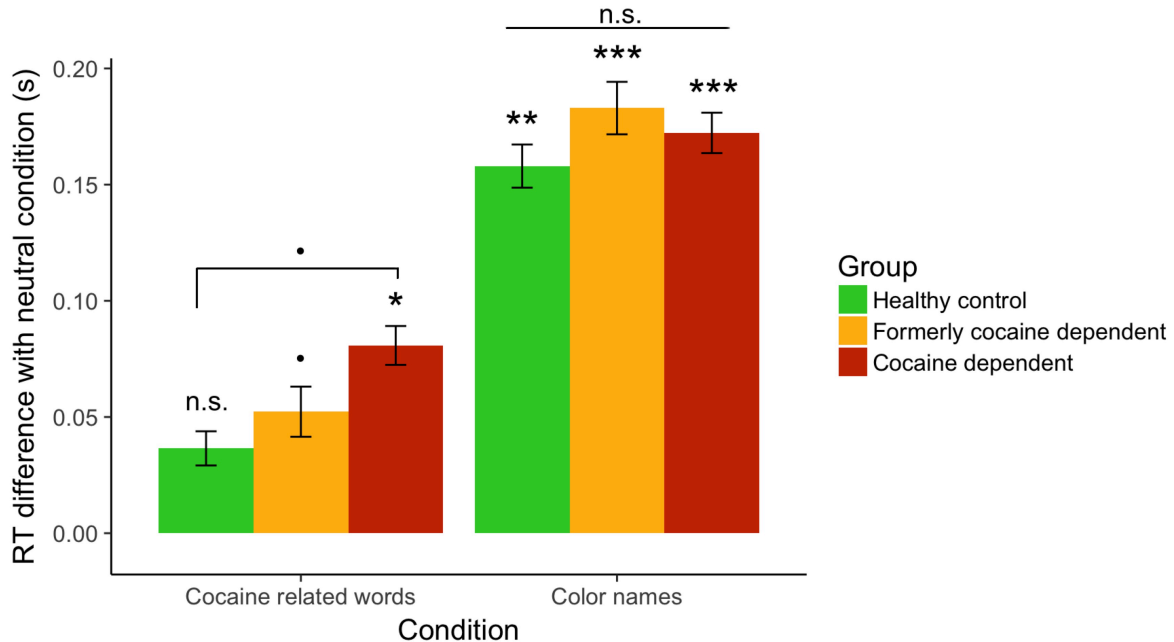
331 The CD group showed a significant slowing in the cocaine condition compared to
332 the neutral condition (Wilcoxon W = 565, p = 0.02), while neither ex-CD group
333 (Wilcoxon W = 207, p = 0.1), nor the HC (Wilcoxon W = 334, p = 0.3) did.

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 $p < 0.05$; ^{ns} $p > 0.1$.

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

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