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

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Abstract

Background

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

Methods

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

Results

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

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

Conclusions

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

1. Introduction

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

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

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

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

In emotional Stroop tasks, the interference is caused by the presence of emotionally salient words, and the slowing is thus caused by the attention towards 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

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

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

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

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

2. Methods

2.1. Participants

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

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

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

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

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

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

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

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

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

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

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

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

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

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

2.2. Task Design

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

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

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

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

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

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

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

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

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

2.3. Choice of words

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

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

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

2.4. Procedure

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

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

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

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

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

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

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

2.5. Data analysis

2.5.1. Power calculation

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

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

2.5.2. Accuracy assessment

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

2.5.3. Reaction time calculation

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

2.5.4. Statistical analysis

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

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

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

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

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

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

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

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

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

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

Significance threshold was set at p = .05.

3. Results

3.1. Demographic characteristics

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

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

Table 1: Demographic and clinical data.

3.2. Main analysis

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

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

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

interference (Jonckheere-Terpstra JT < 391, p > 0.2).

Mean accuracies and reaction times for the different groups and types of words are in Table 2.

	Healthy controls		Formerly cocaine-dependent (Ex-CD)		Cocaine dependent (CD)	
	Response time (ms)	Error rate (%)	Response time (ms)	Error rate (%)	Response time (ms)	Error rate (%)
Neutral Words	824 ± 130	1 ± 1	919 ± 158	1 ± 3	905 ± 140	3 ± 7
Colour Words	984 ± 190	1 ± 3	1,102 ± 181	5 ± 6	1,085 ± 183	5 ± 8
Cocaine Words	860 ± 153	1 ± 1	969 ± 122	1 ± 2	995 ± 180	3 ± 6

Interference (RT difference)

	Healthy controls	Formerly cocaine-dependent (Ex-CD)	Cocaine dependent (CD)	Statistical significance
Colour Words – Neutral Words	160 **	183 ***	177 ***	0.4
Cocaine Words – Neutral Words	36 ^{ns}	50$^{\cdot}$	81 *	0.03

Table 2: Mean Accuracy and Reaction Time (± standard deviation) for the different groups and types of words. Statistical significance of the difference between the interference and zero: *** p<0.001; ** p<0.01; * p<0.05; $^{\cdot}$ p<0.1; ^{ns} p>0.1. The statistical significance column shows the p-value for overall between-groups comparisons for both interference effects.

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

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

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

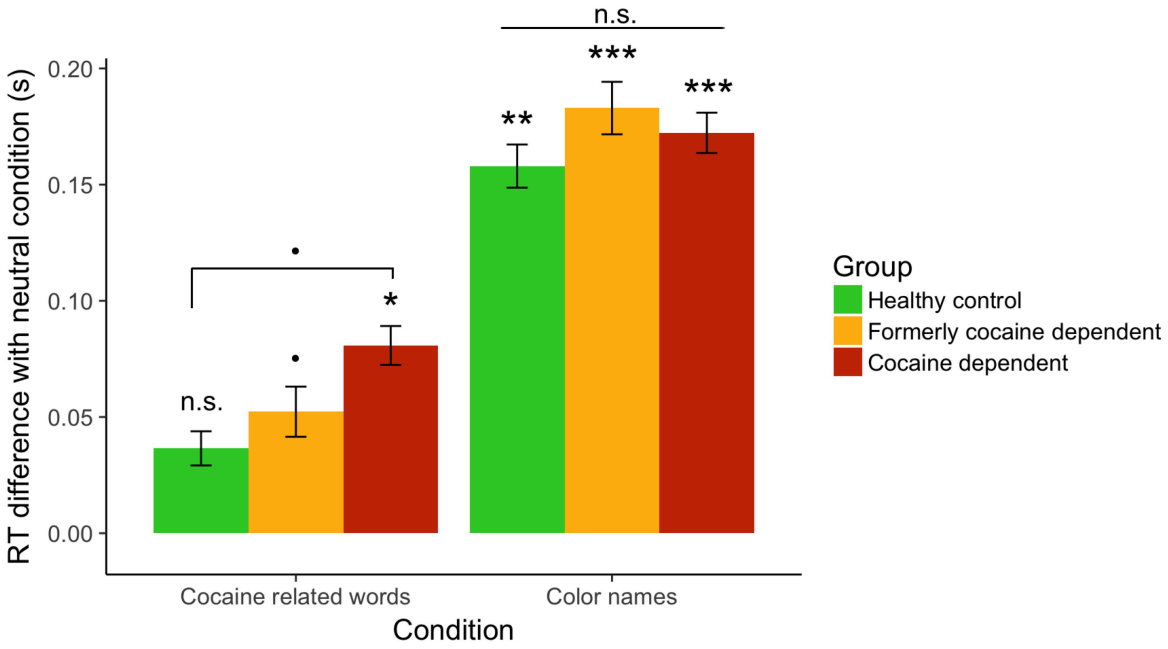

Figure 1: Emotional (cocaine) Stroop effect and colour Stroop effect for the different groups. Stars above each bar denote significance level of the difference between interference sizes and zero; stars on dashes above

groups of bars denote significance level of the difference between these bars. Notes: *** p<0.001; ** p<0.01; * p<0.05; ns p>0.1.

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

4. Discussion

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

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

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

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

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

However, unlike what has been reported with other substances (Field and Cox, 2008), we found no link between addiction severity and AB size. As our sample size 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

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

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

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

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

5. Conclusion

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

size in all three groups.

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