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# Factors associated with the absence of cocaine craving in treatment-seeking individuals during inpatient cocaine detoxification

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**ABSTRACT**

**Background:** Anecdotal evidence suggests a substantial proportion of individuals with cocaine use disorder do not report craving during inpatient detoxification.

**Objective:** To examine prevalence and clinical correlates of consistent absence of cocaine craving among inpatients during detoxification. We hypothesized that craving absence would be associated with less severity of cocaine use, depression, and anxiety. Alternative explanations were also explored.

**Methods:** Craving absence (i.e., non-cravers) was defined as a daily score of zero across two separate craving visual analogue scales in each of the inpatient days. Participants scoring ≥1 on ≥1 day were considered cravers. Severity of cocaine use disorder as well as in-treatment depression and anxiety were assessed. Alternative contributors included presence of cocaine and other substances in urine at admission, in-treatment prescription of psychotropic medications, treatment motivation, executive function, interoception, and social desirability.

**Results:** Eighty-seven participants (78.2% males) met criteria as either non-cravers ($n = 29$; 33.3%) or cravers ($n = 58$; 66.7%). Mean length of admission in non-cravers and cravers was, respectively, 10.83 and 13.16 days. Binary logistic regression model showed that non-cravers scored significantly lower than cravers on cocaine use during last month before treatment (OR, 95% CI; 0.902, 0.839–-0.970), in-treatment depression (OR, 95% CI; 0.794, 0.659–0.956), and in-treatment prescribing of antipsychotics (OR, 95% CI; 0.109, 0.014–0.823). Model prediction accuracy was 88.9%.

**Conclusions:** One in three patients undergoing inpatient detoxification experienced absence of craving, linked to less cocaine use, better mood, and less antipsychotics use. Findings may inform pretreatment strategies and improve treatment cost-effectiveness.

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## Introduction

Patients with substance use disorders (SUD) can experience cravings after stopping substance use or when exposed to drug primes and cues or stress (1). There is considerable inter-individual variability in craving levels. Studies conducted in laboratory settings to evaluate cue-induced craving have distinguished between high-cravers and low-cravers (2–4). The same distinction applies in clinical studies that have assessed spontaneous craving (5,6). Other studies have even distinguished between cravers and non-cravers after discrete or short-term assessments of craving (7–9). However, there is very little research on *consistent* absence of any manifestation of craving in active SUD, probably because it seems counterintuitive for most clinicians.

The genuineness of the phenomenon of consistent absence of spontaneous craving is highly relevant for the diagnosis and treatment of SUD. The genuine absence of craving in individuals not attempting to abstain from a substance was explained by Tiffany (10) as occurring through automatic processes. According to Tiffany, substance use can occur without cravings or urges by means of automatization, provided that the substances are readily accessible, without hurdles. However, if any such hurdles are present, then non-automatic cognitive processes, defined as "abstinence-avoidance urges," may emerge and drive efforts to use substances. In substance-dependent patients who are attempting abstinence, the hypothesis proposed by Tiffany foresees the emergence of "abstinence-promotion urges," which are non-automatic cognitive

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processes engaged to control long-standing, automatized actions that drive substance use (10). Nevertheless, the consistent absence of craving during substance abstinence can be observed in patients intending to stop substance use.

A retrospective medical record analysis from 195 treatment-seeking individuals found that approximately 23% of these individuals – some of whom were cocaine-dependent – did not spontaneously report any desire or urge to use the drug-of-concern throughout a 14-day inpatient detoxification treatment (11). This absence of craving could be genuine given that these non-cravers also reported lower levels of depression and anxiety than cravers, and depression and anxiety are positively associated with craving (8,12). Moreover, in the same study, non-cravers had reduced need for psychopharmacologic treatment than cravers (11). Altogether, these results suggest that a better understanding of consistent absence of craving could help to improve clinical management of substance craving.

Improving our understanding of *consistent absence of spontaneous cocaine craving* (from this point forward: absence of craving) can contribute to reduce the substantial disease burden associated with cocaine dependence (13). In patients with cocaine use disorder, precarious abstinence in the patients' natural environment requires treatment to prevent relapse. In this situation, an important aim of treatment is to reduce cocaine craving, which is mainly withdrawal-related but also may be cue- and stress-elicited. Indeed, spontaneous cocaine craving is a risk factor for relapse at outpatient facilities (14). Furthermore, spontaneous cocaine craving has also been identified as a risk factor for relapse after discharge from controlled environments in some studies (15) but not in others (16).

In the present study, we explore absence of craving reported by individuals who have failed to achieve sustained cocaine abstinence in outpatient settings. The DSM-5 defines cocaine craving as a *strong* desire or urge to use this substance (17). However, for the purposes of this study, cocaine craving was defined as "any" desire or urge to use cocaine. At present, the prevalence of craving absence is not known. Potentially, absence of craving could characterize a relatively large subgroup of cocaine-dependent patients based on reports indicating low rates of craving during inpatient detoxification (18–20). However, the prevalence of absence of craving among cocaine users could be very low since this phenomenon implies the stable absence of craving after stopping cocaine use, which would be unexpected in treatment-resistant cocaine-dependent patients. Given the consistent association between cocaine craving and depression and anxiety (21–23), we hypothesized that absence of craving – if this is a genuine phenomenon – would be paralleled by relatively low levels of depression and anxiety during detoxification. Several other candidate predictors of absence of craving are discussed below.

Severity of cocaine use disorder likely influences the level of craving experienced by an individual during a period of cocaine abstinence. Moreover, the use of other substances (24) could also impact the extent of cocaine craving during detoxification. Detoxification treatment may reduce craving, although it is highly unlikely that any detoxification treatment would continually suppress all desire to use cocaine. Patient efforts to inhibit craving (25,26) may also be associated with absence of craving. It also makes sense to assume that treatment-seeking individuals who are more motivated to change their cocaine use will make a greater effort to inhibit craving. Importantly, in addition to being motivated to inhibit craving, the patient must have the ability to do so. This ability depends first on the patient's awareness of craving. Notably, damage to the insula, a key brain region for interoception of urges, disrupts tobacco craving (27). Furthermore, patients need to be able to consistently inhibit their cravings. In this regard, some cocaine-dependent patients retain at least a partial ability to cognitively inhibit cue-elicited craving (28–30). For these reasons, interoceptive and executive functions could also be predictors of craving absence. Absence of craving could also be the result of a patient's failure to clearly communicate the presence of existing cravings. Consequently, the role of social desirability biases must be ruled out as potential explanation, particular given the negative relationship between heroin craving and social desirability (31).

This study has three primary aims: 1) to prospectively assess the prevalence of absence of craving during inpatient cocaine detoxification treatment; 2) to determine whether craving absence is paralleled by lower levels of depression and anxiety; and 3) to identify the independent factors involved in absence of craving.

## Methods

This was a prospective, observational, exploratory study conducted from June 2010 through April 2017. The study protocol was approved by the institutional review board of the Santa Creu i Sant Pau Hospital in Barcelona, Spain.

### *Participants*

Inclusion criteria were: age ≥18 years old, fulfillment of DSM-IV criteria for cocaine dependence (32), and patient-requested admission for cocaine detoxification

after failure to achieve sustained cocaine abstinence in outpatient facilities. Exclusion criteria included: 1) admission for reasons other than cocaine detoxification; 2) opioid use disorder during the last year; and 3) the presence of any mental disorder (e.g., neurocognitive disorder) that could hinder clinical assessment. All participants signed an informed consent form. No compensation was provided to subjects for participation in this study.

## Setting and procedure

Participants were consecutively admitted to the inpatient detoxification unit of the Sant Pau Hospital. Participants, physicians, and nurses were informed that the present study was aimed to assess cocaine detoxification, but they did not know that the primary aim was to explore absence of craving. Two psychiatrists (F.B. and S.D-S.) prescribed pharmacological treatments as usual and managed the duration of detoxification according to each patient's clinical condition. For patients whose inpatient treatment was >14 days due to conditions other than substance withdrawal, only data from the first 14 days of hospitalization were used in this study. During the admission period, two psychologists (L. M. and S.A.) performed cognitive assessments after acute withdrawal symptoms had been reduced. The physicians and nurses were blinded to these cognitive assessments.

## Clinical and treatment assessments

### Absence of craving

Cocaine craving was assessed by two modified visual analogue scales (VAS) included in the Cocaine Selective Severity Assessment (CSSA) (33), an 18-item, interviewer-administered measure of cocaine withdrawal severity during the preceding 24 h. Single item approaches to craving assessment (e.g., VAS) has been successfully employed in numerous previous studies (4,6–9,29,30). The study design reflects our intent to balance the risk of inducing craving against the risk of failing to detect it. In particular, we judged that the risk of generating substance craving by assessing craving (34) could be minimized by using VAS. Moreover, we also deemed that the risk of not detecting craving by using a brief, simple form of assessment (i.e., VAS) would be maximized by decontextualizing the assessment of cocaine craving from other cocaine-related symptoms. For this and other reasons, craving was assessed with the CSSA. In the present study, the Spanish version of the CSSA (35) was administered daily between 10 and 11 p.m. by two nurses (A.M. and P.F.).

The two modified VAS measures (i.e., CSSA items #4 and #5) index the intensity ("Please rate the highest intensity of the desire for cocaine you have felt in the last 24 hours") and frequency ("Please identify on the line below, how often you have felt the urge to use cocaine in the last 24 hours") of craving, respectively. Both of these scales are divided by eight hatch marks that are then coded as numerical scores from 0 (item #4 = "No desire at all"; item #5 = "Never") to 7 (item #4 = "Unable to resist"; item #5 = "All the time"), but no numbers are shown. According to CSSA instructions (33,35): (a) the recorded score is the number of the mark closest to the patient's response; (b) responses placed between 0 and 1 are recorded as 1 (rather than 0). This upward scoring criterion even for responses very near to the first hatch mark, together with the fact that number 0 is not shown, make it difficult to definitively distinguish between the absence and presence of cocaine craving. Since this is a major drawback to our purpose of consistently determining absence of craving, we discarded all responses between 0 and 1.

Patients with absence of craving (i.e., non-cravers) were those who (a) reported a score of 0 every day on both items #4 and #5 and (b) completed the items on at least 70% of the days during the hospitalization period to control for lack of engagement (36). Participants who scored ≥1 on both items #4 and #5 on ≥1 day were considered cravers.

### Substance use and dependence

The participants' history of cocaine use and dependence was assessed using an *ad hoc* survey. Total cocaine and other substance use during the month prior to admission was assessed using the Interview for Research on Addictive Behavior (37). The severity of cocaine dependence for the last 6 months was assessed using the Spanish version of the Severity of Dependence Scale (SDS), which includes 5 self-reported items (38,39).

### Detoxification treatment

A urine specimen was collected from each participant at the time of admission. Enzymatic assay was used to determine the presence of ethanol (cutoff value: >2.5 ng/mL). Competitive homogeneous enzyme immunoassay was used to analyze the following substances (cutoff values to establish a positive urinalysis result are shown in brackets): amphetamines (>1000 ng/mL), benzodiazepine (>200 ng/mL), cannabis (>50 ng/mL), cocaine (i.e., benzoylecgonine >300 ng/mL), methadone (>300 ng/mL), and opiates (>300 ng/mL). All analyses

were performed on an automatized platform (Architect CI 16000 from Abbott Diagnostics).

Cocaine withdrawal as a whole was considered the primary treatment target and treated using benzodiazepines and/or antipsychotics. Patients could be given antidepressants, antipsychotics, anxiolytics, and/or mood stabilizers if they presented substance-induced and/or independent mental disorders. Antidipsotropic medications (e.g., disulfiram or naltrexone) were prescribed when appropriate. The psychosocial aspects of the intervention were aimed at maintaining a relaxed, drug-free environment in the inpatient detoxification unit, responding to the therapeutic needs of patients on a 24-h basis, and enhancing patient motivation to change and to continue treatment for cocaine use disorder after discharge.

### Anxiety and depression

Both were assessed thrice weekly using the Spanish versions of the State-Trait Anxiety Inventory (STAI) (40,41), and the Beck Depression Inventory (BDI) (42,43).

### Readiness to change cocaine use

We used the Spanish version of the University of Rhode Island Change Assessment scale (URICA) (44,45). The URICA is a 32-item self-report inventory yielding four scores of participant attitudes regarding stages of change (Precontemplation, Contemplation, Action, and Maintenance) (46). Higher scores indicate a stronger endorsement. We also calculated two composite scores: 1) Readiness to Change and 2) Committed Action. Readiness to Change was obtained by subtracting the Precontemplation score from the sum of the Contemplation, Action, and Maintenance scores (47). The Committed Action score was obtained by subtracting the Contemplation score from the Action score (48).

### Interoceptive and executive functions

The following interoceptive and executive functions were assessed: interoceptive sensitivity, premorbid-IQ, cognitive flexibility, working memory, response inhibition, and decision-making.

*Interoceptive sensitivity*: Heartbeat perception task (49,50). Participants were asked to count the number of heartbeats they felt over various time intervals while the actual heartbeat was simultaneously measured using electrocardiography. Time intervals included three heartbeat trials (35, 25, and 45 s), three time trials (23, 56, and 40 s), and three additional heartbeat trials (23, 56, and 40 s). Time trials were performed to control for time estimation biases (e.g., one beat, 1 s). Time and heartbeat perception inaccuracy were calculated by subtracting estimated values from actual values and dividing this figure by actual values, then multiplying by 100 to express the inaccuracy as a percentage. Heart rate was recorded using the Biopac MP150 system (Biopac Systems Inc., USA).

***Premorbid-IQ.*** Word Accentuation Test (51). This test involves a brief reading test that has been well validated as a proxy of pre-morbid IQ in the Spanish population (52).

***Cognitive flexibility.*** Trail Making Test (53,54) including part A, in which participants are instructed to draw lines between circles in increasing sequential order, and part B, in which they have to connect the circles by alternating between numbers and letters. The main dependent measure is the time required to complete part B minus part A, i.e., an index of cognitive flexibility after subtracting the effect of visual and motor demands.

***Working memory.*** Letter-number sequencing subtest from the Wechsler Adult Intelligence Scale (55). Participants are asked to verbally reproduce a string of letters and numbers by placing the numbers in ascending order and then the letters in alphabetical order. The main dependent measure is the total number of hits.

***Response inhibition.*** Stroop Color-Word Interference Test (56), consisting of four conditions (C): C1 or color naming; C2 or word reading (i.e., the words "red," "blue," and "green" printed in black ink); C3 or inhibition (i.e., the words "red," "blue," and "green" are printed in incongruent colors and participants have to name the color while ignoring the word); and C4 or switching (participants have to alternate between naming the color and reading the word). The main dependent variables were the composite time measures "C3 time minus C1 time" (inhibition time) and "C4 time minus C3 time" (switching time), and the number of inadvertent and self-corrected errors committed in C3 and C4 (inhibition and switching errors, respectively).

***Decision making.*** Original (ABCD) and variant (EFGH) versions of the Iowa Gambling Test (IGT) (57). Both require participants to choose 100 cards from four card decks. In the original version, two of the decks (A and B) are disadvantageous as they produce high immediate gains, but they will take more money than they give long term. The other two decks (C and D) are advantageous, as they result in small and immediate gains, but will yield more money than they take long term. In the variant version, the logic is swapped and advantageous decks yield immediate large losses but

long-term larger rewards. The dependent measures were net scores, calculated by subtracting the number of disadvantageous choices from the number of advantageous choices. In both cases, lower net scores reflect more disadvantageous decision-making performances.

### Social desirability

We used the Spanish version of the Marlowe–Crowne Social Desirability Scale (MC-SDS), which is a 33-item self-report whereby higher scores indicate greater bias (58,59).

### Statistical analysis

Mixed-effects models of repeated-measures analyses were performed to assess whether there was a time effect on CSSA item #4 (intensity of craving) scores in the craving group and to longitudinally compare the non-craving group and craving group on BDI and STAI scores. To identify the factors independently associated with craving absence, we first compared the non-craving and craving groups using $\chi^2$ tests (categorical variables) or *t*-tests (continuous variables). Variables discriminating non-cravers from cravers at the bivariate level with *P* values ≤.10 were considered candidate predictors of absence of craving. Next, the factors independently associated with the likelihood of craving absence were identified by entering the candidate predictors in a binary logistic regression model (entry criterion $P < .05$, removal criterion $P > .10$). All statistical tests were 2-sided. Levels of statistical significance were set at $P < .05$. The IBM SPSS 21 statistical package was used to perform all statistical analyses.

## Results

### Prospective prevalence of absence of craving and socio-demographic characteristics of non-cravers and cravers

Participants were 97 cocaine-dependent patients, all Caucasian. Ten participants were excluded from analyses because they: 1) completed <70% of modified VAS ($n = 2$), or 2) provided ambiguous scores between 0 and 1 in all of the assessment days ($n = 8$). Of the 87 participants included in the analyses, 29 (33.3%) were non-cravers and 58 (66.7%) were cravers. The socio-demographic characteristics of the non-cravers and cravers had similar distributions (mean ± SD): age: 40.79 ± 8.14 vs. 38.83 ± 8.45; $t(85) = 1.035$, $P = .303$; percentage of males: 86.21% vs. 74.12%; $\chi^2$ (1) = 1.650, $P = .199$; and years of education: 14.38 ± 4.64 vs. 13.36 ± 3.49; $t(44.32) = 1.042$, $P = .303$.

### Time course of craving, anxiety, and depression

The length of admission (mean ± SD) among non-cravers and cravers was, respectively, 10.83 ± 2.90 days versus 13.16 ± 2.90 days ($t(85) = -3.542$; $P = .001$). In cravers, there was a significant effect of time on craving intensity ($F(13, 419.666) = 3.754$, $P < .001$) (Figure 1). Craving absence was paralleled by lower anxiety and depression (Figure 2). For anxiety, there were significant main effects for group ($F(1, 113.920) = 13.617$; $P < .001$) and time ($F(13, 318.954) = 2.212$; $P = .009$), but no significant group–time interaction ($F(13, 318.954) = 0.890$; $P = .564$). For depression, there were significant main effects for group ($F(1, 93.677) = 21.900$; $P < .001$) and time ($F(13, 244.854) = 7.180$; $P < .001$), but no interaction ($F(13, 244.854) = 1.719$; $P = .058$).

### Candidate predictors of absence of craving

Compared to cravers (Table 1), non-cravers had later onset of cocaine use ($P = .047$), less cocaine use during the month preceding admission ($P < .001$), less frequent detection of cocaine metabolites in urine at admission ($P = .004$) and less severe cocaine dependence ($P < .001$). Total use of other substances during the month preceding admission was also lower in non-cravers (Table 1), especially for alcohol ($P = .046$). The presence of benzodiazepines in urine was also less common in non-cravers at admission ($P = .024$).

During hospitalization, fewer non-cravers than cravers received antidepressants ($P = .039$) or antipsychotics ($P < .001$). In addition, the daily dose of antipsychotics was lower in non-cravers ($P = .029$) (Table 2). Non-cravers, relative to cravers, had lower scores on the Maintenance subscale of the URICA ($P = .013$), and a trend toward faster inhibition times ($P < .081$) and

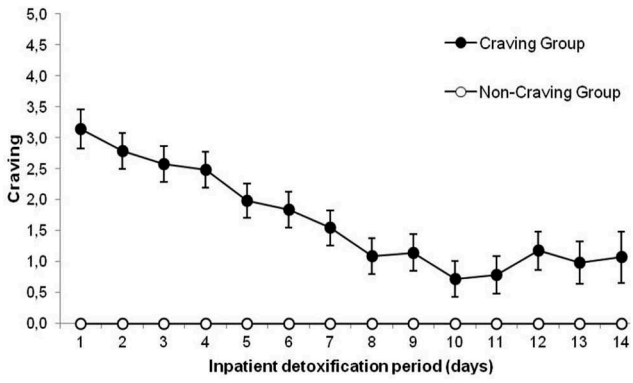


**Figure 1.** Estimated marginal means with standard errors of means for Cocaine Selective Severity Assessment (CSSA)–Item #4 (intensity of cocaine craving) in the non-craving and craving groups. In cravers, there was a significant effect of time on craving intensity (P < .001).

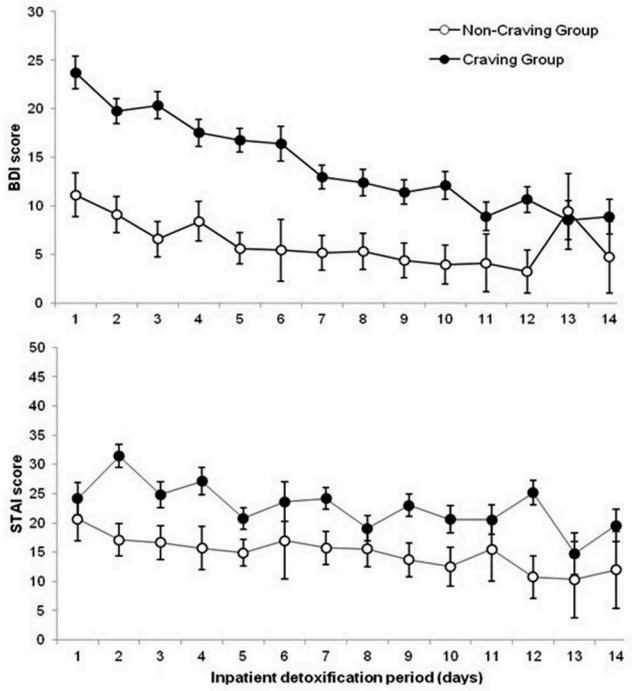


**Figure 2.** Estimated marginal means with standard errors of means for the Beck Depression Inventory (BDI) and State-Trait Anxiety Inventory (STAI) scores according to mixed-model repeated-measures analyses in the non-craving and craving groups. For BDI scores, there were significant main effects for group (P < .001) and time (P < .001), but no significant group–time interaction (P = .058). Likewise, for STAI scores there were significant main effects for group (P < .001) and time (P = .009), but no interaction (P = .564).

less switching errors in the Stroop ($P$ < .076). Finally, non-cravers scored higher than cravers on the Marlowe–Crowne Social Desirability Scale ($P$ = .001) (Table 3).

### *Factors independently associated with absence of craving*

Table 4 shows the factors that were independently associated with the likelihood of presenting craving absence, namely: amount of cocaine used in the month preceding admission (OR, 95% CI; 0.902, 0.839–0.970) and – during the hospitalization period – administration of antipsychotics (0.109, 0.014–0.823), and depression scores (0.794, 0.659–0.956). The correct prediction rate (i.e., total number of cases correctly identified/total cases included in the analysis) was 88.9%. The positive and negative predictive values were 92.7% and 80.8%, respectively.

## Discussion

Our findings suggest that absence of craving is a phenomenon that clinicians and researchers should be aware of during inpatient cocaine detoxification: one in three participants experienced it, and they exhibited distinctive profiles characterized by less cocaine use before admission and lower depression and pharmacological treatment needs. The base rates are consistent with those reported in prior (less controlled) studies (18–20) and the link with (low) depression and anxiety supports the validity of the absence of craving construct (21–23). Since cocaine use patterns, depression, and antipsychotic medication accounted for a considerable percentage of variance (74%), it seems clear that interventions targeted at promoting the precursors of craving absence are warranted.

The influence of lower cocaine use in the 30 days prior to admission on craving absence suggests this phenomenon is linked to differences in severity of cocaine use disorder. In support of this proposition, we also found that non-cravers were less likely to present benzoylecgonine in urine at admission and also had lower SDS scores. The therapeutic implication of these results is that reducing cocaine use before admission is important to reduce craving during detoxification, which aligns with the notion of "pretreatment" as a way to improve response to treatments for SUD (60,61). If not possible to reduce cocaine use before admission, clinicians should at least prevent bingeing immediately before admission – a common clinical phenomenon, usually described as "a farewell" by Spanish patients (62). Patients should be made aware of the consistent relationship between recent severity of cocaine use and craving. This issue could be addressed in preparatory sessions for patients on the admissions waitlist.

The observational design of this study does not allow us to determine whether lower depression and less antipsychotics promote craving absence. Both factors could also be subsequently associated with craving given that the administration of antipsychotics to ameliorate symptoms associated with cocaine craving such as paranoia (22), and depression may increase the risk for cocaine craving. Thus, the fact that non-cravers received antipsychotics more frequently does not clarify whether antipsychotics worsen cocaine craving-which is what a meta-analysis of clinical trials found (63), or whether, to the contrary, these are the most effective medications for reducing cocaine craving, as a meta-analysis of original reviews concluded (64). Similarly, the fact that cravers received antidepressants more frequently than non-cravers does not speak to the effectiveness of these medications to relieve depression or craving during detoxification. Depression and cocaine craving could be reduced with medications such as ketamine, which have shown to be efficacious to rapidly treat major depression (65) and cue-induced cocaine craving (66). During detoxification, treating depression is also relevant to preventing post-discharge craving, as studies have shown that the higher the level of depression prior to

**Table 1.** Comparison of non-cravers versus cravers regarding cocaine use disorder and use of other substances.

| | Non-cravers | Cravers | Comparison | | |
|---|---|---|---|---|---|
| | (*n* = 29) | (*n* = 58) | *t* or $\chi^2$ | *gl* | *P* |
| *Cocaine use and dependence* | | | | | |
| Age of onset of use (years) | 22.21 (5.53) | 19.78 (5.20) | 2.015 | 85 | .047 |
| Age of onset of problematic use (years) | 31.52 (8.42) | 28.60 (8.33) | 1.497 | 82 | .138 |
| Months without use from use onset | 55.10 (49.70) | 60.71 (90.64) | −0.273 | 70 | .786 |
| Main route of administration % | | | 3.806 | 2 | .149 |
| Nasal | 100 | 87.93 | | | |
| Intravenous | 0 | 3.45 | | | |
| Inhalation | 0 | 8.62 | | | |
| History of treatment | | | | | |
| Without previous treatment % | 24.14 | 24.14 | 0.0 | 1 | 1.0 |
| Number of episodes | 2.59 (1.57) | 3.55 (3.23) | −1.520 | 85 | .132 |
| Age of first treatment (years) | 35.72 (9.58) | 31.81 (9.27) | 1.832 | 84 | .070 |
| Severity of Dependence Scale | 8.03 (2.71) | 10.38 (2.67) | −3.847 | 85 | <.001 |
| Total use last month[a] (g) | 7.52 (10.78) | 25.03 (20.89) | 5.125 | 83.55 | <.001 |
| Cocaine in urine at treatment entry % | 51.72 | 81.03 | 8.111 | 1 | .004 |
| *Other recent substance use*[b] | | | | | |
| Total use last month[a] | | | | | |
| Alcohol (units)[c] | 88.60 (154.68) | 176.03 (243.71) | 2.023 | 79,77 | .046 |
| Benzodiazepines (mg)[d] | 10.0 (52.92) | 49.11 (162.38) | 1.637 | 74.04 | .106 |
| Cannabis (joints) | 13.21 (52.04) | 47.39 (114.93) | 1.885 | 82.64 | .063 |
| Tobacco (cigarettes) | 423.41 (348.22) | 555.59 (376.30) | 1.582 | 85 | .117 |
| Substances in urine at treatment entry % | | | | | |
| Alcohol | 10.3 | 17.2 | 0.833 | 1 | .362 |
| Benzodiazepines | 17.2 | 41.4 | 5.069 | 1 | .024 |
| Cannabis | 31.0 | 37.9 | 0.401 | 1 | .527 |

Results presented are means (standard deviation) unless otherwise indicated. Statistically-significant results are highlighted in bold.
[a]Total use last month equals average daily dose x days of use (up to 30 days).[37]
[b]Data on the recent use of other substances (e.g., amphetamines) or urine detection of amphetamines, methadone, or opiates are not included because these substances were never used by or detected in >2 non-cravers or cravers.
[c]One unit of alcohol equals 10 g of alcohol.
[d]Benzodiazepine use includes only the use of these substances without a medical prescription.

cocaine administration, the higher is the cocaine-primed craving (67,68).

Neither social desirability nor interoceptive function were independent predictors of craving absence. These negative results further support the likelihood that absence of craving is genuine rather than simply resulting from response biases (high social desirability) or problems to identify urge feelings (interoceptive dysfunction). In terms of motivation to change, non-cravers scored lower than cravers on the URICA Maintenance scale. One possible explanation for this unexpected result is that responses to the URICA are particularly

**Table 2.** Comparison of non-cravers versus cravers regarding inpatient detoxification treatment.

| | Non-cravers | Cravers | Comparison | | |
|---|---|---|---|---|---|
| | (*n* = 29) | (*n* = 58) | *t* or $\chi^2$ | *gl* | *P* |
| Duration (days) | 10.83 (2.90) | 13.16 (2.90) | −3.542 | 85 | .001 |
| Patients treated % | | | | | |
| Antidepressants | 72.4 | 89.7 | 4.256 | 1 | .039 |
| Antidipsotropics[a] | 55.2 | 50.0 | 0.207 | 1 | .649 |
| Antipsychotics | 44.8 | 89.7 | 20.564 | 1 | <.001 |
| Benzodiazepines | 62.1 | 70.7 | 0.658 | 1 | .417 |
| Mood stabilizers | 24.1 | 31.0 | 0.449 | 1 | .503 |
| Average daily dosage[b] (mg/d) | | | | | |
| Antipsychotics | 65.96 (157.39) | 150.91 (173.44) | 2.219 | 85 | .029 |
| Benzodiazepines | 10.43 (26.30) | 16.58 (24.82) | 1.069 | 85 | .288 |
| Tobacco smoking allowed[c] % | 6.9 | 19.0 | 2.216 | 1 | .137 |
| Type of discharge % | | | 0.524 | 1 | .469 |
| Medical | 93.10 | 96.60 | | | |
| Against medical advice | 6.90 | 6.90 | | | |

*Note*. Results presented are means (standard deviation) unless otherwise indicated. Statistically-significant results are highlighted in bold.
[a]Antidipsotropics include acamprosate, cyanamide, disulfiram, and naltrexone.
[b]Doses of antipsychotics and benzodiazepines are equivalent doses of chlorpromazine and diazepam, respectively.
[c]Smoking was allowed in the inpatient detoxification unit for the first 12 months of the study; after that point, smoking was prohibited to comply with a change in Spanish law.

**Table 3.** Comparison of non-cravers versus cravers regarding anxiety and depression, state of change for cocaine use, interoceptive and executive functions, and social desirability.

| | Non-cravers | Cravers | Comparison | | |
|---|---|---|---|---|---|
| | (*n* = 29) | (*n* = 58) | *t* | *gl* | *P* |
| *Anxiety and depression*[a] | | | | | |
| State-Trait Anxiety Inventory | 15.18 (8.30) | 23.22 (8.55) | −4.174 | 85 | <.001 |
| Beck Depression Inventory | 6.16 (4.61) | 14.52 (7.76) | −6.278 | 82.34 | <.001 |
| *State of change for cocaine use (URICA)* | | | | | |
| Precontemplation | 1.78 (0.55) | 1.72 (0.47) | 0.497 | 85 | .621 |
| Contemplation | 4.38 (0.42) | 4.32 (0.40) | 0.733 | 83 | .466 |
| Action | 4.40 (0.47) | 4.39 (0.39) | 0.133 | 84 | .895 |
| Maintenance | 3.84 (0.48) | 4.12 (0.49) | −2.540 | 85 | .013 |
| Readiness to change[b] | 10.91 (1.37) | 11.11(1.24) | −0.682 | 82 | .497 |
| Commitment action[c] | 0.32 (2.00) | 0.43 (3.00) | −0.171 | 82 | .865 |
| *Interoceptive and executive functions* | | | | | |
| Heartbeat perception task (% inaccuracy) | 38.88 (26.65) | 48.54 (24.55) | −1.617 | 76 | .110 |
| Word Accentuation Test (hits) | 22.34 (4.39) | 23.19 (3.21) | −1.021 | 85 | .310 |
| Trail Making Test | | | | | |
| Part A (s) | 36.44 (12.87) | 36.28 (12.24) | −0.056 | 82 | .955 |
| Part B (s) | 81.00 (32.01) | 93.76 (36.14) | 1.511 | 77 | .135 |
| Part B (mistakes) | 0.92 (1.50) | 1.23 (2.13) | 0.647 | 76 | .519 |
| Letter Number Sequencing WAIS (hits) | 9.33 (3.61) | 8.85 (2.75) | 0.645 | 77 | .521 |
| Stroop Color-Word Interference Test | | | | | |
| Inhibition time (s) | 20.46 (9.95) | 24.74 (10.77) | −1.768 | 84 | .081 |
| Switching time (s) | 10.46 (11.08) | 10.26 (13.15) | 0.071 | 84 | .943 |
| Inhibition errors | 0.46 (0.84) | 0.41 (1.16) | 0.206 | 84 | .837 |
| Switching errors | 0.82 (1.31) | 1.71 (2.44) | −1.799 | 84 | .076 |
| Iowa Gambling Task | | | | | |
| ABCD | 2.37 (31.28) | 3.69 (28.62) | −0.192 | 83 | .848 |
| EFGH | 20.22 (33.56) | 22.84 (31.51) | −0.347 | 81 | .729 |
| *Marlowe–Crowne Social Desirability Scale* | 16.55 (4.89) | 13.16 (4.37) | 3.285 | 85 | .001 |

URICA: University of Rhode Island Change Assessment Scale; WAIS: Wechsler Adult Intelligence Scale. Results presented are means (standard deviation). Statistically-significant results are highlighted in bold.
[a]Values are the average of all assessments conducted thrice weekly during admission.
[b]Readiness to change = contemplation + action + maintenance − precontemplation.
[c]Commitment action = action − contemplation.

downward biased by social desirability (69), which was higher in non-cravers than cravers. An individual's ability to inhibit emotional states also failed to predict craving absence, which makes it difficult to explain absence of craving in the ongoing context of cocaine abstinence and occasional exposure to cocaine-related cues and/or stress. Based on the Implementation Intentions theory (70), we speculate that, in non-cravers, plans to inhibit craving during admission triggered automatic control processes, which efficaciously prevented the emergence of craving. This suggests that automatization processes may underpin the absence of craving in individuals who do not attempt abstinence, as proposed by Tiffany (10), and in treatment-seeking individuals attempting to abstain from substances.

This study has practical implications for the treatment of cocaine craving during inpatient detoxification. Notably, our findings point to absence of craving as a valuable clinical marker of lower severity of cocaine use disorder. In addition, early identification of craving absence can improve treatment cost-effectiveness by informing matched interventions. On the other hand, an increased awareness among clinicians with regard to the existence of absence of craving may help to minimize or prevent the risk of inducing craving by administering "triggering" assessments. Artificially inducing cocaine craving could be therapeutically inappropriate since it may increase psychological distress and relapse risk. Nevertheless, clinical judgment is essential to determine, on a case by case basis, whether craving absence is genuine and indicative of the

**Table 4.** Multivariate binary logistic regression model of factors associated with consistent absence of spontaneous cocaine craving.

| Variables | *B* | Wald $\chi^2$ | *P* | *OR* | 95% *CI* |
|---|---|---|---|---|---|
| Total use of cocaine during last month (g) | −0.103 | 7.746 | .005 | 0.902 | 0.839–0.970 |
| Severity of Dependence Scale | −0.348 | 3.427 | .064 | 0.706 | 0.488–1.021 |
| Benzodiazepines in urine at entry to detoxification treatment (%) | −0.497 | 0.292 | .589 | 0.608 | 0.100–3.689 |
| Treatment with antidepressants during detoxification | −1.256 | 0.766 | .381 | 0.285 | 0.017–4.739 |
| Treatment with antipsychotics during detoxification | −2.216 | 4.618 | .032 | 0.109 | 0.014–0.823 |
| Maintenance subscale (URICA) | −1.761 | 2.323 | .127 | 0.172 | 0.018–1.655 |
| Beck Depression Inventory | −0.230 | 5.900 | .015 | 0.794 | 0.659–0.956 |
| Constant | 15.750 | 7.640 | .006 | 6921948.488 | |

*OR*: odds ratio; *CI*: confidence interval; URICA: University of Rhode Island Change Assessment scale. Statistically-significant tests are highlighted in bold.

presence of a less severe cocaine use disorder, as established in the DSM-5 (17), or, by contrast, due, for example, to poor treatment engagement.

This study has three main limitations. First, we cannot rule out limitations in detecting craving absence. To achieve a balance between sensitivity and specificity to detect naturally-occurring craving, we asked patients to indicate the intensity and frequency of any desire or urge for cocaine experienced during the last 24 h on two instruments (modified VAS), both of which are included in a specific tool (the CSSA) designed to assess cocaine withdrawal. More research is needed to determine whether other approaches to measuring cocaine craving – that is, in terms of complexity and frequency of assessment – would yield similar findings to those obtained in this study. Second, despite the relevance of cocaine withdrawal for cocaine craving during detoxification, this variable was not included among the candidate predictors of absence of craving because we are not aware of any validated cocaine withdrawal assessment instrument that does not include craving as one of the items. Finally, the findings of this study may not be applicable to patients who predominantly use cocaine-free base (inhaled) or intravenous cocaine hydrochloride rather than intranasal cocaine hydrochloride (as was the case for the participants in this study) given the relevance of recent cocaine exposure for absence of craving.

This is the first study to investigate absence of spontaneous cocaine craving. In the future, other potential sources of craving absence such as Implementation Intentions (70) and/or alexithymia (9) should be investigated. In addition, the findings presented here support the need to conduct experimental studies to evaluate the effect of antipsychotic medications and depression treatment on craving during cocaine detoxification. Finally, absence of craving should be assessed through prospective studies that focus on the course of cocaine use after hospital discharge given that the predictive validity of substance craving with regards to substance use is the key determinant of its clinical relevance (71).

## Declarations of interest

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