Does craving for cocaine mediate cocaine use? Analysis of a randomized controlled pilot trial of memory-focused cognitive therapy

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Abstract
Cocaine use disorder (CUD) is a debilitating psychopathology, with no recommended medication therapy or specific psychological intervention. Memory-focused cognitive therapy (MFCT) is a novel psychotherapy for CUD, theorized to modify and reconsolidate cocaine craving-related memories for cognitive and behavioral control. A pilot randomized controlled trial indicated that this therapy is associated with reduced craving and cocaine use. With an 80% confidence interval (CI) set for null hypothesis testing, we conducted an exploratory causal mediation analysis with confounder adjustment to determine whether increased cocaine abstinence following MFCT is mediated by reduced craving experience and increased emotion regulation. Participant data on the Difficulties in Emotion Regulation Scale did not meet screening evaluation as a potential mediator. Cocaine craving (assessed by the frequency version of the Craving Experiences Questionnaire) was associated

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with a total treatment effect of MFCT on cocaine abstinence at follow-up (1.499; 80% CI 1.114 to 1.970; \( p = .012 \)). A significant natural indirect effect indicated that reductions in cocaine use were strongly mediated by reduced frequency of craving experience (1.753; 80% CI: 1.334 to 2.936; \( p < .0001 \)). This study provides exploratory evidence in support of the theoretical action for MFCT and underscores the importance of craving as a therapeutic target.

**Keywords**
Cocaine use disorder, cognitive behavioral therapy, craving, mediation, memory, reconsolidation

**Introduction**

Cocaine use disorder (CUD; Diagnostic and Statistical Manual [DSM-5]; American Psychiatric Association, 2013) is a debilitating psychopathology. In DSM-5, CUD has 11 symptoms, spanning increased tolerance, withdrawal symptoms, urges to use cocaine (craving), and several behavioral, health, and social problems associated with chronic consumption.

Among these symptoms, influential models of addiction position the cognitive-affective construct—craving—in a key disorder maintaining role (Robinson & Berridge, 1993; Tiffany, 1990; West, 2006). Craving is a highly subjective construct. It is clear from patient reports that the content and strength of craving varies widely. An episode can be brief or protracted and distressing. Etiologically, craving can be understood as the product of a drug exposure and associative learning process in which previously drug-neutral situations, objects, people, and sensations/moods that are present when cocaine is obtained become conditioned stimuli (CS; O’Brien, Childress, McLellan, & Ehrman, 1992). An encountered CS (or a direct drug-related cue such as the sight of cocaine or cocaine paraphernalia) can trigger a process of cognitive elaboration in which memory of past drug use—often in the form of a vivid sensory mental image (May et al., 2014; May, Andrade, Panabokke, & Kavanagh, 2004)—induces a desire for pleasure or the need to alleviate anxiety, stress, or cocaine-related withdrawal symptoms (Baker, Piper, McCarthy, Majeskie, & Fiore, 2004; Koob, Caine, Parsons, Markou, & Weiss, 1997). Negative reinforcement, in particular, can be very strongly motivating for some people with CUD, leading to problems with the regulation of emotion (Cheetham, Allen, Yucel, & Lubman, 2010; Fox, Axelrod, Paliwal, Sleeper, & Sinha, 2007).

In CUD, cocaine-related imagery can drive the maintenance of pro-drug (approach) thoughts, appraisals, and dysfunctional beliefs (Andrade, May, & Kavanagh, 2012; Conway, Meares, & Standart, 2004). These cue-induced responses can persist long into abstinence and, if not controlled, can cause relapse (Parvaz, Moeller, & Goldstein, 2016). It is also important to recognize that if a person with CUD has immediate access to cocaine, there may be minimal or no craving-related elaboration (Tiffany, 1990). However, if there is a delay in obtaining cocaine, or there is ambivalence with the desire to be abstinent, craving is likely to be strong, distressing, and highly motivating (Kavanagh, Andrade, & May, 2005).

There have been many efforts to develop an effective therapy for CUD. However, to date, there are no licensed medications or guideline-recommended specific psychosocial interventions (National Institute for Health and Care Excellence, 2007). Among the latter, cognitive behavioral therapy (CBT) has been the most widely trialed intervention. A meta-analysis of 53 randomized controlled trials targeting alcohol or another drug disorder calculated that stand-alone CBT is associated with a small overall standardized mean difference for the treatment effect versus control (Hedge’s \( g = .154 \); Magill & Ray, 2009). A more encouraging picture emerged when the authors pooled results from trials that combined CBT with another psychosocial intervention (typically general drug counseling). This strategy was associated with a medium effect size (\( g = .305; p < .005; 19 \) trials).

The population of cocaine users is heterogeneous. Some use infrequently (typically powder users), but there is a subpopulation who use smokable (crack) cocaine or cocaine powder very intensively and develop CUD; many with considerable unmet treatment need. In England in 2016–2017, it was estimated that there were 760,000 powder cocaine users and 181,000 crack users in the general population (Home
Office, 2017; Public Health England, 2017a). In that year, 42,403 people presented to community addiction treatment clinics for help with cocaine-related problems (16,892 powder cocaine and 25,511 crack) of whom 52% had a co-occurring opioid use disorder (Public Health England, 2017b). Community services offer people with CUD general counseling but many do not engage with this intervention or discontinue treatment after a short time. Among those who are retained in treatment, continued crack cocaine use is a significant predictor of poor response to medication for opioid use disorder (Marsden et al. 2012; Marsden et al. 2019).

Against this background—and encouraged by the potential for a CBT intervention to be effective when offered alongside ongoing general counseling and support—we developed a novel cognitive therapy intervention with the goal of helping people to better recognize, modify, and control cocaine craving-related thoughts, emotions, and behavior. Our memory-focused cognitive therapy (MFCT) is a 15-week, outpatient, individual psychotherapy (Marsden et al., 2017). In addition to a formulation-driven assessment and with use of, cognitive restructuring and behavioural experiments, MFCT adapts to CUD the fear memory reliving, imagery rescripting, and memory reconsolidation paradigm successfully used for the treatment of posttraumatic stress disorder (PTSD) (Brewin, Gregory, Lipton, & Burgess, 2010; Grey, Young, & Holmes, 2002; Holmes & Mathews, 2010). Our MFCT therapy protocol also includes a cue-induction procedure to elicit images and affective responses as therapy targets (Hon, Das, & Kamboj, 2016; Xue et al., 2012).

In psychotherapy, an important part of the evidence-gathering process for a new intervention is to address theoretical hypotheses of how treatment causes change (Kazdin, 2007; Murphy, Cooper, Holton, & Fairburn, 2009). This is typically done by conducting a causal mediation analysis (Hayes, 2014; MacKinnon, 2008). A causal mediation analysis tests whether there is evidence that the psychotherapy exposure is related to changes in a hypothesized mediator and whether the mediator is associated with changes in a subsequent outcome. A randomized controlled trial provides the logical design conditions for causal inference, because participants are randomly allocated to the levels of therapeutic exposure.

Prior to the analysis of the developmental study (Marsden et al., 2018), the statistical analysis plan for the primary and secondary outcome measures was registered (Centre for Open Science; https://www.osf.io/3kf2j/). The results showed that compared to an assessment-only control, the intervention was associated with lower levels of craving (bias corrected Hedge’s $g = -1.62$; 95% confidence interval (CI) $-2.45$ to $-0.80$; the primary outcome measure) and more abstinent days ($g = 1.19$; 90% CI 0.54 to 1.84; the drug use secondary outcome measure). In that report, we stated our plan to determine if craving and emotion regulation mediate cocaine use, thereby giving evidence of the MFCT’s theoretical change mechanism.

In this article, we present the results of an exploratory causal mediation analysis to estimate the extent to which MFCT is associated with cocaine abstinence through craving experience and emotion regulation. We predict that reduced craving and improved emotion regulation mediate observed treatments effects of MFCT at follow-up.

**Method**

**Design, setting, and participants**

Data for the present study were from a completed and published single-site, 15-week, 2-arm, randomized controlled trial contrasting MFCT (the intervention; $n = 16$) to an assessment and cocaine cue-induction only group (the control; $n = 14$).

The published protocol provides a detailed description of the study procedures and interventions (Marsden et al., 2017). Briefly, the intervention comprised three 90-min pre-randomization assessments; two 30-min cocaine cue-induction procedures; five 120-min individual MFCT sessions over consecutive days; and three 60-min MFCT-relapse prevention discussions and research follow-ups at 1 week, 1 month, and 3 months conducted as personal interviews at the clinic. The control group received the three-session prerandomization assessment, the two cue-induction procedures, and participated in the three research follow-ups only.

The trial was done at an English National Health Service community addictions clinic operated by South London and Maudsley Trust and at the National Institute for Health and Research and Wellcome Trust Clinical Research Facility at King’s College Hospital, London. Ethical approval for the protocol was granted by the UK National Research Ethics Service.

Patients (aged 18 years and over) receiving ongoing general drug counseling were eligible for the trial if they were diagnosed with CUD (structured...
Study exclusion criteria were current non-abstinent alcohol use disorder, uncontrolled severe mental health disorder, current PTSD, and suicide planning in the past month or a suicide attempt in the past 6 months. All patients provided their informed written consent.

**Measures**

The following clinical research measures were used for the analysis (see Figure 1 for timing during the study):

**Difficulties in Emotional Regulation Scale (DERS).** The DERS (Gratz & Roemer, 2004) is a 36-item self-report measure of current emotion regulation. It includes four components: awareness and understanding, acceptance, ability to control impulses in the presence of negative affect, and access to emotion regulation strategies. Items are rated using a 5-point scale (almost never to almost always, 0–5; total score, 36–180). Higher scores indicate more difficulty in emotion regulation. Participants completed the DERS at baseline and at 1-month follow-up and the instrument was screened as a potential mediator for the analysis.

**The Craving Experiences Questionnaire—frequency version (CEQ-F).** The CEQ-F (May et al., 2014) is an 11-item, self-report measure of the frequency of intensity, imagery, and intrusiveness aspects of craving in the past 2 weeks (adapted for the present study). Each item is rated using an 11-point scale (0–10; total score: 0–110). Participants completed the CEQ-F at baseline and at 1-month follow-up and the instrument was screened as a potential mediator for the analysis.

**Treatment Outcomes Profile (TOP).** The TOP (Marsden et al., 2008) is a structured, clinician-administered interview for substance use disorder treatment outcome research. It includes a calendar prompt, time line follow-back method to record drug use during the prior 28 days. Participants completed the TOP at baseline and 3-month follow-up. The outcome measure for the analysis was the number (count) of days abstinent (NDA) from cocaine at the 3-month follow-up.

**Urine Drug Screen (UDS; Alere Toxicology).** To indicate recent drug use at the 3-month follow-up (and to verify self-report using Cohen’s kappa statistic), we used an instant result immunoassay device to detect the primary cocaine metabolite (benzoylcegonine) in urine.

**Statistical analysis**

Some description is warranted on our conceptual approach for the causal mediation analysis. Rather than follow the traditional method of assessing mediation (Baron & Kenny, 1986), we used the counterfactual framework (Valeri & Vanderweele, 2013; VanderWeele, 2015).
In Baron and Kenny’s regression equation approach (see Figure 2, Panel 1),Path c’ represents the direct effect of the exposure on the outcome. Path a’ estimates the effect of the exposure on the mediator and Path b’ shows the effect of the mediator on the outcome. Taken together, Paths a’ and b’ express the indirect effect of the exposure on the outcome via the mediator. This approach has served researchers very well—but it cannot estimate exposure-mediator interactions or handle non-continuous outcome measures (Holland, 1986).

VanderWeele’s counterfactual framework was developed to address these limitations (see Figure 2, Panel 2). Here, the estimation of effects is achieved by comparing observed and hypothetical outcomes for the intervention and control groups, on the assumption of “exchangeability” (i.e., that people assigned to the control group [A = 0] would respond in the same way as people assigned to the intervention group [A* = 1] had they been assigned to the intervention, and vice versa; Robins & Greenland, 1992).

A causal mediation model decomposes the total effect (TE) into a direct effect (i.e., the effect of treatment [A] on outcome [Y; A = 0 vs. A* = 1]) and the natural indirect effect (NIE). There are two types of direct effect—a controlled direct effect (CDE) and a natural direct effect (NDE). The CDE is computed by holding the mediator to a constant. The NDE is computed by holding the mediator to the unexposed (control) level, allowing for natural variation. The CDE and NDE are equivalent unless there is an exposure-mediator interaction. The NIE captures the effect of the mediation pathway (i.e., the average change in Y if the exposure is fixed to the level of the intervention and the mediator changes accordingly [i.e., A = 0 to A* = 1]; VanderWeele, 2015).

All analysis was done in Stata (version 15.0; StataCorp, 2017) in four steps. First, the data were screened using Little’s test (command: mcartest), with the intention to use multiple imputations (command: mice) to manage missing values provided that...
missingness was independent of the unobserved and observed data.

Second, we compared baseline and 1-month follow-up values between the groups on variables for the analysis, with a 95% CI for the comparison of measures at 1-month follow-up, because this was the level of precision set for the primary outcome in the original trial.

Third, univariate regression models were fitted to demonstrate significant associations between treatment and mediator; mediator and outcome; and treatment and outcome—each fitted univariably and multivariably to identify potential confounding. At baseline, the following participant measures were used as covariates: sex, age, months of regular cocaine use, months of general drug counseling, and CEQ-F score.

Finally, the causal mediation analysis was done using the command paramed (Dunn et al., 2015). Paramed supports the use of count-based outcome measurement (as used here) and gives standard errors (SE), CI, and parameter estimates for the TE, CDE, NDE, and NIE by the delta method. Given the small sample size and exploratory nature of the analysis, these parameters were estimated by bootstrapping with 80% CIs for hypothesis testing.

Results

Participant enrolment and missing data

Fifty-eight patients were screened for the study, of whom 35 were enrolled. As planned, 30 participants completed the assessment phase and were randomized to the control group (n = 14) and the intervention group (n = 16).

All participants completed the 1-month follow-up, except one member of the control group who declined to complete the DERS. All participants, bar one from each group, completed the 3-month follow-up. A non-significant Little’s test statistic supported use of multiple imputation for the missing DERS total score, $\chi^2(16) = 14.50; p = .561$, and the two missing values on the NDA outcome, $\chi^2(36) = 11.38; p = 1.000$.

Baseline characteristics and group differences on emotion regulation and craving

There was good group balance on baseline characteristics (Table 1). The overall CEQ-F sample mean at baseline was 62.7 (SD 20.2). The CEQ-F had good internal reliability (Cronbach’s $\alpha$ .83). The overall sample mean for the DERS at baseline was 103.3 (SD 26.29) with excellent internal reliability ( $\alpha$ .93).

Table 2 presents the summary values on the variables for the causal mediation model at baseline and the two follow-ups by the group.

At baseline, there were no group differences on the measures of cocaine use, CEQ-F, and DERS. Compared to the control group, participants in the intervention group had lower CEQ-F scores at 1-month follow-up ($g = -1.62; 80\% CI: -2.45$ to $-0.80$). The intervention was also associated with greater NDA at the 3-month follow-up ($g = .38; 80\% CI: 0.30$ to $1.28$). There was complete concordance between self-report and UDS data (i.e., all participants who reported cocaine use in the past 7 days had a cocaine positive UDS, and all participants who reported no cocaine use in the past 7 days had a negative UDS; $\kappa = 1.00$).

Table 1. Participant characteristics at baseline.

| Variable                                      | Control (n = 14) | Intervention (n = 16) |
|-----------------------------------------------|-----------------|-----------------------|
| Male                                          | 9 (64%)         | 11 (69%)              |
| Age (years)                                   | 45.0 (6.5)      | 43.3 (6.7)            |
| Months of regular cocaine use (IQR)           | 108.0 (69–150)  | 94.5 (60–120)         |
| Months in treatment at enrolment (IQR)        | 5.0 (1.0, 25.5) | 8.5 (2.5, 53.5)       |
| DSM5 CUD diagnosis (severity)                  |                 |                       |
| Moderate (4–5 symptoms)                       | 4 (29%)         | 3 (19%)               |
| Severe (6–11 symptoms)                        | 10 (71%)        | 13 (81%)              |
| Medication for co-occurring opioid use disorder |               |                       |
| Oral methadone (mg/day)                       | 5 (55.0)        | 6 (61.7)              |
| Sublingual buprenorphine (mg/day)             | 4 (13.0)        | 5 (14.4)              |

Note: DSM = diagnostic and statistical manual; CUD = cocaine use disorder; SD = standard deviation; IQR = interquartile range. Data are number of participants, mean (SD), or median (IQR).
For the DERS, there was no statistically significant group difference at 1-month follow-up ($g = -0.45$; 80% CI: $-0.93$ to 0.02).

**Causal mediation analysis**

**Assumptions for mediation.** Univariate regression models were first fitted to each model pathway. Separate linear regression models tested the direct effect of treatment on the mediator (Path a') to meet assumptions for mediation. The intervention was associated with lower scores on the CEQ-F at 1-month follow-up, $F(1, 28) = 20.99$; adjusted $R^2 = .408$; $p < .0001$. However, the intervention was not associated with any meaningful change on the DERS, $F(1, 28) = 1.63$; adjusted $R^2 = .021$; $p = .212$.

To test the effect of the CEQ-F on 3-month NDA outcome, a Poisson regression model was fitted to the NDA outcome. Lower CEQ-F scores at 1-month were associated with greater cocaine abstinence, likelihood ratio (LR) $X^2(1) = 80.67$; $p < .0001$; pseudo $R^2 = .252$. The intervention was also associated with increased NDA at 3 months, LR $X^2(1) = 21.16$; $p < .0001$; pseudo $R^2 = .666$. Higher DERS score at 1 month was associated with less abstinence at 3 months, LR $X^2(1) = 27.73$; $p < .0001$; pseudo $R^2 = .087$. However, since the DERS scores at 1 month were not associated with the intervention, it did not meet the minimum requirement for mediation and this variable was dropped from further analysis.

**Identification of covariates.** Table 3 presents the results of univariable and covariate-adjusted regression models. The univariable models fitted indicated that months of regular cocaine use ($p = .035$), baseline CEQ-F ($p = .030$), and trial group ($p < .0001$) were all predictors of 1-month CEQ-F score. However, in the multivariable model, only trial group was associated with CEQ-F score (adjusted $R^2 = .479$; $p = .002$).

Age ($p = .001$), months of regular cocaine use ($p = .003$), baseline CEQ-F ($p < .0001$), baseline cocaine use ($p < .0001$), and trial group ($p < .0001$) were all predictors of change on the outcome. Then, in an adjusted model (pseudo $R^2 = .201$), sex ($p = .043$), baseline CEQ-F ($p = .006$), baseline cocaine use ($p = .001$), and trial group ($p < .0001$) were all associated with outcome.

Based on the adjusted models for 1-month craving and 3-month cocaine abstinence, sex, baseline CEQ, and baseline cocaine use were included in the final model as potential confounders (Table 4). The model was run bootstrapped with 10,000 replications.

**Mediation analysis**

Overall, there was a significant association of the intervention on NDA outcome (TE 1.499; 80% CI 1.114 to 1.970; $p = .012$). With no evidence of an exposure–mediator interaction, the CDE and NDE are equivalent, and NDE is reported only herein.

There was no evidence of a significant direct effect (NDE = .855; 80% CI 0.569 to 1.175; $p = .242$) and a rate ratio coefficient close to 1 indicated little-to-no difference between participants receiving the intervention or control through the model’s direct causal

| Table 2. Variables included in the analysis at baseline, 1-month follow-up (potential mediators) and outcome at 3-month follow-up, by study group ($n = 30$). |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Point/variable** | **Control (n = 14)** | **Intervention (n = 16)** | **Difference (95% CI)** | **Effect size (CI)** |
| **Baseline** | | | | |
| Cocaine NDA | $M$ (SD) | $M$ (SD) | $-1.34 (-18.30$ to 15.62) | $-0.06 (-0.78$ to 0.66) |
| CEQ-F | 67.5 (17.00) | 58.5 (22.40) | $-9.00 (-24.05$ to 6.05) | $-0.44 (-1.16$ to 0.29) |
| DERS | 104.71 (22.28) | 102.06 (30.05) | $-2.65 (-17.38$ to 22.68) | $-0.10 (-0.81$ to 0.62) |
| **1-Month follow-up** | | | | |
| CEQ-F | 51.75 (22.72) | 14.77 (21.47) | $-36.98 (-53.51$ to $-20.45$) | $-1.62 (-0.80$ to $-2.45)$ |
| DERS | 98.21 (22.67) | 85.50 (30.58) | $12.71 (-7.67$ to 33.10) | $-0.45 (-0.93$ to $0.02)$ |
| **3-Month follow-up** | | | | |
| Cocaine NDA | 51.55 (35.34) | 77.07 (27.50) | $25.52 (10.44$ to 40.59) | $0.38 (0.30$ to 1.28)$^{b}$ |

Note: $M =$ mean; $SD =$ standard deviation; CI = confidence interval; NDA = number of days abstinent from cocaine past 28 days; CEQ-F = craving experience questionnaire (frequency version), recall period: past 2 weeks (total score, range: 0–110); DERS = Difficulties in Emotion Regulation Scale, recall period: past 2 weeks (total score, range: 36–180); Hedge’s $g$.

$^{a}$Effect size CI advanced specified at 95% CI.

$^{b}$Effect size CI advanced specified at 80% CI.
pathway. This was underscored by the Poisson model (coefficient $-0.156$; 95% CI $-0.419$ to $-0.106$; $p = .242$). The mediating pathway was significant (NIE $= 1.753$; 80% CI 1.334 to 2.936; $p < .0001$), indicating that a reduction in craving at 1-month follow-up was associated with increased abstinence in the participants in the intervention group.

### Discussion

Using data from a randomized controlled trial, we present an exploratory mediation analysis providing preliminary evidence for a mediating effect of the frequency of intensity, imagery, and intrusiveness aspects of cocaine craving (as measured by the CEQ-F) on cocaine abstinence among patients allocated to MFCT.

Both treatment allocation and craving were independently associated with cocaine use and after covariate adjustment, study data suggest a causal effect of MFCT on cocaine abstinence via reduced craving experience. The significant NIE from the causal mediation model provides evidence in support of our hypothesized therapeutic change mechanism. In spite of the small sample, this was a strong effect:

| Variable/path to mediator | Coefficient | 95% CI | SE  | t   | p Value |
|---------------------------|-------------|-------|-----|-----|---------|
| Unadjusted                |             |       |     |     |         |
| Sex                       | 3.455       | -19.652 to 26.561 | 11.280 | 0.31 | .762    |
| Age                       | 1.099       | -0.533 to 2.730    | 0.797  | 1.38 | .179    |
| Months in general counseling | -16.182  | -37.085 to 4.722   | 10.205 | -1.59 | .124    |
| Months regular cocaine use | 21.970   | 1.661 to 42.280    | 9.915  | 2.22 | .035    |
| Baseline CEQ-F            | .560        | 0.057 to 1.064     | 0.246  | 2.28 | .030    |
| Baseline cocaine use      | -.989       | -2.748 to 0.771    | 0.859  | -1.15 | .259    |
| Group                     | -36.981     | -53.515 to -20.446 | 8.072  | -4.58 | <.0001  |

| Model ($R^2$.605; adjusted $R^2$.479) |             |       |     |     |         |
|------------------------------------|-------------|-------|-----|-----|---------|
| Sex                                | 1.532       | -17.455 to 20.519 | 9.155 | 0.17 | .869    |
| Age                                | .315        | -1.000 to 1.630    | 0.634  | 0.50 | .624    |
| Months in general counseling        | -11.660     | -28.403 to 5.083   | 0.163  | -1.44 | .163    |
| Months regular cocaine use          | 12.645      | -6.204 to 31.495   | 0.178  | 1.39 | .178    |
| Baseline CEQ-F                      | .278        | -0.181 to 0.738    | 0.221  | 1.26 | .222    |
| Baseline cocaine use                | -0.493      | -2.076 to 1.090    | 0.763  | -0.65 | .525    |
| Group                               | -29.290     | -46.775 to -11.806 | 8.431  | -3.47 | <.002   |

| Variable/paths to outcome | IRR | 95% CI | SE  | z   | p Value |
|---------------------------|-----|-------|-----|-----|---------|
| Unadjusted                |     |       |     |     |         |
| Sex                       | 1.199 | 0.997 to 1.441 | 0.112 | 1.93 | .053    |
| Age                       | .979 | 0.967 to 0.992 | 0.006 | -3.22 | .001    |
| Months in general counseling | 1.000 | 0.997 to 1.004 | 0.002 | 0.23 | .821    |
| Months regular cocaine use | .773 | 0.654 to 0.914 | 0.066 | -3.01 | .003    |
| Baseline CEQ-F            | -.990 | -0.986 to -0.994 | 0.002 | -5.10 | <.0001  |
| Baseline cocaine use      | 1.038 | 1.023 to 1.053 | 0.007 | 5.17 | <.0001  |
| CEQ-F at 1-month (mediator) | .984 | 0.981 to 0.988 | 0.002 | -8.39 | <.0001  |
| Group                     | 1.494 | 0.1256 to 1.779 | 0.132 | 4.53 | <.0001  |

| Model (pseudo $R^2$.201) |     |       |     |     |         |
|---------------------------|-----|-------|-----|-----|---------|
| Sex                       | 1.238 | 1.007 to 1.522 | 0.131 | 2.02 | .043    |
| Age                       | .995 | 0.982 to 1.009 | 0.007 | -7.3  | .466    |
| Months in general counseling | 1.007 | 0.840 to 1.209 | 0.094 | 0.08 | .937    |
| Months regular cocaine use | .904 | 0.748 to 1.091 | 0.087 | -1.05 | .292    |
| Baseline CEQ-F            | .994 | 0.989 to 0.998 | 0.002 | -2.74 | .006    |
| Baseline cocaine use      | 1.030 | 1.012 to 1.049 | 0.009 | 0.06 | .998    |
| Group                     | 1.420 | 1.168 to 1.726 | 0.141 | 0.00 | <.0001  |

Note: CEQ-F = craving experience questionnaire (frequency version), recall period: past 2 weeks (total score, range: 0–110); IRR = incidence rate ratio; CI = confidence interval; SE = standard error.
once the effect of craving at 1 month was accounted for, the model showed no statistically significant direct effect of MFCT on outcome.

Based on this analysis, there was no support for the hypothesis that emotion regulation mediates cocaine abstinence after therapy. Reduced DERS scores were associated with the NDA outcome at 3-month follow-up, but this was an independent effect that was not linked to the intervention. However, it would be wrong to miss the opportunity to help patients in this area. Previous studies have suggested that individuals with CUD show stronger responses to emotional stimuli (Aguilar de Arcos, Verdejo-Garcia, Peralta-Ramirez, Sanchez-Barrera, & Perez-Garcia, 2005) and emotion regulation can improve as abstinence is sustained (Fox et al., 2007). It is possible that a lack of association between emotion regulation and treatment in our study may in part be because the DERS (and the CEQ-F) does not capture motivations to use drugs to change emotional state. Substance use as a strategy for coping with negative affect (and associated craving) is likely to play an important role in use and relapse and may be a more relevant predictor than the general aspects of emotion regulation addressed in the DERS.

The present analysis supports assessing and targeting craving experience to inform psychological treatment of CUD (Marsden et al., 2014). While it is not currently feasible to directly target subthreshold, cue-induced responses, MFCT targets cognitive and affective elaborations with the aim of diminishing the strength of future craving experiences. By capitalizing on the malleability of memory reconsolidation processes, our novel psychotherapy appears to reduce drug approach cognitions and responses to cocaine conditional cues, so that subsequent craving experiences are better controlled (Kavanagh et al., 2005). Better cognitive control is likely to increase self-efficacy when exposed to high-risk situations (Sklar, Annis, & Turner, 1999) and may lead to reductions in activity in reward regions in the brain (Volkow et al., 2010).

Nevertheless, as we have noted, craving does not always precede cocaine use. Some people with CUD find that cocaine seeking has become highly automatized and if there is immediate drug access, there may be minimal, if any, craving, and cognitive elaboration. Our efforts to help patients become aware of automatic processes may provide some protection to enable a process of reflection and alternate action.

In the context of the wider literature, there is mixed evidence on the role of craving in predicting cocaine use and a number of studies have concluded that craving does not reliably predict cocaine use (Miller & Gold, 1994; Weiss, Griffin, & Hufford, 1995). However, more recent studies favor craving as a predictor of cocaine-seeking (Da Silveira, Doering-Silveira, Niel, & Jorge, 2006; Preston et al., 2009) and relapse.

### Table 4. Causal mediation model, adjusted for covariates.

| Estimates (Poisson model)          | Coefficient | 95% CI            | SE  | p Value |
|-----------------------------------|-------------|-------------------|-----|---------|
| Model (pseudo R²:325)             |             |                   |     |         |
| Sex                               | 0.200       | 0.008 to 0.392    | .099| .041    |
| Baseline cocaine use              | 0.021       | −0.004 to 0.039   | .010| .188    |
| Baseline CEQ-F score              | −0.004      | −0.008 to 0.001   | .002| .993    |
| CEQ-F (mediator)                  | −0.016      | −0.021 to −0.011  | .004| <.0001  |
| Group                             | −0.156      | −0.419 to 0.106   | .134| .242    |

| Summary of effects                | Coefficient | 80% CI            | SE* | p Value |
|-----------------------------------|-------------|-------------------|-----|---------|
| NDE                               | 0.855       | 0.569 to 1.175    | .240| .242    |
| NIE                               | 1.753       | 1.334 to 2.936    | .875| <.0001  |
| TE                                | 1.499       | 1.114 to 1.970    | .356| .012    |

Note: CEQ-F = craving experience questionnaire (frequency version); CI = confidence interval; SE = standard error; NDE = natural direct effect, equivalent to CDE without mediator-outcome interaction; NIE = natural indirect effect; TE = total effect; CDE = controlled direct effect.

*Bootstrapped.
It is important to note that memory reconsolidation interventions are at a relatively early stage of development (Exton-McGuinness & Milton, 2018; Monfils & Holmes, 2018). However, the literature is growing with encouraging findings from psychological laboratory studies with users of nicotine, heroin, alcohol, and cocaine (Germeroth et al., 2017; Hon et al., 2016; Xue et al., 2012) and pharmacological interventions (e.g., propranolol; Lonergan et al., 2016; Saladin et al., 2013; Xue et al., 2017). Taken together, these interventions suggest that memory-reconsolidation techniques can reduce craving and subsequent drug-seeking. To our knowledge, our study is the first to apply memory reconsolidation approaches in the addiction clinic setting. Replication studies by other groups are now warranted.

Study strengths include the experimental design, a registered analysis plan, statistical control over confounding, and a counterfactual framework analysis of causal mediation. We also acknowledge several limitations. Although in line with recommendations for pilot studies, this was a small sample study and the results must be regarded as exploratory and in need of replication. A longer follow-up period up to 12 months is recommended to examine the robustness of MFCT-based cocaine abstinence against time, given the relapsing nature of CUD. Nevertheless, the present findings are encouraging and give impetus for future superiority randomized controlled trials of MFCT alongside general counseling for people with primary CUD and as an adjunctive intervention for patients with concurrent CUD and opiate use disorder (Marsden et al., 2019).

At present, CUD is a significant and hard-to-treat public health problem with limited treatment options and it is crucial to understand the mechanisms underlying potential new treatments. This study positions craving as an important mediator in reducing cocaine use in participants receiving MFCT.

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Notes
1. People with nonabstinent alcohol use disorder were judged at risk of presenting to the Clinical Research Facility with intoxication at a level precluding admission (alcohol breath test screening to a maximum of 30 mg/ml).
2. In the original protocol, we were concerned that a patient with untreated posttraumatic stress disorder might not be able to accept or have a negative reaction to a memory relieving procedure, so this exclusion was on safety grounds.

References
Aguilar de Arcos, F., Verdejo-Garcia, A., Peralta-Ramirez, M. I., Sanchez-Barrera, M., & Perez-Garcia, M. (2005). Experience of emotions in substance abusers exposed to images containing neutral, positive, and negative affective stimuli. Drug and Alcohol Dependence, 78, 159–167. doi:10.1016/j.drugalcdep.2004.10.010.
American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Arlington, VA: American Psychiatric Publishing.
Andrade, J., May, J., & Kavanagh, D. K. (2012). Sensory imagery in craving: From cognitive psychology to new treatments for addiction. Journal of Experimental Psychology, 3, 127–145.
Baker, T. B., Piper, M. E., McCarthy, D. E., Majeskie, M. R., & Fiore, M. C. (2004). Addiction motivation reformulated: An affective processing model of negative reinforcement. Psychological Review, 111, 33–51. doi:10.1037/0033-295x.111.1.33.
Baron, R. M., & Kenny, D. A. (1986). The moderator-mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. Journal of Personality and Social Psychology, 51, 1173–1182.
Brewin, C. R., Gregory, J. D., Lipton, M., & Burgess, N. (2010). Intrusive images in psychological disorders: Characteristics, neural mechanisms, and treatment implications. Psychological Review, 117, 210–232. doi:10.1037/a0018113.
Cheetham, A., Allen, N. B., Yucel, M., & Lubman, D. I. (2010). The role of affective dysregulation in drug addiction. Clinical Psychology Review, 30, 621–634. doi:10.1016/j.cpr.2010.04.005.
Conway, M., Meares, K., & Standart, S. (2004). Images and goals. Memory, 12, 525–531. doi:10.1080/09658210444000151.
Crisis-Christoph, P., Connolly Gibbons, M. B., Barber, J. P., Hu, B., Hearon, B., Worley, M., & Gallop, R. (2007). Predictors of sustained abstinence during psychosocial treatments for cocaine dependence. Psychotherapy Research, 17, 240–252. doi:10.1080/10503300600818210.
Da Silveira, D. X., Doering-Silveira, E., Niel, M., & Jorge, M. R. (2006). Predicting craving among cocaine users. Addictive Behaviors, 31, 2292–2297. doi:10.1016/j.addbeh.2006.02.022.
Dunn, G., Emsley, R., Liu, H., Landau, S., Green, J., White, I., & Pickles, A. (2015). Evaluation and validation of social and psychological markers in randomised trials of complex interventions in mental health: A methodological research programme. Health Technology Assessment, 19, 1–115, v–vi. doi:10.3310/hta19930.
Exton-McGuinness, M. T. J., & Milton, A. L. (2018). Reconsolidation blockade for the treatment of addiction: Challenges, new targets, and opportunities. Learning & Memory, 25, 492–500. doi:10.1101/lm.046771.117.
First, M. B., Williams, J. B. W., Karg, R., & Spitzer, R. L. (2015). Structured clinical interview for DSM-5 disorders—clinician version (SCID-5-IV) [Instrument]. Arlington, VA: American Psychiatric Association.
Fox, H. C., Axelrod, S. R., Paliwal, P., Sleeper, J., & Sinha, R. (2007). Difficulties in emotion regulation and impulse control during cocaine abstinence. Drug and Alcohol Dependence, 89, 298–301. doi:10.1016/j.drugalcdep.2006.12.026.
Germeroth, L. J., Carpenter, M. J., Baker, N. L., Froeliger, B., LaRowe, S. D., & Saladin, M. E. (2017). Effect of a brief memory updating intervention on smoking behavior: A randomized clinical trial. JAMA Psychiatry, 74, 214–223. doi:10.1001/jamapsychiatry.2016.3148.
Gratz, K. L., & Roemer, L. (2004). Multidimensional assessment of emotion regulation and dysregulation: Development, factor structure, and initial validation of the Difficulties in Emotion Regulation Scale. Journal of
Holland, P. W. (1986). Statistics and causal inference. Hayes, A. F. (2014).
Hon, T., Das, R. K., & Kamboj, S. K. (2016). The effects of Home Office. Statistical Bulletin 11/17. (2017). Holmes, E. A., & Mathews, A. (2010). Mental imagery in Grey, N., Young, K., & Holmes, E. (2002). Cognitive\nLonergan, M., Saumier, D., Tremblay, J., Kieffer, B., K o o b , G . F ., Cain e, S . B ., P a r s o n s , L ., M a r k o u , A ., & Kazdin, A. E. (2007). Mediators and mechanisms of change in psychotherapy research. Annual Review of Clinical Psychology, 3, 1–27. doi:10.1146/annurev.clinspsy.3.022806.091432.
Koon, G. F., Caine, S. B., Parsons, L., Markou, A., & Weiss, F. (1997). Opponent process model and psychosocial intervention in treatment-resistant maintenance opioid agonist therapy: A pragmatic, open-label, randomised controlled trial. The Lancet Psychiatry, 6, 391–402. doi:10.1016/S2215-0366(19)30009-5.
May, J., Andrade, J., Kavanagh, D. J., Feeney, G. F., Gullo, M. J., Statham, D. J., ... Connor, J. P. (2014). The craving experience questionnaire: A brief, theory-based measure of consummatory desire and craving. Addiction, 109, 728–735. doi:10.1111/add.12472.
May, J., Andrade, J., Panabokke, N., & Kavanagh, D. (2004). Images of desire: Cognitive models of craving. Memory, 12, 447–461. doi:10.1080/0965821044000061.
Miller, N. S., & Gold, M. S. (1994). Dissociation of “conscious desire” (craving) from and relapse in alcohol
meta-analysis of randomized controlled trials. Journal of Studies on Alcohol and Drugs, 70, 516–527.
Marsden, J., Eastwood, B., Ali, R., Burkinshaw, P., Chohan, G., Copello, A., ... Day, E. (2014). Development of the addiction dimensions for assessment and personalised treatment (ADAPT). Drug and Alcohol Dependence, 139, 121–131. doi:10.1016/j.drugalcdep.2014.03.018.
Marsden, J., Eastwood, B., Jones, H., Bradbury, C., Hickman, M., Knight, J., ... White, M. (2012). Risk adjustment of heroin treatment outcomes for comparative performance assessment in England. Addiction, 107, 2161–2172. doi:10.1111/j.1360-0443.2012.03971.
Marsden, J., Farrell, M., Bradbury, C., Dale-Perera, A., Eastwood, B., Roxburgh, M., & Taylor, S. (2008). Development of the treatment outcomes profile. Addiction, 103, 1450–1460. doi:10.1111/j.1360-0443.2008.02284.x.
Marsden, J., Goetz, C., Meynen, T., Mitcheson, L., Stillwell, G., Eastwood, B., ... Grey, N. (2017). Memory-focused cognitive therapy for cocaine use disorder: Rationale, design and protocol for an external pilot randomised controlled trial. Contemporary Clinical Trials Communications, 8, 264–273. doi:10.1016/j.conctc.2017.10.009.
Marsden, J., Goetz, C., Meynen, T., Mitcheson, L., Stillwell, G., Eastwood, B., ... Grey, N. (2018). Memory-focused cognitive therapy for cocaine use disorder: Theory, procedures and preliminary evidence from an external pilot randomised controlled trial. Ebiomedicine, 29, 177–189. doi:10.1016/j.ebiom.2018.01.039.
Marsden, J., Stillwell, G., James, K., Shearer, J., Byford, S., Hellier, J., ... Mitcheson, L. (2019). Efficacy and cost-effectiveness of an adjunctive personalised psychosocial intervention in treatment-resistant maintenance opioid agonist therapy: A pragmatic, open-label, randomised controlled trial. The Lancet Psychiatry, 6, 391–402. doi:10.1016/S2215-0366(19)30009-5.
Magill, M., & Ray, L. A. (2009). Cognitive-behavioral treatment with adult alcohol and illicit drug users: A

and cocaine dependence. *Annals of Clinical Psychiatry*, 6, 99–106.

Monfils, M. H., & Holmes, E. A. (2018). Memory boundaries: Opening a window inspired by reconsolidation to treat anxiety, trauma-related, and addiction disorders. *The Lancet Psychiatry*, 5, 1032–1042. doi:10.1016/S2215-0366(18)30270-0.

Murphy, R., Cooper, Z., Hollon, S. D., & Fairburn, C. G. (2009). How do psychological treatments work? Investigating mediators of change. *Behaviour Research and Therapy*, 47, 1–5. doi:10.1016/j.brat.2008.10.001.

National Institute for Health and Care Excellence. (2007). *Guideline for drug misuse in over 16s: Psychosocial interventions*. Retrieved from https://www.nice.org.uk/guidance/cg51/resources/drug-misuse-in-over-16s-psychosocial-interventions-pdf-975502451653.

O'Brien, C. P., Childress, A. R., McLellan, A. R., & Ehrman, R. (1992). Classical conditioning in drug-dependent humans. *Annals of the New York Academy of Sciences*, 654, 400–415. doi:10.1111/j.1749-6632.1992.tb25984.x.

Paliwal, P., Hyman, S. M., & Sinha, R. (2008). Craving and use during daily life. *Psychopharmacology (Berl)*, 207, 291–301. doi:10.1007/s00213-009-1655-8.

Public Health England. (2017a). *Estimates of the prevalence of opiate use and/or crack cocaine use (2016-17)*. UK: Public Health England. Retrieved from https://www.gov.uk/government/publications/opiate-and-crack-cocaine-use-prevalence-estimates-for-local-populations#history.

Public Health England. (2017b). Adult substance misuse statistics from the National Drug Treatment Monitoring System (NDTMS) 1 April 2016 to 31 March 2017. Retrieved from https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/658056/Adult-statistics-from-the-national-drug-treatment-monitoring-system-2016-2017.pdf.

Robins, J. M., & Greenland, S. (1992). Identifiability and exchangeability for direct and indirect effects. *Epidemiology*, 3, 143–155.

Robinson, T. E., & Berridge, K. C. (1993). The neural basis of drug craving: An incentive-sensitization theory of addiction. *Brain Research Reviews*, 18, 247–291.

Rohsenow, D. J., Martin, R. A., Eaton, C. A., & Monti, P. M. (2007). Cocaine craving as a predictor of treatment attrition and outcomes after residential treatment for cocaine dependence. *Journal of Studies on Alcohol and Drugs*, 68, 641–648. doi:10.15288/jsad.2007.68.641.

Saladin, M. E., Gray, K. M., McRae-Clark, A. L., Larowe, S. D., Yeatts, S. D., Baker, N. L., . . . Brady, K. T. (2013). A double blind, placebo-controlled study of the effects of post-retrieval propranolol on reconsolidation of memory for craving and cue reactivity in cocaine dependent humans. *Psychopharmacology (Berl)*, 226, 721–737. doi:10.1007/s00213-013-3039-3.

Sinha, R., Garcia, M., Paliwal, P., Kreek, M. J., & Rounsaville, B. J. (2006). Stress-induced cocaine craving and hypothalamic-pituitary-adrenal responses are predictive of cocaine relapse outcomes. *Archives of General Psychiatry*, 63, 324–331. doi:10.1001/archpsyc.63.3.324.

Sklar, S. M., Annis, H. M., & Turner, N. E. (1999). Group comparisons of coping self-efficacy between alcohol and cocaine abusers seeking treatment. *Psychology of Addictive Behaviors*, 13, 123–133. doi:10.1037/0893-164X.13.2.123.

StatCorp. (2017). *Stata statistical software: Release 15*. College Station, TX: StatCorp.

Tiffany, S. T. (1990). A cognitive model of drug urges and drug-use behavior: Role of automatic and nonautomatic processes. *Psychological Review*, 97, 147–168.

Valeri, L., & Vanderweele, T. J. (2013). Mediation analysis allowing for exposure-mediator interactions and causal interpretation: Theoretical assumptions and implementation with SAS and SPSS macros. *Psychological Methods*, 18, 137–150. doi:10.1037/a0031034.

VanderWeele, T. J. (2015). *Explanation in causal inference: Methods for mediation and interaction*. Oxford, UK: Oxford University Press.

Volkow, N. D., Fowler, J. S., Wang, G. J., Telang, F., Logan, J., Jayne, M., . . . Swanson, J. M. (2010). Cognitive control of drug craving inhibits brain reward regions in cocaine abusers. *NeuroImage*, 49, 2536–2543. doi:10.1016/j.neuroimage.2009.10.088.

Weiss, R. D., Griffin, M. L., & Hufford, C. (1995). Craving in hospitalized cocaine abusers as a predictor of outcome. *American Journal of Drug and Alcohol Abuse*, 21, 289–301.

Weiss, R. D., Griffin, M. L., Mazurick, C., Berkman, B., Gastfriend, D. R., Frank, A., . . . Moras, K. (2003). The relationship between cocaine craving, psychosocial
treatment, and subsequent cocaine use. *American Journal of Psychiatry, 160*, 1320–1325. doi:10.1176/appi.ajp.160.7.1320.

West, R. (2006). Towards a comprehensive theory of addiction. *Drugs and Alcohol Today, 6*, 28–32. doi:10.1108/17459265200600011.

Xue, Y.-X., Deng, J.-H., Chen, Y.-Y., Zhang, L.-B., Wu, P., Huang, G.-D., … Lu, L. (2017). Effect of selective inhibition of reactivated nicotine-associated memories with propranolol on nicotine craving. *JAMA Psychiatry, 74*, 224–232. doi:10.1001/jamapsychiatry.2016.3907.

Xue, Y. X., Luo, Y. X., Wu, P., Shi, H. S., Xue, L. F., Chen, C., … Lu, L. (2012). A memory retrieval-extinction procedure to prevent drug craving and relapse. *Science, 336*, 241–245. doi:10.1126/science.1215070.

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