



Memory-focused cognitive therapy for cocaine use disorder: Rationale, design and protocol for an external pilot randomised controlled trial[☆]

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ABSTRACT

Introduction: Cocaine use disorder (CUD) is a debilitating condition characterised by maladaptive cocaine-related memories and impaired cognitive and behavioural control. There are no evidence-supported pharmacotherapies and only weakly effective psychological interventions specific for CUD. Our novel Memory-focused Cognitive Therapy (MFCT) aims to modify cocaine-related memories to reduce craving and drug use.

Methods: This is a single-centre (outpatient), 15-week, two-arm, pilot randomised controlled trial (RCT) to address feasibility, safety, quality and preliminary efficacy. Thirty participants (adults ≥ 18 years; current CUD) will receive ongoing standard care (treatment-as-usual [TAU]) during the study and will be randomised (1:1) to a control or intervention group. The control group will receive 3 \times 90min CUD cognitive case conceptualisation assessments and 2 \times 30min cocaine-related cue-induction procedures (*in vivo* presentation of images and objects). Experimental group participants will receive 3 \times 90min CUD cognitive case conceptualisation assessments; 2 \times 30min cue-induction procedures; and individual MFCT (5 \times 120min; daily for 1 week; with 3 relapse prevention follow-ups over 3-months). All study participants will complete research follow-ups at 1-week, 1-month and 3-months. The experimental and control groups will be compared on the mean score on the frequency version of the Craving Experience Questionnaire at 1-month (primary outcome measure). Secondary outcomes include: percentage of days abstinent and longest period of continuous abstinence from cocaine (past 28-days at 1-month follow-up); urine drug screen and CUD diagnosis (DSM-5).

Conclusions: We will conduct a full external pilot RCT of a novel, MFCT for CUD. The findings will inform the case, and necessary modifications, for a substantive study.

1. Introduction

Cocaine is a powerful, addictive stimulant associated with a substantial global burden of disease. Approximately 1 person in 16–20 becomes addicted within the first year of initiation [1]. In 2010, 6.9 million people were addicted worldwide, with 15.9 cocaine-related disability adjusted life years per 100,000 [2]. Cocaine use disorder is the formal psychiatric diagnosis (CUD; Diagnostic and Statistical Manual [DSM-5]) [3]; and the conceptually identical ‘cocaine dependence’ diagnosis in the International Classification of Diseases (ICD-10) [4].

There has been a sustained effort to develop more effective

treatments for CUD. To date, the results of medications studies have been disappointing. Unlike opioids, alcohol and nicotine, no effective medication for CUD has been identified after systematic review of efficacy trials. Among the psychosocial interventions for CUD, Cognitive Behavioural Treatment (CBT) is among the most extensively studied. Meta-analysis of 53 controlled trials for CUD and other substance use disorders, estimated that CBT achieves only a small overall treatment effect (standardised mean difference effect size [ES] over comparison conditions of 0.15; 95% confidence interval [CI] 0.07 to 0.24) [5].

Trials of novel pharmacotherapies are continuing (mainly in the USA), but our current focus is on an integrated cognitive behavioural approach as an adjunct to standard pharmacological and psychosocial

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care. In a recently completed trial among people with opioid use disorder (OUD), we used a cognitive case conceptualisation and treatment formulation-based approach [6] to identify motivational, cognitive and behavioural change methods matched to the patient's need, experience, preference and social resources [7]. In most cases, we have found our patients to very readily engage in this collaborative process and be motivated and explore drug conditioned cues and discuss their responses.

A specific impetus for the present study lies with our experience of providing trauma-focused cognitive therapy to patients with substance use disorder and post-traumatic stress disorder (PTSD [8]). PTSD is a common comorbidity among the substance use disorder population in the NHS with a prevalence range of 26–52% [9]. At first glance, fear and drug craving symptoms and cognitions appear categorically different - but we see several similarities. Both are maintained by the activation of cue-associated memories, with sensory matched triggers eliciting mental images and motivating maladaptive (disorder maintaining) coping strategies. Change methods used in cognitive therapy for PTSD include imaginal and *in vivo* exposure to help the patient relive and elaborate a trauma memory; discriminate memory triggers; increase interoceptive awareness; cognitively restructure maladaptive appraisals and sensory images; and build adaptive emotion regulation coping skills.

This therapy is supported by studies showing that consolidated memories can be destabilised and modified during a 'reliving' procedure. This involves the patient describing the trauma in the first person present tense as if it were happening now and reporting visual, auditory, physical and emotional information. Meta-analysis of cognitive therapy trials for PTSD show that treatment increases the likelihood of PTSD remission when compared to a wait-list control group (14 studies; $n = 716$; relative risk [RR] 0.47; 95% CI 0.37 to 0.59) or alternative interventions therapies (5 studies; $n = 286$; RR 0.71; 95% CI 0.56 to 0.89) [10]. The combination of imaginal exposure, *in vivo* exposure and cognitive restructuring of maladaptive appraisals has also been shown to be more effective in reducing PTSD symptoms than prolonged exposure alone [11]. Trauma-focused cognitive therapy is now the first-line treatment for PTSD [12].

To our knowledge, there have been no trials which use memory reconsolidation techniques to help people with CUD elicit, elaborate and re-consolidate cocaine-related memories to achieve cognitive and behavioural control. We have developed a novel memory-focused cognitive therapy (MFCT) for this purpose. It has been designed to be an adjunct to TAU but does not (at present) target people with comorbid CUD and PTSD.

MFCT has five sequential components:

- (1) a cognitive case conceptualisation of CUD maintaining processes to inform the treatment plan;
- (2) education about cocaine's cognitive and physical effects;
- (3) cocaine-related cue-induction to elicit images and affective responses;
- (4) memory reconsolidation procedures; and
- (5) standard CBT techniques (e.g. behavioural experiments of cocaine-related expectancies; skills for adaptive emotion regulation).

In a recent trial with abstinent heroin users, more people assigned to an *in vivo* drug-related exposure protocol dropped out and relapsed compared to placebo psychotherapy [13], so the safety of our cue-induction procedure (in terms of craving mediated cocaine use) should be established.

In this protocol paper, we describe the rationale, design, methods, safety procedures, statistical analysis plan, strengths and limitations for an external pilot randomised controlled trial (RCT) of MFCT. An 'external' RCT is a miniature trial, with full protocol implementation, outcome measures collected, and data analysed, reported and set aside [14].

2. Methods

2.1. Study design

This is a single-centre (UK National Health Service [NHS] outpatient addictions clinic), 15-week, two-arm, external pilot RCT of MFCT for CUD.

There is no consensus for a standard comparison group analogous to placebo treatment in pharmacotherapy research. Psychotherapy trials sometimes use a wait-list comparator or active reference psychotherapy (presented as a credible alternative). However, in the UK substantive, superiority treatment trials funded by the National Institutes for Health Research (NIHR) are designed to compare a new healthcare technology to the current standard NHS intervention [15]. Therefore, in the present study all participants will receive TAU with adjunctive study procedures. In order to check on safety of the cue-induction procedure, the control group will additionally receive a three-session cognitive case conceptualisation assessment and two cocaine-related cue-induction procedures. The intervention group will receive TAU, plus the cognitive case conceptualisation assessment, the two cocaine-related cue-induction procedures and an individual programme of MFCT and relapse prevention.

All participants will complete clinic-based, psychology assistant administered, one-to-one interview follow-ups at 1-week, 1-month and 3-months timed from the second cue-induction procedure. The 3-month follow-up was added to the study after we secured additional research funding via a protocol amendment shortly after commencement of fieldwork. After completion of the final 3-month follow-up, control group participants will be able to request to receive MFCT as received by the intervention group if time and resources allow.

Blinding of research follow-ups is not feasible for the present study. We considered the option to have our Senior Psychology therapists nested or crossed across the two arms of the trial; but given that the present design has a comparison group receiving TAU, assessment and cue-induction procedures only, we judged that a *crossed* approach is optimal (i.e. therapists perform assessment and cue-induction with all participants).

The trial will be conducted following the ethical principles of the World Medical Association's Declaration of Helsinki for research involving human subjects and is registered with the ISRCTN (number: 16462783). The study has been designed to conform to UK National Institute for Health Research guidelines [16], the Template for Intervention Description and Replication (TIDierR) for reporting behaviour change interventions [17], guidance on developing complex behavioural interventions [18], the CONSORT extension for pilot randomised controlled trials [19].

All members of the study team have been trained in Good Clinical Practice by King's Health Partners Clinical Trials Office (<https://www.khpcto.co.uk>). Participant written consent forms, study protocol and clinical research forms have been reviewed and approved by the UK National Research Ethics Service (London-Fulham Research Ethics Committee; reference: REC 153/LO/0656). The participant information sheet will describe the study rationale, design and procedures.

2.2. Study setting

This is an outpatient study conducted at an NHS and Academic Health Sciences Centre in London, United Kingdom (UK). Participant screening, enrolment, assessment and follow-ups will be conducted at a specialist community addiction treatment clinic in the London Borough of Lambeth (operated by South London and Maudsley NHS Mental Health Foundation Trust).

At the clinic, treatment is delivered by a multi-disciplinary team with psychiatry, psychiatric nursing, psychology and social work specialties. At admission patients are assigned to a member of the team (known as a *keyworker*) for case co-ordination. The treatment services

provided at the clinic are summarised in Section 2.5 below.

At this stage in the development and evaluation of our therapeutic procedures, all cue-induction procedures and MFCT sessions will be held at the National Institute for Health Research and Wellcome Trust, King's Clinical Research Facility (CRF), King's College Hospital. This is a specialist outpatient facility for medical research.

2.3. Study aims

The purpose of the study is to undertake a full external pilot of MFCT. Our working hypothesis is that relative to controls, participants who receive MFCT will have less intense and intrusive cocaine-related craving experiences and this will help them reduce their cocaine use or abstain. At this preliminary stage, there are no cost-effectiveness questions. However, if we proceed to a definitive study, we would collaborate with health economic researchers to determine cost-effectiveness of MFCT.

There are 5 overall research questions, as follows:

- (1) Is the level of loss to follow-up at the primary endpoint minimally acceptable?
- (2) Is there sufficient delivery fidelity for MFCT?
- (3) Are the interventions safe?
- (4) Is MFCT associated with reduced craving experience that is at least as large as the overall effect from meta-analysis?
- (5) Is MFCT associated with reduced cocaine use that is at least as large as the overall effect from meta-analysis?

2.4. Theoretical framework and format for the intervention

People presenting for treatment typically report maladaptive cocaine-related memories and a strong motivation to use the drug. A repeating 'binge' cycle is often reported, with intense cocaine use over several days followed by little or no use, and then further intense use. It has long been recognised that cocaine's reinforcing effects are mediated by the release and reuptake prevention of dopamine and noradrenaline; while the past 15 years has seen major advances in understanding the neuro-behavioural systems involved [20,21]. Behaviourally, the essence of CUD is a habit process marked by a transition from choice to impairment of control, and underpinned by conditioned stimuli (drug-neutral and drug-related) which are strongly motivating [22]. Contemporary learning models of cocaine addiction include conditioning, reinforcement, attention, affective, and motivational components. Although drug seeking does not always follow a strong, intrusive urge or desire, *craving* is positioned in contemporary accounts as an important mediator of drug use [23,24].

People with CUD report craving experiences that vary widely in specific subjective content, intensity and duration, but usually persist long into abstinence. Intrusive craving may occur unexpectedly, but is strongly expected as an intrusive thought in contexts which have been paired repeatedly with cocaine seeking and/or consumption. Exposure to drug-neutral and drug-specific conditioned stimuli (including positive and negative mood, places, people, drug paraphernalia, objects, smells and sounds [25]) is thought to activate an automatic implicit process (initially pre-conscious) which is often reported to takes the form of a vivid sensory image. Typically, after a basic emotional response, an elaborated cognitive process follows in which well-consolidated memories of past cocaine use are recalled and linked to complex affect and various activated drug-related beliefs and expectancies, such as future pleasure or relief of negative mood [26,27].

Craving reduction has long been a therapeutic target in the clinical laboratory. For example, in an early study, O'Brien and colleagues found that people with CUD who were exposed to drug-related images and paraphernalia quite quickly reported significant decreases in craving and autonomic activity [28]. Various forms of cue-exposure therapy (CET) have been trialled involving repeated non-reinforced

presentation of stimuli to achieve extinction of craving (typically over 10 sessions). However, there have been positive and negative results reported: for example, in one study there was no increase in cocaine use after repeated exposure [29]; in another trial, more people assigned to CET dropped out and relapsed to heroin use [14]). Meta-analysis has concluded that CET is not superior to comparison conditions [30,31].

As an alternative to extinction, various cognitive training procedures have been trialled with the goal of strengthening self-control through targeting enhanced working memory [32] and modifying cognitive bias [33–35]. Unfortunately, working memory training has also failed meta-analysis [36]; and to date, cognitive bias modifications have achieved mixed results. A recent critique noted that experimental targets are likely to be strongly influenced by fluctuating contexts in the environment [37]; a limitation also identified for CET.

In this study, we ask whether MFCT helps to modify cocaine-related memories, and improve patients' cognitive and behavioural control. There are convergent lines of comparative and clinical research that provide support for this hypothesis. For example, Everitt and colleagues have shown that consolidated heroin and cocaine memory response in rats can be reactivated and then disrupted to abolish a drug conditioned response [38,39]. Xue's group used a memory reconsolidation procedure with video drug cues to reduce subsequent heroin craving [40]. Recently, Hon, Das & Kamboj used a destabilising procedure among at-risk drinkers in support of the hypothesis that individual alcohol-related memories can be modified [41].

The cognitive conceptualisation for our intervention is grounded in Beck's generic cognitive and information processing model and its application to cocaine [42,43]. We have been influenced by Tiffany's work on automatic and non-automatic craving [44] and West's conceptualisation of dynamic exteroceptive and interoceptive craving processes [45].

Through literature review and discussion, we adapted change methods from cognitive therapy for PTSD to CUD (protocols from the UK [46,47] and USA [48,49]). Research using cue-exposure/reactivity procedures has also influenced our thinking; but rather than aim for extinction, we intend to compile a set of multi-sensory triggers, specific to the individual, and use this set of cues to help induce and elaborate cocaine-related cognitions (and with results used to inform MFCT and patient response).

During planning, we considered a standard once weekly format or a more intensive option for the therapy sessions. We were mindful that many of our patients with CUD exhibit a repeating pattern of response to TAU: stopping or substantially reducing cocaine use in the first few weeks of treatment; but then cycling through periods of relapse, unplanned discharge and re-admission.

After informal discussion with members of the target clinical population, we judged that a relatively intensive format could be acceptable and effective. A trial showing that trauma-focused cognitive therapy for PTSD delivered in 1-week was as effective as therapy delivered in 3-months was also influential in our decision to format the intensive phase of MFCT for CUD across a single week [50].

2.5. Study population and treatment-as-usual

The study population is adults (≥ 18 years) with current primary CUD, or current comorbid CUD and opioid use disorder (OUD) who are enrolled in community addiction treatment. Targeting the population with co-occurring CUD and OUD is important because this group accounts for a major proportion of clinical admissions in England.

All screened patients will be self- or professional-referred from primary care or other specialist services and then nominated by their keyworker as potentially eligible for the study. There will be no media recruitment. Study participants will be receiving either:

- (1) Psychosocial TAU (primary CUD): fortnightly keyworker appointments of ~30–60 min for harm reduction advice, general

Table 1
Participant inclusion and exclusion criteria.

Inclusion criteria
For a participant to be enrolled into the study they must fulfil all the following inclusion criteria:
(1) Aged 18 ≥ years (no upper limit) with current diagnosis of CUD;
(2) Current use of cocaine (verified by clinical record) in past 28 days;
(3) Enrolled in treatment at specialist NHS community addictions clinic for at least 14 days;
(4) Voluntarily seeking treatment and able to attend the centre and CRF as required;
(5) Stable accommodation;
(6) Sufficient English fluency to receive psychosocial therapy;
(7) Possession of a personal phone and ability to nominate at least one locator individual to assist with arranging research appointments.
Exclusion criteria
Otherwise eligible individuals will be excluded from the study for any of the following:
(1) Current non-abstinent, alcohol use disorder (from clinical record);
(2) Clinically significant physical health conditions that may compromise safety, or compliance with the study protocol;
(3) Suicide planning (past 30 days) or suicide attempt (past six months);
(4) Co-occurring CUD and PTSD
(5) Clinically significant or uncontrolled severe mental health problems (including but not limited to psychosis, bipolar disorder, schizoaffective disorder) and/or history or evidence of organic brain disease or dementia that may compromise safety or compliance with the protocol;
(6) Current legal proceedings which are likely to result in incarceration;
(7) Participation in a substance use disorder treatment study in past three months.

counselling, support to access local services; or

- (2) Oral opioid agonist pharmacotherapy TAU for opioid use disorder (comorbid CUD), using methadone, buprenorphine, or buprenorphine-naloxone and involving fortnightly keyworker appointments of ~30–60 min (as above) and regular medical review.

We will record participant demographic and clinical characteristics and attendance for keyworker appointments via the clinic's electronic patient information system. The participant inclusion and exclusion criteria for the study are summarised in [Table 1](#).

2.6. Cognitive conceptualisation of the maintenance of CUD

At a screening and informed consent visit (baseline; ~60 min to complete), current CUD, alcohol consumption and related problems, social status, opioid agonist medication and self-reported days of cocaine and heroin use will be recorded. Participants will then attend a 3 × 90-minute CUD cognitive case conceptualisation assessment with a Senior Psychologist and Psychology Assistant in a clinical interview room at the clinic. With the participant's consent these sessions will be audio recorded. The objective will be to develop collaboratively a working hypothesis of how CUD is being maintained. A micro-formulation will be based on recent typical (and unusual) episodes of cocaine use and will include contexts, triggers, physical sensations, elaborated cognition (attention, memories, beliefs, appraisals [emotional 'hotspots']), motivation, coping strategies, actions, problematic affective and behavioural responses, post-cocaine use evaluations and problems following a structure summarised in [Table 2](#).

2.7. Cocaine-related cue-induction procedure

Materials for cocaine-related cue-induction procedure will be compiled by the participant between assessment sessions and from the session audio record. Reflecting the individualised approach to this trial, we will assemble a set of materials selected by the patient to have potential to induce cocaine-related cognitions (see [Table 3](#)).

The procedure will be overseen by a Senior Psychologist and Psychology Assistant at the CRF. The participant will be first asked to take an alcohol breath test on arrival (BACtrack Mobile Pro; [https://](https://www.bactrack.com)

www.bactrack.com). A maximum level will be set at 30 mg of alcohol per 100 mL of blood (a minimum threshold for reliable detection of cognitive function impairment [51]). Participants providing a result above this limit will be asked to wait at a rest area at the CRF for a further test (~1 h later), or the session will be re-scheduled.

After alcohol screening, the participant will be seated in a quiet private room (opaque window) facing a table on which a member of the study team will place the opaque card box containing the above items and with the lid closed. The participant will be given a general summary of the contents and audio track (previously agreed music, TV, ambient sounds, and brief 'clips' of their voice) and then asked to sit quietly during a 2-minute baseline with both feet on the ground (initiated by a tone).

Following this baseline, a series of 7 single tones (each 1-minute apart) will instruct the participant to remain seated and open the box and take out the content of each layer (i.e. looking at each local environment photographs for 1 min, followed by reading the text for 1 min, followed by looking at the photographs of internal locations and objects, followed by holding each object and allowing thoughts and feelings to flow). The sixth tone will instruct the participant to replace all items into the box for 1-minute and then close the lid. The final tone will mark the onset of a 2-minute rest period before completion of the procedure and subsequent craving safety checks. There will be some arm movement during the procedure relating to opening the box and retrieving objects.

2.8. Memory-focused cognitive therapy

Each MFCT session will be facilitated by a Senior Psychologist and Psychology Assistant. A structured programme of 5 sessions (in 1-week) will be book-ended by the two cue-induction procedures. The aim will be to review and utilise the participant's experience of the cue-induction procedure during the therapy process, identifying specific sensory images and cognitive/affective elaborations.

Therapy will be structured, with the patient progressing through review and updating of the CUD maintenance hypothesis, reliving and elaboration of recent target cocaine episode(s), cognitive restructuring (outside reliving), reliving and consolidated memories, and restructuring sensory images, negative appraisals and complex emotional responses related to consolidated cocaine-related memories (see [Table 4](#) for summary of therapy content and progression) as well as our use of general CBT techniques.

2.9. Research assessments

The following measures will be recorded prior to randomisation, during the intervention and at follow-up (as shown in parentheses; see [Table 5](#) for summary):

2.9.1. Structured clinical interview for DSM-5 disorders – clinician version (SCID-CV [52]; completed for at baseline and 3-month follow-up)

The SCID-CV contains a checklist of 11 symptoms (presence or absence) to diagnose the severity of current CUD (mild: 2–3 symptoms; moderate: 4–5; severe: ≥6). The American Psychiatric Association's definition for early CUD remission will be applied at 3-month follow-up (i.e. without substance use disorder criteria [except] craving, using the "on maintenance therapy" specifier as appropriate [opioid agonist treatment in this context]).

2.9.2. Addiction Dimensions for Assessment and Personalised Treatment (ADAPT [53]; baseline, 3-month follow up)

The ADAPT is a 14-item instrument used for drug addiction treatment planning and outcome evaluation with three-subcales: cocaine addiction severity, coexisting health and social problems, and recovery strengths.

Table 2
CUD cognitive case conceptualisation, focusing on recent cocaine use episodes.

Cognitive process	Response
Implicit-autonomous	<ul style="list-style-type: none"> ● <i>Associative memory representations</i>: places/events, people, objects, sounds, sensations, smells; ● <i>'Fast' thoughts</i>: drug-related low-level cues: sensory images, focus of attention;
Explicit-reflective	<ul style="list-style-type: none"> ● <i>Autonomic (interoceptive) and basic emotion</i>: breathing, heart rate, sweating, surprise, gut sensations, fear, anger. ● <i>Episodic/autobiographical/declarative memory</i>: recall of events, knowledge/appraisal of self and facts; ● <i>Controlled attention/working memory</i>: elaboration, Interpretation, conditional/instrumental beliefs, rules; ● <i>Elaborated cognition and autonomic response</i>: craving, ambivalence, physical sensations, complex emotion.
Motivational-behavioural	<ul style="list-style-type: none"> ● <i>Plans and intentions</i>: automatic (non-conflictual), deliberative (under conflict), cocaine expectancies; ● <i>Desistence or drug-approach</i>: coping strategies, drug seeking; ● <i>Cocaine behaviours</i>: preparation, consumption, actions, motor stereotypy, unwanted behavioural, complex affect (e.g. suspiciousness), post-cocaine use evaluations.

Table 3
Materials for cocaine-related cue-induction procedure.

<ul style="list-style-type: none"> ● A set of 10 × 15 cm printed colour photographs (about 4–6) taken by the participant using a provided digital camera of external locations s/he judges are related to cocaine in their local area (e.g. streets, pubs, meeting places, ATMs, places used for drug taking) [For privacy, the participant will be instructed to not photograph any person]; ● A short, specific (time/place) verbatim description from the audio-record in which the participant describes a specific recent situation, and their report of mental images, verbal thoughts, affect, physical sensations, expectancies and actions to the point of using cocaine (~200 words; printed on A5 card); ● A set of 10 × 15 cm colour photographs (about 4–6) taken by the participant of internal places and objects related to cocaine in their home (e.g. rooms, tables, chairs, drug cocaine wraps, pipes and other paraphernalia); ● A set of cocaine-related objects (about 2–6 items, according to cocaine form and route of administration (e.g. used drug wraps [bags, 'cling' film], bank notes, pipes, lighters, needles/syringes, injection equipment); ● An audio-track to be played during the cue-induction procedure which will include sounds the participant recalls are present during a recent cocaine use episode (e.g. TV show, track playing on radio, sounds from the street, and 1–3 brief (~10 s) excerpts from the assessment sessions in which the participant describes craving experiences.

These materials will be placed in an opaque card box (30 × 23 × 8 cm) using a sheet of A4 card to separate the materials in the container in the above order (i.e. external images at the top and objects at the bottom).

2.9.3. Treatment Outcomes Profile (TOP [54]; completed for cocaine (both forms) and heroin at baseline; 1-month and 3-month follow-up)

The TOP is the standard national instrument for monitoring the outcomes of public substance use disorder treatment services in England. It uses a structured, calendar-prompt, 'timeline follow-back' procedure [55] to maximise accuracy of drug use reporting (past 28-day

Table 4
Change methods used in MFCT for CUD.

Intervention	Method/purpose
Socialising/psychoeducation	<ul style="list-style-type: none"> ● Learning and memory processes in addiction; maintaining factors: misinterpretation of cognitions, avoidance, thought suppression and coping strategies; ● 'Reclaiming life': activities previously valued; self-growth;
Reliving (imaginal and <i>in vivo</i> exposure)	<ul style="list-style-type: none"> ● Rationale for cue-induction, imaginal and <i>in vivo</i> cue-induction, reliving and imagery re-scripting. ● Identifying and reconstructing sequence of target episodes, video/movie metaphor; first person tense; ● Timelines, start/end and chunking memory (scenes), craving and emotion 'hotspots' (rating craving strength); ● Reviewing reliving (listening to audio recording at home).
Cognitive restructuring	<ul style="list-style-type: none"> ● Discriminating drug cue-conditioned triggers (now versus then for each trigger); ● Activating pro-drug target beliefs (evaluating evidence for and against; alternative perspective for recovery); ● Restructured meanings.
Reliving, updating, re-scripting	<ul style="list-style-type: none"> ● Activating consolidated drug-related memory; updating ('what I know now'; evidence for appraisals; alternative perspective/belief); ● Ratings of craving belief strength before and after;
Behavioural experiments, relapse prevention	<ul style="list-style-type: none"> ● Restructuring sensory images (running image forward); new perspectives; manipulate image/re-script; grounding. ● Life re-claiming activities and evaluation; ● Coping with high risk emotions and situations (e.g. boredom, anger, people/drug dealers/context, decisions, abstinence violation effect); ● Location visits (e.g. ATM machines; street corners) and testing assumptions; ● Blueprint, scheduling time and future goals.

recall).

2.9.4. Craving Experience Questionnaire (CEQ-F [frequency] and CEQ-S [strength] [56]; CEQ-F completed for cocaine at baseline, 1-month and 3-month follow-up (recall: past 2 weeks; past 7 days for 1-week follow-up)

CEQ-S completed after cue-induction and for previous 24 h during 5-day cognitive therapy. The 11-item version of the CEQ captures intensity, imagery, and intrusiveness aspects of craving. Following discussion with the instrument's developer, the structure and item content was preserved, entering 'cocaine' into the wording for each item.

2.9.5. Difficulties in Emotion Regulation Scale (DERS [57]; baseline, 1-month follow-up)

The DERS is a 36 item self-report scale which records emotional dysregulation in six subscales: non-acceptance, goals, impulse, aware, strategies and clarity. We have been struck by our patients' cocaine relapse vulnerability relating to stress and basic emotions (e.g. anger) and the DERS is included as an exploratory change measure.

2.9.6. Urine drug screen (UDS; detection sensitivity: 300 ng/ml; 1-week, 1-month and 3-month follow-up)

A tamper-proof, instant result, immunoassay device (E-Z Split Key Cup; www.concateno.com) will screen for recent use of cocaine (primary metabolite: benzoylcegonine). The device uses a control line and a temperature sensor (required range: 92°–96 °F) to indicate that a valid test has been done. For most regular cocaine users, benzoylcegonine can be detected for approximately seven days after drug use [58].

Table 5
Study timeline and measures.

Activity/measure	Baseline [2 weeks]	R														
		Study week (from randomisation)														
		1	2	3	4	5	6	7	8	9	10	11	12	13		
Screening/enrolment	X															
Assessment	X															
Cocaine cue-induction		X														
MFCT		X														
DSM-5	X															X
ADAPT	X															X
CEQ-F	X		X					X								
CEQ-S		X														
TOP (PDA)	X							X								X
TOP (LCA)	X							X								
UDS			X					X								X
DERS	X															X
HR		X														
(HRV) LF		X														
(HRV) HF		X														
(HRV) LF/HF		X														
(HRV) rMSSD		X														
EDA		X														
Adverse events form		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Participant payments ^a	X	X	X				X									X

Note.
 R, randomisation.
 MFCT, memory-focused cognitive therapy.
 ADAPT, Addiction Dimensions for Assessment and Personalised Treatment.
 CEQ-F, Craving Experiences Questionnaire (frequency version).
 CEQ-S, Craving Experiences Questionnaire (strength version).
 TOP, Treatment Outcomes Profile (TOP).
 PDA, percentage days abstinent (cocaine).
 LPA, longest period of continuous abstinence (days).
 UDS, urine drug screen.
 DERS, Difficulties in Emotion Regulation Scale.
 HR, heart rate.
 HRV (heart rate variability).
 LF, low frequency power.
 HF, high frequency power.
 LF/HF, ratio of low frequency to high frequency power.
 rMSSD, Root Mean Square of the Successive Differences.
 EDA, electrodermal activity.
^a Participant payments (attendance time offset and using retail store vouchers) according to local recommendations for patient and public involvement [70]: 1-hour assessment session (20 GBP); each attendance at CRF (including 1 h return travel time [50 GBP]; each follow-up (20 GBP).

2.9.7. Heart rate variability (HRV; cue-induction sessions; memory reliving during therapy)

For autonomic response, data acquisition will be via a photoplethysmography sensor (MIO LINK wristband; www.mioglobal.com) placed on the participant's non-dominant arm. Data capture will be via low-energy connection (Bluetooth 4.0) to a data recorder (Heart Rate Variability Logger; www.marcoaltini.com) and exporting raw inter-beat interval data for analysis. Volume pulse (heart rate [HR]) and beat-to-beat intervals will be recorded to compute the following frequency-domain and time-domain HRV parameters: low frequency power (LF; 0.04–0.15 Hz), high frequency power (HF; 0.15–0.40 Hz), the ratio of low frequency to high frequency power (LF/HF), and the Root Mean Square of the Successive Differences (rMSSD; the square root of the mean of the squares of successive differences between adjacent beat-to-beat intervals). 20% in-device error correction will be used to remove motion and ectopic beat artefacts. We are aware that HRV data is ideally captured via chest strap devices; but these are inconvenient in this application. There will be some arm movement during the cue-induction procedures and for the most part the participant will sit quietly during the memory reliving sessions, although some participants may move their arm/body while restructuring images.

2.9.8. Electrodermal activity (EDA; cue-induction sessions; memory reliving)

EDA data acquisition will be via two silver chloride electrodes (measuring electrical conductance in microSiemens with sampling at 256 Hz) attached by Velcro to the third and fourth distal phalanges on the participant's non-dominant hand to a digital sampling unit (Vilistis-4; www.vilistus.com) and connected to a laptop computer for processing. EDA data will be annotated with a timestamp, normalized and consolidated to 1 sample per second.

2.10. Participant randomisation and procedure

Participant randomisation will be initiated after completion of the 3-session CUD cognitive case conceptualisation assessment. The participant will be informed of their trial arm allocation before the close of this session so they can organise their time for the following week.

The randomisation procedure (with random varying blocks) will be independently managed by the King's College London Clinical Trials Unit (King's CTU; www.ctu.co.uk) using a web-accessed computer programme. Participants will be allocated to one of the two trial arms with a ratio of 1 and with no stratification factors. The procedure will be initiated by a member of the trial research team using a unique participant identification number and date of birth.

Following randomisation, control arm participants will attend the outpatient clinical research facility for 2 days (targeted for Monday and Friday) to receive the following:

- 2 x 9-minute cocaine cue-induction procedures (30 min for each procedure including instructions plus 30 min rest) scheduled for day 1 and day 5;
- At completion of each induction there will be a 30-minute 'talk down' procedure to check on craving level, with a general discussion, and a light meal before leaving.

Following randomisation, experimental arm participants will attend the outpatient clinical research facility for 5 consecutive days to receive the following:

- 2 x 9-minute cocaine-related cue-induction procedure (30 min for each procedure including instructions) scheduled for day 1 and day 5;
- 5 x 120-minute individual sessions of memory-focussed cognitive therapy. Sessions will be scheduled for days 1–5. We will encourage and facilitate participants to listen to session audio recordings and homework assignments overnight;
- At completion of each cue-induction procedure and therapy session a 30-minute 'talk down' procedure to check on craving level, with general discussion, attention shift exercise (as needed), and a light meal before leaving the CRF.

2.11. Outcome measures

2.11.1. Primary outcome

The study was funded by the UK National Institute for Health Research (NIHR) Biomedical Research Centre at SLAM, as part of change mechanism research. Given the putative role of cognitive control and reduced craving for this MFCT intervention, we selected the total score on the CEQ-F at 1-month follow-up as the primary outcome measure.

2.11.2. Secondary and exploratory outcomes

The secondary outcomes are:

- percentage of self-reported cocaine days abstinent [PDA] during the prior 28 days (1-month follow-up);
- longest period (days) of continuous cocaine abstinence [LPA] from cocaine in the prior 28 days (1-month follow-up);
- UDS (1-week, 1-month and 3-month follow-up);
- DSM-5 and ADAPT for CUD (3-month follow-up);

The exploratory outcomes are:

- heroin PDA and LPA (1-month and 3-month follow-up);
- DERS (1-month follow-up);
- HRV parameters (LF, HF, LF/HF, rMSSD; CRF week);
- EDA (CRF week).

2.12. Sample size calculation

We need enough participants to make a reasonable assessment of our feasibility and pilot questions and to estimate parameters to inform a future substantive study. There is no definitive method for judging the required sample size for pilot RCTs; however, there are several minimum 'rule of thumb' suggestions in the literature. With the expected pooled standardised effect size for adjunctive CBT from meta-analysis in the small-medium range, we will follow Browne's recommendation to randomise 30 participants [59]. We emphasise that a sample of 30 participants is not sufficient to infer efficacy of the intervention, and our results for group differences on the outcome

measures offer only preliminary evidence for efficacy and need to be interpreted with caution.

2.13. Analytical methods

We will report on the participant recruitment rate and reasons for drop-out before randomisation. In addition to demographic description of the sample, we will record time in treatment before study enrolment, number of keyworker TAU sessions attended and TAU treatment status.

This plan for the primary and secondary analyses is registered at the Centre for Open Science (<https://www.osf.io/3kfzj/>). Data analysis will be done using SPSS, Stata and KUBIOS software (the latter for the HRV analysis [60]) after completion of all follow-up and data management tasks, following the intention-to-treat principle.

Given the small sample size, if the deviation from normality is substantial, then ES may be computed following an appropriate transformation of the target variable (e.g. natural log). We will conduct a preliminary, conventional analysis of outcome (alpha set at 0.05 for the primary outcome; 0.10 for the secondary outcomes and 0.20 for the exploratory outcomes) with hypothesis testing inferred by whether the respective 95%, 90% and 80% confidence intervals include the null.

2.13.1. Analysis of the quantitative research questions and hypotheses

1. Is there no more than minimally acceptable loss to follow-up?

H^1 . Study attrition (loss to follow-up at 1-month) will not exceed 20% in each arm. This is a standard target for treatment studies in the addictions field.

2. Is there sufficient delivery fidelity for MFCT?

H^2 . Therapist practice will meet clinical standards, as evidenced by a random 5% sample of audio recordings independent rated and reaching at least a score of 3 on each item of the assessment and therapy versions of the Cognitive Therapy Scale-Revised [CTS-R; 61]).

3. Are the interventions safe?

H^3 . No more than 40% of participants in each arm of the trial will report an increase in craving between the first and second cocaine cue-induction procedure greater than the Minimally Detectable Change (MDC) for the strength version of the Craving Experiences Questionnaire (CEQ-S; recall period: past 5min). We set the 40% threshold from the relapse rate among participants in a recent study who received cue-exposure [19].

4. Is our memory-focused cognitive therapy associated with reduced craving that is at least as large as the ES from meta-analysis?

H^4 . The standardised effect size for the primary outcome associated with the experimental group will be not less than 0.31. This is the estimate for the effectiveness of CBT with psychosocial intervention [13] which is equivalent to our design in which participants receive TAU plus cognitive therapy.

5. Is our therapy associated with reduced cocaine use that is at least as large as the standardised ES from meta-analysis?

H^5 . The standardised effect size for secondary cocaine use outcomes associated with the experimental arm will be not less than 0.15. This is the ES estimate for the effectiveness of CBT on reductions in cocaine and opioid use from meta-analysis [13].

2.13.2. Response measures

For the main analyses, we will calculate:

- Mean difference in CEQ-F score at 1-month (primary outcome) with pooled SD for bias corrected ES (Hedge's g [62]);
- Bayes Factor [63] using the 0.31 ES from meta-analysis as the prior expectation of effectiveness, with a half-normal distribution for calculation, and with a criterion of ≥ 3.0 as relative evidence for the alternate hypothesis and < 0.30 as evidence supporting the null;
- To identify potential randomisation stratification factors for a definitive study - and subject to preliminary evidence of efficacy - we will determine the mean difference for the CEQ-F at 1-month follow-up by total months of regular cocaine use at enrolment; route of illicit drug administration (oral/smoke versus injection); and TAU (opioid medication, psychosocial only), and run an exploratory, appropriately adjusted regression model with a post hoc assessment of unmeasured confounding [64];
- The mean difference between trial arms on change in HRV and EDA parameters between first and second cue-induction and Hedge's g ES;
- The MDC for the CEQ-S using the instrument's 0.83 reliability coefficient for calculation of the mean standard error [65];
- The proportion of the experimental and control group that have increased post cocaine cue-induction above the MDC for the CEQ-S;
- Cohen's U_3 [66] will be calculated as a descriptive indicator of MFCT success. This parameter is a descriptive measure of *within-subjects* change for the intervention in comparison to the control. We will first compute the difference between baseline and 1-month follow up on the primary and secondary outcomes for the control group and calculate an ES using the group baseline SD. We will calculate an ES for each member of the intervention group and then report the overall proportion that exceeds the median ES of the control group;
- The proportion of negative UDS test results (with relative risk) for cocaine metabolite at 1-week, 1-month and 3-month follow-up;
- The proportion of participants in each arm meeting CUD diagnosis (by severity, with number-needed-to-treat) and ADAPT profile at 3-month follow-up.

To inform a future study, we also plan the following exploratory analyses:

- Mean difference between trial arms on change in DERS between baseline and 1-month and Hedge's g ES;
- A causal mediation analysis (performed using Stata's **paramed** command) including trial group and 1-month CEQ-F as an intermediate outcome in the pathway to 3-month change in cocaine use. We will screen for univariate associations with each outcome for the following baseline covariates: months of regular cocaine use, oral or injecting cocaine administration, heroin use in the past month and enrolment in opioid agonist maintenance therapy. Along with sex, age, and the baseline score on each outcome measure, we will consider whether to include one of these pre-randomisation factors as a covariate (selecting one variable with the largest ES that is significant with an 80% CI). Standard errors will be estimated by bootstrapping with 5000 replications;
- A Bayesian Framework assessment for the strength of evidence obtained to inform the case for a substantive trial [67]. We will set an 80% threshold for the probability of achieving a meaningful difference using *pessimistic* and *optimistic* prior beliefs from meta-analysis (standardised ES 0.13; 95% CI -0.08 to 0.35 [CBT effect on change in cocaine, stimulant and opioid use] and ES 0.31; 95% CI 0.12 to 0.49 for CBT with psychosocial interventions, respectively [5]).

2.13.3. Management of missing data

To inform our exploratory analysis, we will screen data in an effort to identify the mechanism that has generated missing data (i.e. not missing at random [NMAR], missing at random [MAR], and missing

completely at random [MCAR]). NMAR is non-ignorable and statistical inference is only achieved if the reason for missingness is modelled. MAR refers to the propensity for missingness to be unrelated to the missing data, but related to the observed data. It is generally not possible to screen for MAR because it requires knowledge of unavailable information. MCAR refers to missingness that is independent of the nature of observed and unobserved data. We will use Stata's **mcartest** command for a chi-square test of MCAR as proposed by Little [68]. On the expectation that a missingness mechanism is at least MAR, appropriate imputation of missing data will be undertaken.

2.14. Therapy monitoring, study timeline, data management and governance

Subject to participant consent, the pre-randomisation assessment sessions will be audio recorded and the cue-induction procedure and MFCT therapy sessions will be video recorded. A 5% random sample of these assessment sessions and cognitive therapy sessions will be taken for independent clinician assessment using the assessment and therapy versions of the CTS-R, respectively.

The first participant was enrolled on 15.07.2015 (study month 1). Given resources and estimated rate of admission and internal referrals to the study, we estimated that the study will take 2.3 years to complete: last participant randomised by month 15 and last participant to complete final follow-up in month 24. Data management, analysis and reporting is targeted for completion by month 28.

Participants' personal data will be stored securely on individualised source data worksheets. After completion of all follow-ups and prompt entry of data, the dataset will be reviewed for accuracy and then analysed. All adverse events will be recorded and reported immediately. A Trial Management Group will meet at regular points during fieldwork and to review results and research products/manuscripts.

3. Discussion

There is a pressing need for more effective treatment for CUD. To date psychotherapeutic interventions appear to have the best chance of success, but the ES from current CBT approaches is modest and has been insufficient for the UK National Institute for Health and Care Excellence to recommend routine use in addiction clinics [69]. There have also been several efficacy trials combining pharmacotherapies and psychotherapies for CUD as well as contrasts between individual and group delivery formats, but no best practice approach has been identified. Capitalising on convergent lines of laboratory research on cue-exposure, attentional processes, and successful methods of treating PTSD, we see merit in the study of a MFCT for CUD. Developed and studied in a real-life NHS clinical setting, the present trial is expected to deliver a good, science-driven test of this novel therapy to evaluate progression potential.

We believe this RCT will have several strengths. Firstly, informed by the practice of trials in biomedical research and relevant meta-analysis, we have set clear research questions as a science-driven pathway to inform progression potential to a substantive study (i.e. attrition not greater than 20%; therapist practice meeting standard criteria on the CTS-R; no more than 40% of participants reporting an increase in craving experience between the first and second cocaine-related cue-induction procedure; a medium effect size [0.31] for the preliminary efficacy assessment of craving; and a small effect size [0.15] for cocaine use outcomes). This will be a relative small trial, but Bayes Factors will inform the sensitivity of our efficacy assessments.

Second, our cognitive case conceptualisation approach is designed to tailor MFCT to the individual to promote collaboration and flexibility over a fixed session-specified therapeutic manual. Third, the primary outcome is well-defined and connects to the theoretical mechanism of action for this structured psychological intervention. This is supported with secondary outcomes to capture change in the intensity and pattern

of cocaine use. Fourth, we ask a set of questions (with a pre-specified analysis plan) to evaluate the case for progression to a full-scale, definitive trial if there are promising efficacy findings and sufficient evidence of feasibility and quality. We will also identify necessary changes to future design, process and measures. Fifth, conducting the study in a single real-life NHS clinic enables us to focus our resources; and the use of TAU provision (with normal access to local ancillary services) increases external validity within the UK public addictions treatment system (and similar addiction treatment systems internationally).

We also acknowledge several limitations. Firstly, we recognise that this small-scale study is, by definition, underpowered to assess efficacy but our capture of clinical outcomes is a valid exercise and Bayes Factors will inform whether we have in hand evidence in favour of the null, the alternative hypothesis, or whether the study data is insensitive. Second, our findings will be limited to application in substance use disorder treatment clinics with access to psychologists with appropriate training in CBT. Third, for resource reasons we were not able to blind researchers conducting the follow-ups to the participant's group allocation which risks a social desirability bias (but is offset to some degree by use of the UDS measure for the cocaine use outcomes). Fourth, we recognise that participants in the experimental arm will have twice as much study contact time relative to control arm participants, (controls will receive 9hrs of assessment, intervention and follow-up contact, compared to 18.5hrs among the intervention group). A future substantive study should address this in the design (e.g. potential to use a time-balanced placebo control such as guided relaxation).

In reports to a scientific journal will evaluate the study questions and the case (with necessary adjustments to design, procedures and measurements) for progression to a substantive RCT.

Authors' contributions

J.M. (chief investigator) developed the concept in collaboration with C.G., N.G., L.M. and T.M. The statistical analysis plan was developed by J.M., C.G. and B.E. J.M. drafted the manuscript with C.G. and with input from all authors. All authors read and approved the final version before submission for publication.

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Competing interests

The authors declare that they have no financial investment or personal relationships with other people or organizations that could inappropriately influence or benefit this research.

For the past three years, J.M. declares investigator-led, educational grant funding from Indivior (administered by Action-on-Addiction) for a study of personalised psychosocial intervention for non-response to opioid agonist treatment (ARC Trial), and support from NIHR (HTA) for a trial of extended-release naltrexone. He acknowledges part-time employment as Senior Academic Advisor for the Alcohol, Drugs and Tobacco Division, Health Improvement, Public Health England and consultancy with the US National Institute on Drug Abuse, Centre for Clinical Trials Network. He received honoraria from Merck Serono (2015; clinical oncology training); Martindale (2017; expert meeting on OUD); and Indivior (via PCM Scientific) as co-chair (2015, 2016) and chair (2017) for the conference on Improving Outcomes in Treatment of Opioid Dependence.

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response to opioid agonist treatment (ARC Trial).

J.S. is a researcher and clinician who has worked with a range of types of treatment and rehabilitation service-providers. JS is supported by the NIHR BRC for Mental Health at SLaMHFT and KCL. He has also worked with a range of governmental and non-governmental organizations, and with pharmaceutical companies to seek to identify new or improved treatments from whom he and his employer (KCL) have received honoraria, travel costs and/or consultancy payments. This includes work with, during past 3 years, Martindale, Reckitt-Benckiser/Indivior, MundiPharma, Braeburn/Camrus (none of these activities relate to the study being reported here).

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All other authors declare no competing interests.

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