Research Paper

Memory-Focused Cognitive Therapy for Cocaine Use Disorder: Theory, Procedures and Preliminary Evidence From an External Pilot Randomised Controlled Trial

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ABSTRACT

Background: Cocaine use disorder (CUD) is a debilitating condition with no NICE-recommended medication or specific psychosocial interventions. In the United Kingdom (UK), general counselling (treatment-as-usual; TAU) is widely delivered, but has limited effectiveness. We tested the feasibility, safety and preliminary efficacy of a novel, adjunctive psychosocial intervention for CUD, called 'memory-focused cognitive therapy' (MFCT).

Methods: We did a two-arm, external pilot randomised controlled trial at a specialist community National Health Service addictions clinic in London, UK. 30 adults (≥18 years), voluntarily seeking treatment for CUD (enrolled ≥14 days; all with moderate-to-severe DSM5 CUD), were individually randomised (1:1) to a control group (ongoing TAU; 3×90 min CUD cognitive conceptualisation assessments; 2×30 min cocaine-related cue-induction procedures; and 3×30 min research follow-ups); or to an intervention group (ongoing TAU; 3×90 min cognitive conceptualisation assessments; 2×30 min cocaine-related cue-induction procedures; 5×120 min, one-to-one, MFCT sessions [in 1 week]; and 3×60 min research follow-ups and MFCT-relapse prevention).

The primary outcome was the total percentage score on the frequency version of the Craving Experiences Questionnaire (CEQ-F) at 1-month follow-up after the intensive intervention week (clinical endpoint; recall period past 2 weeks; higher score indicating greater craving). Secondary outcomes at the 1-month follow-up were percentage days abstinent (PDA) from cocaine, and longest period (days) of continuous abstinence (LPA) in the prior 28 days.

Outcomes were analysed as an unadjusted group mean difference (with Hedge's *g* effect size [ES]) and a 95% Confidence Interval [CI] for the primary outcome and a 90% CI for the secondary outcomes. Exploratory, multivariable linear (primary outcome) and Poisson regression models (secondary outcomes), with sex, age, months of regular cocaine use, baseline outcome score, and group estimated the effectiveness of the intervention. The trial is registered with the ISCRTN (ISRCTN16462783).

Findings: Between July 15, 2015, and November 27, 2016, 58 patients were assessed for eligibility and 30 participants were randomised (14 to the control group and 16 to the intervention). With outcome data collected for all participants at the endpoint, the intervention group mean CEQ-F score (14·77; SD 21·47) was lower than the control group mean (51·75; SD 22·72); ES -1·62; 95% CI -2·45 to −0·80.

MFCT was associated with more cocaine abstinence in the intervention group (PDA 85·94; SD 18·96) than the control group (PDA 54·59; SD 30·29); ES 1·19; 90% CI 0·54 to 1·84. There was also greater maximum abstinence in the intervention group (LPA 15·69; SD 10·10) than the control group (6·00; SD 7·36); ES 1·06; 90% CI 0·41 to 1·70. Exploratory, confounder-adjusted regression models for this preliminary effect supported the treatment association for reduced craving experiences (CEQ-F Coef. -28·25; 95% CI -45·15 to −11·35); more abstinence (PDA Incidence Rate Ratio [IRR] 1·56; 95% CI 1·31 to 1·88); and greater maximum abstinence (LPA IRR 2·56; 95% CI 1·96 to 3·35), although relative weak unmeasured confounding could overturn these model-adjusted exposure-outcome associations.

There were four serious adverse events (among three participants). None were judged related to study procedures or interventions.

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Interpretation: In this first external pilot randomised controlled trial of MFCT for CUD, we have shown that the intervention and control procedures and acceptable feasible and safe, and report preliminary evidence that MFCT is associated with reduced craving and increased abstinence. These findings support progression to a substantive trial.

1. Introduction

Cocaine is a powerfully addictive stimulant linked to a substantial global burden of disease (Degenhardt et al., 2014). There are several forms of cocaine, including a hydrochloride powder (taken by nasal insufflation or by injection) and a solid alkaloid (known as *crack*, and usually inhaled after heating). Injecting and smoking cocaine induces euphoria and confidence for ~5–15 min, with dose-dependent increases in heart rate, blood pressure and body temperature. The pleasurable, reinforcing effects of nasally administered powder cocaine are less intense, but longer-lasting (~45 min) (Jeffcoat et al., 1989). Long-term cocaine use is associated with co-occurring psychological disorders (Rounsaville et al., 1991; Fox et al., 2007) and physical complications (including cardiovascular and pulmonary disease (Gradman, 1998)).

18·3 million people aged 16–64 use cocaine each year worldwide (United Nations Office on Drugs and Crime, 2016), and 6·9 million people worldwide are addicted (cocaine use disorder [CUD] is the psychiatric diagnosis in DSM5) (American Psychiatric Association, 2013). In England and Wales, cocaine is the most commonly used drug after cannabis. In 2015/16, 725,000 (2·2%) of people in England and Wales aged 16–59 used the powder form (Home Office, 2016); while in 2014/15, 183,000 people used crack (Hay et al., 2017).

1.1. CUD as a Learned Disorder

There is substantial evidence showing that CUD can develop rapidly through adaptive learning processes which are mediated by conditioning, motivation and inhibition (Redish et al., 2008; Köpetz et al., 2013). There are well-studied neurobiological circuits (and drug-class specific neurotransmitter models) underpinning psychoactive substance use disorders. These circuits are found in the frontal-striatal region and the nucleus accumbens, amygdala, insula and hippocampus (Volkow et al., 2013; Wise & Koob, 2014; Wilcox et al., 2016).

Learning models of CUD emphasise quick-forming episodic memories of drug reward. They reflect a progressive imbalance between the implicit-autonomous and explicit-reflective cognitive systems which favours the former (Evans, 2008; Posner & Snyder, 1975), coupled with neutral and drug-related exteroceptive stimuli which become cue-associated. As a cocaine habit becomes established, liking and wanting beliefs and expectancies strengthen (Zapata et al., 2010; Everitt & Robbins, 2005) and attention is biased towards conditioned cues (Robinson & Berridge, 1993; Field & Cox, 2008). Those with neurocognitive and emotion regulation impairments may be especially vulnerable to CUD (Baumeister & Vohs, 2016).

With sustained use, there is usually tolerance to cocaine's pleasurable reinforcing effects and decreased responsiveness to natural rewards (Volkow et al., 2010). If the person is able to strike a balance between goals and habits, behavioural control may remain mostly intact, and consumption will be limited in frequency and intensity (de Wit & Dickinson, 2009). However, as implicit-autonomous processes strengthen, many find it very hard to control their impulses and desires to use cocaine (Wiers et al., 2010). Taking crack, in particular, can be highly automatic and irrational. Patients often report that they know that only their first dose of crack results in euphoria. There will be less pleasure obtained from subsequent doses with an increase in anxious thoughts, uncomfortable physical sensations and unwanted behaviors. Yet they re-dose within minutes until their supply is exhausted.

1.2. Craving Experience, Process and Assessment

The subjective experience called *craving* was reintroduced in DSM5 as a diagnostic symptom of substance use disorders. Craving is commonly understood as a powerful desire and emotion. This construct has a long history of theoretical and clinical study in the addictions, particularly in tobacco smoking and alcohol research (Tiffany & Carter, 1998; Tiffany & Wray, 2012). In the clinic, accounts of intense craving, and automatic drug seeking in response, are often reported after a patient encounters a conditioned cue in their environment (such as a place, object, person, or physical sensation such as pain). Craving often intensifies and feels very unpleasant when drug access is prevented or delayed (such as waiting for a drug seller or money to become available), or when an effort is made to resist. There may be autonomic (interoceptive) reactions, including changes in breathing, heart rate and sweating (O'Brien et al., 1990). However, craving is not always intense or persistent, and cocaine seeking is sometimes initiated by low-level desire (Field et al., 2009).

There have been several influential accounts of craving process, including models by Tiffany (1990); West (2006) and Kavanagh and colleagues' Elaborated Intrusion [EI] theory of desire (May et al., 2015; Kavanagh et al., 2009). As applied to cocaine, EI theory describes an episode of craving with two components: an initial, spontaneously intrusive thought, followed by a cycle of elaborative cognition in which well-consolidated memories of past cocaine use are recalled and linked to sensory imagery, basic and complex affect, beliefs and expectancies of future pleasure or negative mood relief. This consciously mediated desire will be stronger if there is sensory vividness (Tiffany & Hakenewerth, 1991; Andrade et al., 2012). We believe there is much to be learned from discussing with a patient the strength, frequency and their interpretation of craving episodes, as well as the type and number of DSM5 CUD harm symptoms experienced.

There is no consensus about how to assess craving generally, or specifically for substance classes. A single dimension or a binary indicator is sometimes used, but we favour a multi-component approach. Based on EI theory, the present study uses the Craving Experiences Questionnaire (CEQ (May et al., 2014)) for cocaine, implemented as an 11-item measure of the frequency of the following recent craving experiences: intensity (wanted, needed, had a strong urge); imagery (pictured it, imaged the taste, the smell, the effects and how your body would feel); and intrusiveness (trying not to think of cocaine, frequency of intrusive thoughts, difficulty in thinking about anything else).

1.3. Treatment of CUD

Unlike opioids, nicotine and alcohol, there is no approved treatment medication for CUD (Fischer et al., 2015). Several psychosocial interventions have been trialled, with Cognitive Behavioural Treatment (CBT) the most extensively studied. Meta-analysis shows CBT is better than no treatment for CUD; but when evaluated alongside active comparators, CBT achieves only a small standardised effect size (ES) associated with reduced cocaine use (0·15; 95% Confidence Interval [CI] 0·07 to 0·24) (Magill & Ray, 2009). Meta-analysis is more encouraging for CBT when it is delivered as an adjunctive intervention to TAU (ES 0·31; 95% CI 0·12 to 0·49) (Magill & Ray, 2009). However, the National Institute for Health and Care Excellence does not recommend CBT or other psychosocial interventions for CUD

specifically, aside from a behaviour therapy for couples (National Institute for Health and Clinical Care Excellence, 2017).

In England in 2015/16, 150,000 people sought help for CUD from National Health Service (NHS) and third-sector clinics (Public Health England, 2016). These patients were typically offered one-to-one, fortnightly, ongoing, general counselling (treatment-as-usual [TAU]; ~45 min per session). In an observational study of 94,166 patients in the English public treatment system with CUD in 2015/16, 42·9% were still using cocaine after three months of TAU and 50·4% had left treatment by 6 months (Public Health England, n.d.). Clearly, clinicians need better interventions for CUD.

1.4. Origins of Memory-Focused Cognitive Therapy

Influences on the development of this novel, memory-focused cognitive therapy (MFCT) include our efforts to tailor treatment for CUD and OUD (Marsden et al., 2014, 2017a); the role of mental imagery in assessment and psychological therapy for anxiety and mood disorders (Bewin et al., 2010; Holmes & Mathews, 2010).

We have been struck by the enduring effects of conditioned cocaine-cues for our patients. Could reactions which induce desire for cocaine be extinguished through repeated non-reinforced cue exposure? There is a longstanding literature on this question, but results have been mixed and meta-analysis has concluded that this therapy is not superior to comparison conditions (Conklin & Tiffany, 2002; Martin et al., 2010). However, if we shift the goal away from extinction, we think there is merit in using cue-induction procedures as a means of helping the patient elicit cocaine-related cognitions for use in treatment.

MFCT also adapts treatment techniques successfully developed for post-traumatic stress disorder (PTSD) (Ehlers & Clark, 2000; Foa et al., 2007). Trauma-focused cognitive therapy (the first-line intervention for PTSD (National Collaborating Centre for Mental Health, 2005)) uses imaginal and in vivo exposure to help the patient relive and elaborate a trauma memory; discriminate memory triggers; increase interoceptive awareness; and cognitively restructure maladaptive appraisals and sensory images. Could these methods be adapted for use with CUD?

At first glance, approach-based, craving-related cognitions in CUD and avoidance-based, fear-related cognitions in PTSD seem quite different. However, the respective craving and fear responses in both disorders are maintained to a greater extent by the activation of cue-associated memories, which elicit mental images and motivate maladaptive and disorder maintaining coping strategies.

There is also comparative and clinical laboratory evidence that consolidated drug memory response can be reactivated and disrupted to abolish a drug conditioned response (Hellemans et al., 2006; Lee et al., 2006) and reduce future craving experience (Xue et al., 2012; Hon et al., 2016).

Supported by this trial and laboratory evidence, we developed a protocol with the goal of reconsolidating targeted cocaine memories to help the patient achieve cognitive and behavioural control (see Section 2.2.6. for description of treatment procedures).

Following a trial which showed that cognitive therapy for PTSD can be delivered effectively in 1-week, we developed MFCT as a relatively intensive therapy (Ehlers et al., 2014). We noted a trial that reported increased drop-out and relapse among participants exposed to drug-related images and objects (Marissen et al., 2007), so judged it important to verify the safety of our cue-induction procedure and determine if this would activate craving and cocaine use.

1.5. Aims and Research Questions

As a science-driven phase in MFCT development and informed by guidelines and progression criteria for pilot studies (National Institute for Health Research), we did an external pilot randomised controlled trial (RCT). An external pilot RCT is a miniature trial (with full protocol implementation and outcome measure collection) with the data analysed, reported and then set aside (National Institute for Health Research).

The research questions were as follows (see Section 2.4. for list of linked hypotheses):

(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 ES from meta-analysis?
(5) Is MFCT associated with reduced cocaine use that is at least as large as the overall ES from meta-analysis?

2. Methods

2.1. Study Design and Setting

This was a single-site, 15-week, two-arm, external pilot RCT. Ethical approval for the protocol was granted by the UK National Research Ethics Service (London-Fulham Research Ethics Committee: 153/LO/0656). The study is registered with the International Standard Randomised Controlled Trial registry (ISRCTN164627831).

The research questions and statistical analysis plan were pre-registered with the Open Science Framework (Open Science Framework, 2017) and the protocol published (Marsden et al., 2017b). Results in this paper are reported following the CONSORT pilot RCT extension (Eldridge et al., 2016) and the Template for Intervention Description and Replication (Hoffmann et al., 2014).

All participants received TAU at a community NHS clinic operated by South London and Maudsley NHS Trust (the clinic, herein). For participants with primary CUD, this was fortnightly, one-to-one, counselling with a nurse or drug worker. For co-occurring CUD and OUD, TAU was counselling plus opioid agonist maintenance treatment (oral methadone, buprenorphine, or buprenorphine-naloxone medication).

All assessments and follow-ups were done face-to-face in a private interview room at the clinic. For safety reasons (and to facilitate session video recording) the cocaine cue-induction procedure, and the intensive phase of MFCT, were done locally at the outpatient National Institute for Health Research and Wellcome Trust Clinical Research Facility (CRF) at King's College Hospital, London.

Six weeks after the trial started, we secured additional funding for a 3-month follow-up and relapse prevention session. Consent materials were amended after securing ethical approval. This was implemented in time for all participants.

2.2. Participants and Procedure

2.2.1. Inclusion and Exclusion Criteria

The study eligibility criteria were: (1) age ≥ 18 years; (2) voluntarily seeking treatment for CUD; (3) enrolled in TAU for ≥14 days; (4) current (any) use of cocaine in past 28 days (verified by clinical record); and (5) sufficient English fluency to receive psychosocial therapy.

The exclusion criteria were: (1) suicide planning in the past month, or suicide attempt in the past six months; (2) uncontrolled mental or physical health conditions; (3) current non-abstinent alcohol use disorder; (4) co-occurring CUD and PTSD; (5) legal proceedings risking incarceration; (6) participation in a substance use disorder treatment study in the past three months.

2.2.2. Referral, Screening and Enrolment

All participants were recruited from the clinic. A psychology assistant (C.G.) screened participants to the planned rate of one per week. Patients were told that the aim was to evaluate a new cognitive therapy

for CUD; that all participants would be assessed and undergo two co-caine cue-induction procedures, with a randomly-selected group then receiving MFCT. All participants provided their written informed consent.

A senior psychologist (J.M.) diagnosed CUD for all potential participants using the Structured Clinical Interview for DSM5 (SCID (First et al., 2015); corresponding to categories F14·10 and F14·20 in ICD-10). Participants then completed a C.G. administered, 1-h, baseline interview which included the Treatment Outcome Profile (TOP (Sobell & Sobell, 1996); a 'timeline follow-back' structured interview to record each day of cocaine use in past 28 days), and the CEQ-F (recall period, past two weeks; item response: 'not at all' to 'constantly' [0−10]; item scores summed as a total score [percent-age] for tabulation.

2.2.3. Cognitive Conceptualization

After completion of the baseline interview, all participants were invited to attend three, 90-min, cognitive conceptualisation assessments, during the following fortnight. The aim was to develop a functional for-mulation of CUD maintenance, focusing on recent drug use situations, recalled images, sensations, beliefs/appraisals, avoidance/coping strate-gies, cocaine use and post-drug use evaluations. These sessions were fa-cilitated by a senior psychologist (J.M., L.M. or T.M.) and assisted by C.G. Session audio-recording was by consent. An independent clinician rated a 5% random sample of recordings from different participants using the 10-item assessment version of the Cognitive Therapy Scale-Revised (CTS-R) (Blackburn et al., 2001).

Between the first and second assessment, each participant was asked to: (1) take point-of-view digital pictures of drug-associated neu-tral cues (e.g. street corners, parks, pubs/bars, automated teller ma-chines [ATM], bank notes, lighters, hallways, chairs and tables); and (2) collect a selection of personal cocaine-related objects (e.g. used drug wraps, pipes, sealed syringes, scrapers [for collection cocaine resi-due from inside pipes], cleaning equipment, and objects used to sniff cocaine).

We reviewed pictures taken with the participant and agreed which ones to print (typically four-eight photographs, 15 × 10 cm), and which objects to bring in (typically three-six items). We also transcribed the participant's verbatim description of a recent craving experience (~200 words printed on A5 card). These materials were placed in an opaque, lidded card box (30 × 23 × 8cm) using sheets of A4 card to sep-arate them in the following order: outdoor photographs at the top, then craving description, indoor photographs, and lastly cocaine-re-lated objects. A five-minute audio recording of the participant de-scribing craving experiences, and other sounds recalled was also included (e.g. TV show often watched; traffic noise; music playing when using cocaine).

2.2.4. Randomisation

At the end of the third cognitive conceptualization session, the participant was assigned (1:1) to the control or the intervention group, using a web-accessed, computer-generated random sequence (with random varying blocks, and no stratification factors) indepen-dently managed by the King's College London Clinical Trials Unit. A study identification number and the participant's date-of-birth was entered into the randomisation system by C.G. It was not feasible to mask group allocation. The participant was immediately informed of their allocation.

2.2.5. Control Group Cue-induction Procedure

In addition to continuing TAU, we invited participants in the con-trol group to attend the CRF twice (on Monday and Friday) to com-plete a nine-minute cocaine cue-induction procedure and research measures (30 min). On arrival, the participant was asked to take an alcohol breath-test (BACtrack Mobile Pro; www.bactrack.com) with 30 mg/ml set as the upper limit (Peterson et al., 1990)). If

they tested above this limit, they were invited to wait within the CRF to re-test, or re-schedule. In session, the participant was asked to sit at a table in a private room. The closed card box was put on the table. After 2 min, the participant was asked to open the lid and, for the next 5 min, to retrieve and hold each item in turn, and focus on any images, sensations and emotions elicited (see protocol for full description (Marsden et al., 2017b)).

After a further two-minutes, they completed the strength version of the CEQ for cocaine (CEQ-S; recall: past 5 min). As required, a 'talk down/attention shift' procedure was then used to help the participant return any elicited craving to zero, or to a level no higher than on arrival. A light meal was provided with rest for 30 min. After completion of the second cue-induction (repeated verbatim), each participant was invited to attend two C.G.-administered, 30-minute research follow-ups, at 1-week, 1-month and 3-months.

2.2.6. Memory-Focused Cognitive Therapy

In addition to continuing TAU, we invited intervention group partic-ipants to complete the two cue-inductions (as described in Section 2.2.5.), with immediate discussion of the participant's interpretation of craving-related images and emotions to guide their therapy.

MFCT was five, 120-minute sessions (scheduled on consecutive weekdays) and two 60-minute relapse prevention sessions follow-ing the research follow-ups after 1-week, 1-month, and 3-months (time anchored from the end of the intensive therapy week). This was a structured one-to-one intervention (therapist's manual available on request). All sessions were delivered by a senior psychologist (J.M., L.M or T.M.) with video recording by consent. An independent clinician rated a 5% random sample of recordings from different participants using the 12-item therapy version of the CTS-R. Ongoing practice reflection was by clinical supervision as well as clinical practice reviews in the Trial Management Group.

Treatment included education about cocaine's effects on thoughts, mood and behaviors, and the following sequential components:

(1) <u>Hypothesis of SUD maintenance</u>: Drawing on detailed de-scriptions of recent cocaine use episodes (and any successful episodes in which craving was resisted) gathered during the conceptualization sessions, the goal of this component was to identify (and then update during treatment) a testable, id-iosyncratic theory of how CUD was maintained. Unlike the memory of a single traumatic event, CUD patients have hun-dreds of different cocaine use episodes and consolidated memories that could prevent meaningful synthesis. However, in our experience most patients have regular and repeating patterns of drug use in a small number of locations. In most cases, typical recent episodes can be easily identified. A for-mulation recorded information collected by Socratic questioning, using the following linked model:

A. *Implicit-Autonomous*: (1). Associative memory representations (places/events, people, objects, sounds, sensations, smells); (2). 'Fast' thoughts (drug-related low-level cues, sensory images, focus of attention); (3). Autonomic (interoceptive) and basic emotion (breathing, heart rate, sweating, surprise, gut sensations, fear, anger).

B. *Explicit-Reflective*: (1). Episodic/autobiographical/declarative memory (recall of events, knowledge/appraisal of self and facts); (2). Controlled attention/working memory (elaboration, interpre-tation, conditional/instrumental beliefs [rated on a 0–10 strength scale], rules); (3). Elaborated cognition and autonomic response (craving [desire/urge using the language and concepts used by the patient and rated on a 0–10 strength scale], ambivalence, phys-ical sensations, complex emotion).

C. *Motivational-Behavioural*: (1). Plans and intentions (automatic [non-conflictual], deliberative [conflictual], drug use expectan-cies); (2). Desistence or drug-approach (coping strategies, drug

seeking); (3). Cocaine use behaviors (preparation ritual, consumption, actions, unwanted behaviors [e.g. motor stereotypy], complex affect [e.g. suspiciousness], post-cocaine use evaluations and beliefs).

The aim of the formulation was to identify episodes with the strongest craving elaboration linked to use-maintaining beliefs and emotions which could later be updated with an alternative appraisal (e.g. "cocaine will block my worries"; "cocaine will take the pain away"; "using will stop me craving and I won't want more"; "the quality from this drug seller has always been the best"; "I should buy more crack now, so I won't need to go out and get more").

(2) Memory reconsolidation and coping strategies: The treatment goals were to reconsolidate memories of cocaine use, tackle maladaptive beliefs, reduce problematic behaviors and support coping strategies. There were four components:

A. Socialising: (1). Discussing the rationale for reliving (identifying images and emotions); (2). Reconstructing the structure or linear sequence of a target memory (discussion of theory that cognitive control will improve if the memory is recalled in the first person/ first tense and then updated); (3). Stressing the safety of the clinical environment for reliving (importance of discriminating *then* from *now* thoughts and emotions; noticing how induced desire reduces over time).

B. Eliciting cocaine memories: (1). Therapist-guided with a focus on sensory detail to maximise vividness; recording craving and emotional responses [rated on a 0–10 strength scale]; (2). Reliving of elicited memory, with markers for the start and end of the memory [identifying key scenes], as needed and focusing on emotional 'hotspots', sensory images and meanings [e.g. "My palms are sweaty and my heart is pounding"; 'I can feel the wrap of cocaine between my fingers"; "I see the cloud of cocaine in front of me as I exhale"; "I am pathetic and will never be able to control my cravings"]. This is comparable to the identification of peri-traumatic 'hotspot' meanings in PTSD fear memory (Grey et al., 2002).

C. Cognitive restructuring and imagery re-scripting: (1). In vivo exposure to personal cocaine-related objects and drug-related photographs (patient identification of alternative appraisals [e.g. "that's just a street corner; it doesn't have to mean drug selling"; "that's just a plastic bottle; it doesn't have to mean crack smoking"]; (2). Cognitive restructuring outside of memory reliving (e.g. discriminating drug-neutral and drug-conditioned triggers: "it's just an ATM; it doesn't have to mean a source of money for cocaine"]; evaluating evidence against pro-drug beliefs and alternative perspectives [e.g. "using cocaine makes my worries worse not better"; "actually, that seller often has rubbish drugs"]; (3). Cognitive restructuring within reliving (e.g. repeatedly holding an image in mind and updating with new information or an alternative appraisal); (4) Repeated imagery re-scripting by manipulating images (e.g. running an image forward from desire to the end of an evening when the cocaine supply is exhausted; turning away from approaching a seller's car and walking home; bringing to mind a positive sensory image).

D. Stopping dysfunctional behaviors and coping strategies: (1). Recovery-promoting activities (cooking a meal; spending time with family members; listening to session audio recordings; keeping a diary of positive experiences); (2). Behavioural experiments (engaging in new or dropped social activities; testing reactions when in cocaine-associated places; holding old drug paraphernalia, and visiting public locations related to drug use; (3). Applying coping strategies (responding to craving by noticing images, sensations and emotions, and acknowledging these as normal responses to a memory, but then shifting attention [e.g. changing the topic of conversation; brining to mind an alternative sensory image]).

2.3. Outcome Measures

The primary outcome measure was the percentage total score on the CEQ-F at 1-month follow-up.

There were two secondary cocaine use outcomes. Here, there is no gold-standard, primary drug use endpoint for CUD treatment trials. It is not possible to reliably infer the quantity of cocaine consumed, and while total abstinence is sometimes used, this is insensitive to the response profile of a patient who is almost completely abstinent bar a few lapses. However, the count of abstinent days and the duration of continuous abstinence has been recommended by experts (Carroll et al., 2014) and has been recently accepted by the US Food and Drug Administration as clinically meaningful (U.S. Food & Drug Administration, n.d.).

Accordingly, secondary cocaine use outcomes at 1-month follow-up were: (1). percentage days abstinent (PDA); and (2). the longest period (days) of abstinence (LPA) in the prior 28 days. These measures were derived from the TOP interview. The CEQ-F, PDA and LPA outcomes were also recorded at the 3-month follow-up.

There were two exploratory outcomes: (1). the point prevalence for cocaine abstinence by cocaine-negative urine drug screen (UDS; primary metabolite: benzoylecgonine; www.concateno.com; detection sensitivity: 300 ng/ml) at 1-week, 1-month and 3-month follow-up. Typically, among regular cocaine users, benzoylecgonine can be detected for approximately seven days after drug use (Antivenins et al., 2000); (2). DSM5 CUD early remission status at 3-month follow-up.

2.4. Study Hypotheses

We hypothesised that:

H1. Study attrition will not exceed 20% in each arm. This is a common standard for RCTs and bias assurance in evidence-based medicine (Dumville et al., 2006).

H2. 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 CTS-R.

H3. No >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 that the Minimally Detectable Change (MDC) for the CEQ-S (recall period: past 5 min). We set the 40% threshold from the relapse rate among participants in a recent study who received an in-vivo drug cue-reactivity exposure (Marissen et al., 2007).

H4. The standardised ES for the primary outcome associated with the experimental group will be not <0·31. This is the meta-analysis ES for CBT as an adjunct to psychosocial TAU (Magill & Ray, 2009).

H5. The standardised ES for secondary cocaine use outcomes associated with the experimental arm will be not <0·15. This is the estimate of effectiveness for CBT on reduced cocaine use from meta-analysis (Magill & Ray, 2009).

2.5. Sample Size

There is no consensus on the minimum sample size for an external pilot RCT. This is usually determined by the expected ES and available resources and desired timeline. We expected at least a small-to-medium ES, and followed the principle of neither over- or under-estimating the variance of the outcome (Kieser & Wassmer, 1996). Following

expert recommendations for pilot RCTs, we set a planned sample size of 30 participants to be randomised (Lancaster et al., 2002).

We emphasise that a sample of this size is insufficient to demonstrate efficacy of MFCT and the reported between-group effect sizes on outcome measures and the exploratory analyses must be viewed as preliminary evidence and interpreted with caution.

2.6. Statistical Analysis

The analysis was done in Stata 15, by intention-to-treat. Demographic, treatment exposure and outcome measures were summarised by reporting the number of participants (with percentage) for categorical variables, or the mean (with standard deviation [SD]) or median (inter-quartile range [IQR]) for scale or count measures.

For the cue-induction safety assessment (H3), we used the coefficient of reliability for CEQ-S to calculate the mean standard error for the MDC (Bland & Altman, 1986). For the preliminary efficacy analysis, the primary outcome was assessed with a 95% CI. The secondary and exploratory outcomes were assessed using a 90% and 80% CI, respectively.

Differences between the intervention and control groups were estimated by bias corrected Hedge's g ES (Hedges & Olkin, 1985)). As a summary measure of *within-subjects* change from baseline to follow up, we calculated the median ES for the control group and reported the proportion of the experimental group exceeding this (Cohen's U_3 (Cohen, 1988)). A Bayes Factor was also calculated to show evidence for the null or the alternate hypothesis. This is equivalent to a likelihood ratio, with a value of <0·3 or ≥3·0 indicating that the null or alternate hypothesis is correct, respectively (Berger, 2013). A value between 0·3 and 3·0 indicates that the data are insensitive (Beard et al., 2016). An online calculator was used (Dienes, n.d.) specifying a prior ES (0·31 ES from meta-analysis (Magill & Ray, 2009)), and a conservative half-normal distribution.

In the event of missing craving, cocaine use and UDS assessments at the endpoint or exploratory outcome data and DSM data at the 3-month follow-up, and subject to a check on missingness assumptions (Little's *mcartest*), we planned a multiple imputation procedure using the Stata commands *ice* and *uvis* to generate values, with the following auxiliary variables: sex, age, route of cocaine administration and group. For comparison, complete case results are shown in Table S1.

Subject to preliminary efficacy of evidence, we planned a multivariable regression analysis with sex, age, baseline outcome score, and the strongest confounder associated with the primary and secondary outcomes (by ES with 80% CI). In addition, we planned to screen the following baseline variables: months of regular cocaine use; oral/injecting cocaine administration; heroin use in past 28 days. Multivariable linear regression was done for the primary outcome and Poisson regression for the secondary outcomes. Standard errors were estimated by bootstrapping with 5000 replications.

As a sensitivity check on these models, we also calculated the E-value (VanderWeele & Ding, 2017). The E-value is an estimate of the minimum strength of association that an unmeasured confounder would need to account for a treatment-outcome association, conditional on the included covariates. When computed for a continuous outcome, this value is an approximation to the risk ratio scale. The E-value has a minimum value of 1, and is reported alongside a risk ratio measure of its uncertainty, which quantifies the value that the CI for the association would need to shift to the null.

Finally, we calculated the relative risk (RR) for negative UDS data and the number needed to treat (NNT) for DSM5 CUD remission in favour of MFCT.

All adverse events were recorded and classified according to seriousness and the likely relationship to study interventions.

3. Results

3.1. Recruitment and Baseline Characteristics

Between July 15, 2015 and November 27, 2016, we screened 58 patients and enrolled 35 participants (Fig. 1). The final 3-month follow-up was done in February 2017. The main pre-enrolment exclusion was inability to contact using the phone number provided. All participants stated that they wished to quit cocaine use.

Of the 35 participants enrolled, 30 completed the three CUD conceptualisation assessments and were randomised. 14 were allocated to the control group and 16 to the intervention group. All participants accepted this assignment.

The control and intervention groups were well balanced on demographic, clinical and treatment characteristics with the exception of the months of enrolment in CUD TAU before study enrolment (Table 1). The overall mean age was 44·1 years (SD 6·6) and 20 were male (66·7%). The median time in TAU at enrolment was 7·0 months (IQR 1·5–36·0). Cocaine had been regularly used for a median of 96 months (IQR 60·0–123·0). No participant had a DSM5 CUD diagnosis of less than moderate severity, and 23 had severe CUD.

Most participants reported crack cocaine use in the month before enrolment (27 of 30). Three exclusively used cocaine powder. 20 of 30 had concurrent OUD and all of this group were stabilised on oral opioid agonist therapy.

The overall sample mean on the CEQ-F at baseline was 62·7 (SD 20·2). The CEQ-F had good internal reliability (Cronbach's alpha 0·83). Overall, the PDA and LPA in the preceding 28 days was 45·7% (SD 21·9) and 3·9 days (SD 4·6), respectively, reflecting the intermittent nature of cocaine use which is typical in this population.

3.2. Protocol Adherence

At the 1-week follow-up, we interviewed 27 of 30 participants. Two intervention participants were unavailable due to family visits; one control participant was unwell. For the 1-month follow-up (endpoint), we interviewed all 30 participants. This follow-up was done after 39·9 days (SD 8·1) in the control group and 39·6 days (SD 8·0) in the intervention group. All participants were enrolled in TAU.

At the 3-month follow-up we interviewed 28 of 30 participants. At this point, two control participants and one intervention participant had been discharged from TAU. We failed to follow-up one participant from each group (both had been discharged well before three months).

After the 1-month follow-up, we lost contact with two intervention participants for many weeks. However, towards the close of fieldwork, we successfully resumed contact and completed follow-up. Both interviews were done 12 months post-randomisation. With these two outlying times removed, the mean time in the study was 151·0 days (SD 37·81) with no evidence of a difference between the groups (151·93 days [SD 32·96] in the control group and 150·07 days [SD 43·40] in the intervention group).

The median number of TAU sessions attended in the control and intervention groups was four (IQR 1–6) and three (IQR 2–6), respectively. We planned for the CUD conceptualisations to commence in the week post-enrolment and be completed within two weeks. The majority did; however, nine participants attended their first session between 11 and 26 days, and seven completed their assessments in 21 days.

3.2.1. Treatment Fidelity

All participants, bar one member of the control group, gave consent for session audio/video recording. For the therapist evaluation, eight sessions with different participants were randomly selected (four audio recordings of assessments and four video recordings of MFCT sessions). All items on the assessment and therapy versions of the CTS-R were rated as competent (i.e. scored 3 or greater). The median total
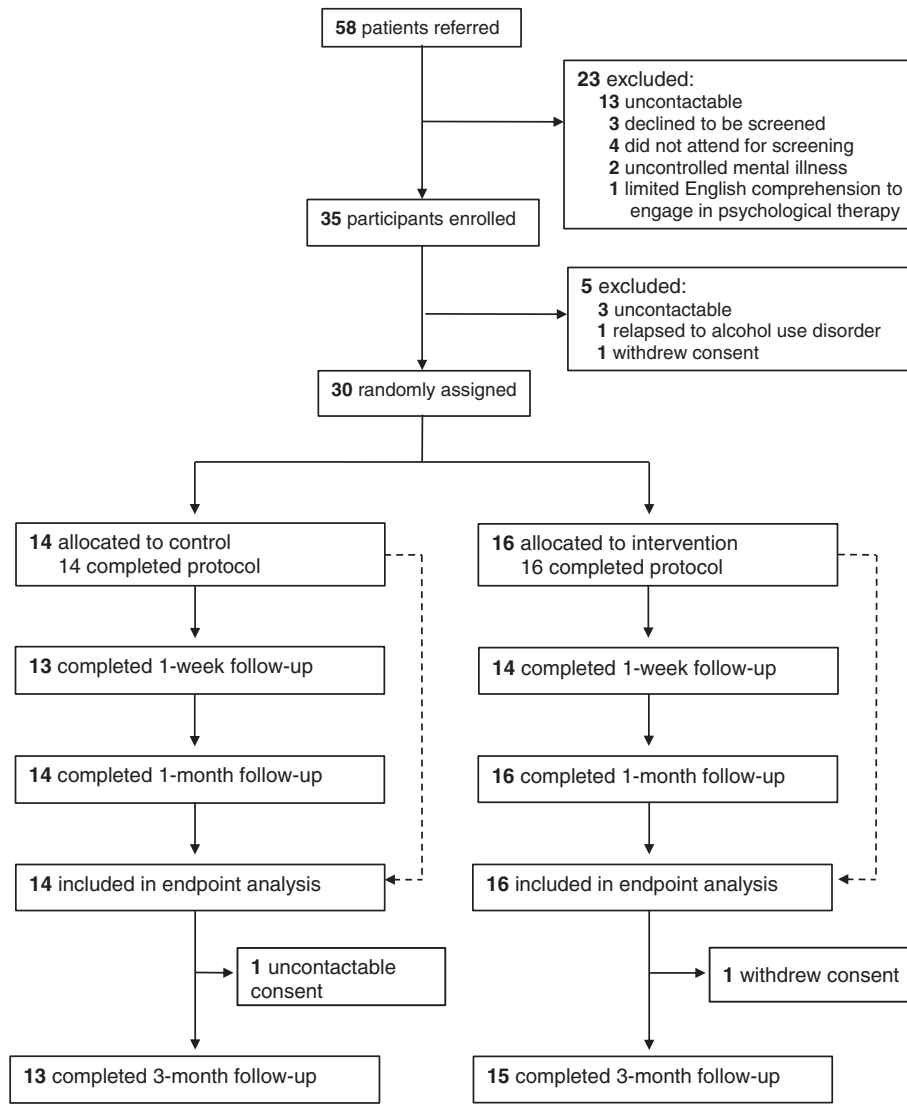
Fig. 1. Trial profile.

score across for the assessment and therapy tapes was 4·5 (IQR 4·5, 4·5) and 4·5 (IQR 3·4, 4·5), respectively.

3.2.2. Cue-Induction Safety Assessment

All participants completed their two cue-inductions as scheduled. On their first visit, one control group member needed a second alcohol breath test before proceeding. One intervention participant was above the breathalyser limit on arrival; but after a second test, they were able to complete the session. All other breath tests were zero. 14 of 16 (87·5%). Two control participants (14·3%) and one intervention participant (6·3%) reported a CEQ-S change score which was above the MDC. Both controls remained enrolled in TAU and were UDS-positive for cocaine at the 1-week follow-up. At 1-month, one reported daily use (this was unchanged from enrolment); the other reported using cocaine on 15 of the past 28 days (one day less than for the 28 days prior to enrolment). We were unable to conduct a UDS procedure at 1-week follow-up for the intervention participant; but they reported abstinence for the 28 days prior to the 1-month follow-up (UDS negative).

3.2.3. Treatment Sessions

Intervention group members attended all five daily MFCT sessions (one missed session two; another missed session four). All participants received cocaine memory reconsolidation, with an average of 6·1

procedures per person (SD 2·3; range 1–9), lasting 12·2 min (SD 2·4) each. Table S1 lists the day-by-day MFCT procedures received by each participant in the intervention group.

3.3. Primary and Secondary Outcomes

For the primary outcome (Table 2), the percentage score on the CEQ-F at 1-month follow-up was 14·77 (21·47) for the intervention group and 51·75 (SD 22·72) for the control group (mean difference −36·98; 95% CI −53·51 to −20·45). For the secondary outcomes at the endpoint (Table 2), the intervention group reported significantly more days abstinent from cocaine (PDA mean difference 31·35; 90% CI 12·70 to 49·99), and longer maximum continuous abstinence (LPA mean difference 9·69 days; 90% CI 2·99 to 16·39).

We screened months of regular cocaine use (at the median of 96 months); oral/injecting cocaine administration; heroin use and enrolment in OST for a group difference. Increased months of cocaine use only was associated with a higher CEQ-F (41·55; SD 33·19 versus 19·58; SD 14·86; ES 0·79; 80% CI 8·96 to 34·98; less PDA (63·03; SD 33·09 versus 82·14; SD 19·23; ES -0·66; 80% CI -1·15 to −0·18; but not less LPA (9·71; SD 9·63 versus 13·08; SD 10·68; ES -0·32; 80% CI -8·25 to 1·51). Months of regular use and months of CUD TAU at

Table 1
Baseline characteristics (n = 30).

	Intervention (n = 16)	Control (n = 14)
Patient characteristics		
Male	11 (69%)	9 (64%)
Age, years	43·3 (6·7)	45·0 (6·5)
White British/White Other	11 (69%)	8 (57%)
Black British/Black Other/Mixed	5 (31%)	6 (43%)
DSM5 CUD diagnosis (severity)		
Mild (2–3 symptoms)	0	0
Moderate (4–5 symptoms)	3 (19%)	4 (29%)
Severe (6–11 symptoms)	13 (81%)	10 (71%)
Drug use in past 28 days		
Crack cocaine	15 (94%)	12 (86%)
Smoking	13 (81%)	11 (79%)
Injecting	2 (13%)	1 (7%)
Powder cocaine[a]	1 (6%)	2 (14%)
Heroin use in past 28 days:	9 (56%)	6 (43%)
Smoking	5 of 9 (56%)	3 of 6 (50%)
Injecting	4 of 9 (44%)	3 of 6 (50%)
Treatment characteristics		
Months of regular cocaine use at admission to treatment	94·50 (60·0, 120·0)	108·00 (69·0, 150·0)
Months enrolled in CUD TAU at study enrolment	8·5 (2·5, 53·5)	5·0 (1·0, 25·50)
Current enrolment in opioid agonist therapy[b]		
Methadone (mg/day)	6 (61·7)	5 (55·0)
Buprenorphine, or buprenorphine and naloxone (mg/day)	5 (14·4)	4 (13·0)
Prescribed anti-depressant medication	5 (31·3)	4 (28·6)
Prescribed anxiolytic/sedative medication	1 (6·25)	2 (14·3)
Baseline score on outcome measures		
CEQ-F (primary)	58·5 (22·4)	67·5 (17·0)
PDA (secondary)	45·09 (16·64)	46·43 (27·98)
LPA (secondary)	3·06 (3·17)	4.79 (5·85)

Data are number of participants, mean (SD) or median (IQR).
TAU = treatment as usual; CUD = cocaine use disorder; CEQ-F=Craving Experiences Questionnaire (frequency version); recall period: past 2 weeks (total score, range: 0–100); PDA = percentage days abstinent (PDA) from cocaine in past 28 days; LPA = longest period (days) of continuous abstinence from cocaine in past 28 days.
[a] Oral use only.
[b] One patient in the experimental group enrolled in diamorphine maintenance therapy.

enrolment were also included (the latter given imbalance between the intervention and control (8.5 versus 5.0 months, respectively).

There was a significant association in favour of the intervention (emboldened section of Table 3: CEQ-F [p-value 0·002]); PDA [p-value 0·000]; LPA [p-value 0·000]). For the sensitivity check on unmeasured confounding, the E-value for the analysis of the primary outcome was 2·30 (and 1·00 for the estimate of uncertainty). The E-value (and its uncertainty) for the PDA and LPA secondary outcome measures was 1·57 (1·57) and 1·26 (1·64), respectively, showing that relatively

weak unmeasured confounding would be needed to overturn the observed adjusted association between intervention and outcome with the present data.

3.4. Exploratory Outcomes

With the 3-month follow-up interview missing for one member of the intervention group and one member of the control group, we observed support for the assumption of 'missingness completely at random' (*mcartest* chi-square 11·02; p-value > 0.999), and generated missing outcome values by multiple imputation using the following auxiliary variables: sex, age, route of cocaine administration, months of regular cocaine use and group.

Table 4 shows the imputed and the complete case results for the CEQ-F, PDA and LPA measures at the 3-month follow-up (n = 30). There was evidence for lower craving experience (CEQ-F ES −0·67; 80% CI −33·19 to −5·94) and cocaine use (PDA ES 0·38; 80% CI 0·30 to 1·28; LPA ES 0·70; 80% CI 0·22 to 1·18) in favour of the intervention. The results for the complete case analysis were comparable to the imputed results.

Table 5 shows the negative cocaine UDS results during follow-up. There were more UDS-negatives in the intervention group at 1-week follow-up (RR 5·00; 80% CI 1·34 to 18·67) and the two-case missing imputed results for the 1-month follow-up (RR 6·13; 80% CI 1·69 to 22·19). At the 1-month follow-up, there was complete agreement between UDS results and self-report. Among seven intervention participants with a negative UDS, six reported complete abstinence and one reported using cocaine on five days in the previous 28 days (but abstinence in previous week). The control participant with a negative UDS had a PDA score of 96·43. The trial groups did not differ on the UDS outcome at 3-month follow-up (80% CI 0·81 to 3·80).

Table 6 shows DSM5 status at 3-month follow-up. Two of 14 control participants and 10 of 16 intervention participants were classified as in early CUD remission, respectively (NNT 2; 80% CI 1 to 4). No participants had worsened CUD at this point.

3.5. Adverse Events

We recorded six adverse events: four serious and two non-serious (Table 7). Among the three participants who experienced serious adverse events, no event was judged related to study interventions. One control group participant attended the CRF with injection site bleeding. Several weeks after completing the 1-month follow-up, an intervention group participant was hospitalised after self-harming. At that point, they were positive about the study and continuing in follow-up, and did not believe hospitalisation was related to MFCT. However, they withdrew their consent when contacted for the 3-month follow-up.

Table 2
Group mean score and analysis of primary and secondary outcomes at study 1-month (endpoint; n = 30).

Group score/analysis	Primary outcome	Secondary outcomes	
	CEQ-F	Cocaine PDA	Cocaine LPA
Intervention (n = 16)	14·77 (21·47)	85·94 (18·96)	15·69 (10·10)
Control (n = 14)	51·75 (22·72)	54·59 (30·29)	6·00 (7·34)
Group difference	−36·98 (−53·51 to −20·45)[a]	31·35 (12·70 to 49·99)[b]	9·69 (2·99 to 16·39)[b]
Hedge's g (CI)	−1·62 (−0·80 to −2·45)[a]	1·19 (0·54 to 1·84)[b]	1·06 (0·41 to 1·70)[b]
Bayes factor[c]	259·85	6·59	11·53
Cohen's U₃[d]	14 of 16 (87·5%)	14 of 16 (87·5%)	14 of 16 (87·5%)

CEQ-F, Craving Experiences Questionnaire (frequency version; percentage score; recall period: <2 weeks; PDA, percent days abstinent (SD) from cocaine (recall: past 28 days); LPA, mean longest period (days) of continuous abstinence (SD) from cocaine (recall: past 28 days); CI, confidence interval.
[a] 95% confidence interval.
[b] 90% confidence interval.
[c] Using prior standardised ES from meta-analysis (0·31 (Köpetz et al., 2013)) equivalent to a 30% difference in scores on the CEQ-F; a 17% difference in scores on the PDA measure, and a difference of three days on the cocaine LPA measure in the context of the present study, all in favour of the intervention.
[d] Number of participants in the experimental group with change from baseline to 1-month that is greater than the median change in the control group (using the pooled SD).

Table 3
Multivariable (baseline adjusted) model of primary and secondary outcomes at 1-month follow-up (endpoint; n = 30).

Model/baseline covariate	CEQ-F[†]				
	Coef.	95% CI	SE	z-Score	p-Value
Sex	−0·707	−18·014, 16·600	8·366	−0·01	0·933
Age	0·316	−0·979, 1·611	0·626	0·07	0·619
Months in TAU	−11·34	−27·796, 5·118	7·955	−0·20	0.167
Months regular cocaine use	15·25	−1·387, 31·887	8·042	0·27	0·071
Baseline CEQ-F score	0·326	−0·101, 0·753	0·206	0·23	0·128
Group*	−28·249	−45·151, −11·348	8·170	−0·50	0·002

PDA[‡]					
Model/baseline covariate	IRR	95% CI	SE	z-Score	p-Value
Sex	1·049	0·871, 1·264	0·100	0·51	0·613
Age	0·990	0·978, 1·003	0·006	−1·52	0·127
Months in TAU	1·010	−0·850, 1·201	0·089	0·12	0·908
Months regular cocaine use	0·931	0·777, 1·116	0·086	−0·77	0·442
Baseline PDA score	1·030	1·014·, 1·047	0·008	3·62	0.000
Group*	1·567	1·307, 1·878	0·145	4·86	0·000

LPA[¶]					
Model/baseline covariate	IRR	95% CI	SE	z-Score	p-Value
Sex	1·147	0·901, 1·459	0·141	1·11	0·266
Age	0·972	0·955, 0·988	0·008	−3·35	0·001
Months in TAU	0·915	0·727, 1·151	0·107	−0·76	0·449
Months regular cocaine use	0·895	0·712, 1·125	0·105	−0·95	0·342
Baseline LPA score	1·019	0·993, 1·045	0·013	0·35	0·153
Group*	2·563	1·962, 3·349	0.350	7·48	0·000

CEQ-F, Craving Experienced Questionnaire, frequency version (primary outcome); TAU, Cocaine-use-disorder treatment-as-usual before study enrolment; PDA, percentage days abstinent from cocaine, past 28 days (secondary outcome); LPA, longest period of continuous days abstinent from cocaine, past 28 days (secondary outcome); Coef., beta coefficient; CI, confidence interval; IRR, incident rate ratio; SE, standard error (bootstrapped with 5000 replications); Significant intervention effect emboldened.

[†] F(6,23) 5.68; p = 0·0010; Adjusted R^2 0·492.
[‡] LR X^2 (United Nations Office on Drugs and Crime, 2016) 55·78; p = 0·000; Pseudo R^2 = 0·204.
[¶] LR X^2 (United Nations Office on Drugs and Crime, 2016) 86.85; p = 0·000; Pseudo R^2 = 0·226.
* Coded (0, control; 1, intervention).

Table 5
Urine drug screen results for cocaine at 1-week, 1-month and 3-month follow-up.

Follow-up	Intervention		Control		
	Negative[a]	n	Negative[a]	n	Relative risk
1-week	5	14	1	14	5·00 (1·34 to 18·67)
1-month	7	16	1	14	6·13 (1·69 to 22·19)
3-month[b]	6	16	3	14	1·75 (0·81 to 3·80)

RR, relative risk (80% confidence interval).
[a] Negative for cocaine metabolite.
[b] Two participants with missing outcome data imputed as UDS positive (as 1-month).

For the two non-serious adverse events: one participant received antibiotic treatment from their family doctor for a bacterial infection. The other participant fell asleep in a public place and woke to find property stolen. We judged that this event was probably related to the study intervention due to hypersomnia in the first week of cocaine abstinence.

4. Discussion

In this first external pilot randomised controlled trial of MFCT for CUD, we were able to recruit participants to our expected rate per week, and tested three feasibility hypotheses (H1–H3). There was no attrition at the 1-month endpoint and this interview was done in a timely manner. At 3-month follow-up we were able to interview 28 of 30 participants, although two follow-ups were substantially delayed. Assessments and intervention sessions were also independently rated to a good clinical standard by CTS-R.

For the safety check on cocaine cue-inductions, two control participants and one intervention participant reported increased craving. However, they did not drop out of TAU and their cocaine use was unaltered from baseline. The intervention participant remained enrolled in the clinic's TAU, reported complete abstinence at the endpoint, and had a negative UDS. These findings suggest that CUD patients who are receiving TAU in NHS clinics will accept randomisation; safely accept cue-induction, and have a very good likelihood of follow-up retention to complete research measures.

To inform the case for progression to a substantive RCT, we tested two preliminary efficacy hypotheses (H4–H5). At the endpoint, the group difference was −36·98 percentage points on the CEQ-F (ES -1·62); with a Bayes Factor in support of the intervention (>3), and 14 of 16 intervention participants achieving craving reductions greater than the median of the control group (U_3). MFCT

Table 4
Exploratory analysis of outcomes at 3-month follow-up, with multiply imputed and complete case data.

Group score/estimate	CEQ-F	PDA	LPA
Multiply imputed (n = 30)			
Intervention (n = 16)	24·98 (27·78)	77·07 (27·50)	13·13 (10·85)
Control (n = 14)	44·55 (29·04)	51·55 (35·34)	5·79 (9·96)
Group difference (80% CI)	−19·57 (−33·19 to −5·94)	25·52 (10·44 to 40·59)	7·34 (2·32 to 12·36)
Hedge's g (80% CI)	−0·67 (−1·15 to −0·19)	0·79 (0·30 to 1·28)	0·70 (0·22 to 1·18)
Bayes Factor[a]	4·21	3·41	17·45
Cohen's U_3[b]	14 of 16 (87·50%)	14 of 16 (87·50%)	13 of 16 (81·25%)
Complete case (n = 28)			
Intervention (n = 15)	24·91 (28·75)	78·10 (28·15)	13·60 (11·06)
Control (n = 13)	42·66 (29·31)	52·75 (36·48)	6·15 (10·26)
Group difference (80% CI)	−17·75 (−40·35 to −4·85)	25·35 (0·22 to 50·48)	7·45 (0·87 to 15·78)
Hedge's g (80% CI)	−0·59 (−1·09 to −0·10)	0·75 (0·25 to 1·25)	0·65 (0·16 to 1·15)
Bayes Factor[a]	7·56	10·53	55·96
Cohen's U_3[b]	10 of 15 (66·67%)	11 of 15 (73·33%)	11 of 15 (73·33%)

CEQ-F, Craving Experiences Questionnaire (frequency version; percentage score; recall period: <2 weeks; PDA, percent days abstinent (SD) from cocaine (recall: past 28 days); LPA, mean longest period (days) of continuous abstinence (SD) from cocaine (recall: past 28 days); CI, confidence interval.
[a] Using prior standardised ES from meta-analysis [0·31 (Volkow et al., 2013)) equivalent to a 10% difference in scores on the CEQ-F and cocaine PDA measures, and a difference of three days on the cocaine LPA measure in the context of the present study, all in favour of the intervention.
[b] Number of participants in the experimental group with change from baseline to 3-month (pooled SD) that is greater than the median of the control group.

Table 6

DSM5 CUD status at 3-month follow-up.

	Intervention (n = 16)	Control (n = 14)
Status/number of symptoms[a]		
Early Remission (0 or 1)	10	2
Mild CUD (2–3)	1	0
Moderate CUD (4–5)	3	3
Severe CUD (6–10)	2	9

CUD, cocaine use disorder.

One member of intervention group missing follow-up imputed with one symptom and one member of control group imputed with seven symptoms (both same as baseline).

[a] Does not include DSM5 caving item.

was also positively associated with improvements on the secondary outcomes (PDA ES 1·19; LPA ES 1·06); both were significant at the set 10% error level, and were supported by Bayes Factors (>3); U_3 (14 of 16 intervention participants above the control group median change). We also showed a statistically significant adjusted MFCT-craving and drug use outcome association in our exploratory multivariable regression. Perhaps unsurprisingly, given the small sample here and inclusion of five covariates, our sensitivity check showed that relatively weak unmeasured confounding could overturn the exposure-outcome association.

On the exploratory outcomes, there were statistically significant effect sizes for MFCT on reduced craving and increased abstinence (each Bayes Factor > 3·0). We also observed more cocaine negative UDS results (with almost complete agreement with self-report) at the three follow-ups (although the data were insensitive at 3-month follow-up). At the final follow-up, 10 of 16 intervention participants were judged to be in early CUD remission compared to two of 14 control participants (NNT 2).

4.1. Strengths and Limitations

Study strengths include the pre-registered research questions and analysis plan for transparent progression evaluation. A strength of the study was the broad eligibility criteria which generalise to community NHS settings and the inclusion of patient with primary CUD as well CUD and co-occurring OUD. Previous studies have observed that this clinical population are less likely to respond to, or successfully complete, OUD treatment (Marsden et al., 2012; Eastwood et al., 2016). In the present study, baseline heroin use or enrolment in OST did not moderate CUD outcome, suggesting a relatively stable clinical platform to address cocaine addiction.

Our findings must be considered in the light of several limitations. Firstly, the sample size was small, but it was in-line with recommendations for pilot studies and was pre-determined. Naturally, the preliminary and exploratory nature of the study cannot be over-emphasized.

Table 7

Relation of adverse events to study.

	Control group (n = 14)	Intervention group (n = 16)
Serious adverse event		
Definitively related study	–	–
Probably related	–	–
Unlikely to be related	1	2[a]
Unrelated	–	1
Non-serious adverse event		
Definitively related to study	–	–
Probably related	–	1
Unlikely to be related	–	–
Unrelated	–	1

Data are number of adverse events during the study.

[a] The same participant.

Second, our findings relate to treatment programmes with psychologists who are CBT trained and supervised. CUD is a complex disorder and our view is that an effective psychosocial intervention requires this level of clinical expertise. The UK and many treatment systems has very limited CBT therapist capacity and this issue will need to be addressed if MFCT is found to be effective after further research.

Third, resources precluded blinded outcome assessment and a TAU-only arm and we devoted available resources for this pilot to assessing the safety of the cue-induction process and did not balance the control group for time exposed to study procedures (each control participant had 9 h of contact versus 18·5 h for intervention participants). We acknowledge that this extra contact time could have contributed to the intervention effect. Balancing intervention exposure time is not always done in the literature. In our review of 14 CBT trials for CUD, six studies did not include a time-balanced control. Nevertheless, for a future trial, we judge it important to include a time-balanced control (e.g. guided relaxation, attention placebo, or credible alternative).

Fourth, at this stage our MFCT has not been designed for co-occurring CUD and PTSD. PTSD is a common co-occurrence among the NHS addiction treatment population with a prevalence of 26–52% (Roberts et al., 2015)). These patients are likely to need a specific intervention (Najavits et al., 2007). A trial of prolonged exposure therapy to treat PTSD and polysubstance problems (including cocaine) reported significant improvement in PTSD symptoms, but not in cocaine use (Mills et al., 2012). Further work is therefore needed to explore concurrent or sequential treatment of this patient group.

Fifth, the potential for bias due to our allegiance to the MFCT intervention should also be taken into account. The researcher allegiance effect (i.e. the belief in an intervention's superiority (Leykin & DeRubeis, 2009)) is a well-known concern for developmental studies in psychotherapy. In our study, we brought a level of enthusiasm and commitment to research tasks which might not be shared by others in a future multi-centre trial.

4.2. Possible Mechanisms

While it would be premature to discuss cognitive-behavioural change mechanisms with pilot data, we observed a very encouraging clinical response for the majority of intervention participants. The majority of our participants readily engaged in therapeutic procedures to elicit and reconsolidate cocaine memories. During informal reflections after completion of MFCT, several participants said that the therapy had helped them be much more aware and of situations and also 'slow down' and reflect on encountered craving episodes - noticing elaborated images, emotions and beliefs and using coping response (e.g. checking the evidence for a thought; bringing to mind a positive or negative sensory image as an alternative; self-reassurance; checking intensity of wanting and how this might reduce if attention is shifted).

At this stage, and with the primary and secondary outcomes recorded at the same endpoint, we have not investigated whether there is a causal relationship between craving and subsequent cocaine use. We will now conduct an exploratory, confounder-adjusted, causal mediation analysis (Stata command: *paramed*). With the 1-month CEQ-F positioned theoretically and temporally as a mediator of 3-month cocaine use, we will investigate the natural direct effect and the indirect effect of treatment through craving reduction.

4.3. Implications for Future Research on MFCT

Looking forwards, we judge that the primary outcome of a substantive clinical effectiveness and cost-effectiveness trial should be cocaine use, with UDS as part of the validation procedure. Efforts to help patients reduce the intensity and intrusiveness of craving remain an important intermediate target, but reducing or quitting cocaine use is the most clinically important recovery indicator.

Meaningful reductions in cocaine use could be explored through further patient and public discussion. For example (for alcohol dependence), the European Medicines Agency recommends reporting the number of participants who achieve a 50%, 70% and 90% sustained reduction in alcohol consumption (European Medicines Agency, 2010).

While it is not possible to record the quantity of cocaine consumed with any accuracy (Fischer et al., 2015), a response measure based on an increase in abstinent days to a pre-set level, or a cut-off associated with the maximal treatment effect is straightforward (Falk et al., 2014). We also judge that 3-months is the appropriate primary end-point, and it will probably be important to include time to follow-up in an adjusted analysis model.

CUD is a prevalent and significant public health problem. Meta-analysis has shown that CUD is hard to treat, with very limited treatment options available to clinicians. Our study is a first required step towards securing effectiveness evidence for a new, adjunctive psychological intervention. With positive findings from the present study, we believe there is a strong case to progress to an appropriately powered, RCT to determine the effectiveness of MFCT.

Contributors

J.M. developed the concept in collaboration with C.G., T.M., L.M., J.S. and N.G. TMG members were: J.M., G.S., C.G., T.M., L.M. and N.G. The statistical analysis plan was developed by J.M., C.G. and B.E. (statistician). J.M. led the drafting of the manuscript with C.G. and with input from all authors. All authors read and approved the final version before submission for publication.

Declaration of Interests

The authors declare that they have no financial investment or relationship with any organisation that could inappropriately influence or benefit this research. 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 for the US National Institute on Drug Abuse, Centre for Clinical Trials Network. In the past 3 years, 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. L.M. declares grant funding for an investigator-led, educational grant from Indivior (administered by Action-on-Addiction) for the ARC Trial. He holds no stocks in any company.

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J.S. is a researcher and clinician who has worked with a range of types of treatment and rehabilitation service-providers. He is supported by the NIHR BRC for Mental Health at SLaM and KCL. He has also worked with a range of governmental and non-governmental organisations, 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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ebiom.2018.01.039.

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