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D-Cycloserine combined with cue exposure therapy fails to attenuate subjective and physiological craving in cocaine dependence

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Abstract

Background—Based on preclinical studies showing that the partial *N*-methyl-D-aspartate (NMDA) agonist D-cycloserine (DCS) facilitates extinction of cocaine self-administration and cocaine-induced conditioned place preference, we evaluated whether 50 mg of DCS would reduce craving to cocaine cues when combined with cue exposure (CE) in cocaine dependent humans.

Methods—In this double-blind placebo-controlled pilot study, 47 cocaine dependent participants were randomized to DCS or placebo (PBO), plus CE. Participants received DCS or PBO 30 minutes prior to two CE sessions, conducted one day apart. Craving and heart rate was assessed prior to CE sessions, during CE trials, and after CE trials. These measures were assessed again at a 1-week follow-up (session 3) after the second CE session.

Results—DCS failed to significantly attenuate cocaine cue reactivity based on subjective craving and physiological reactivity (heart rate) compared to PBO. The CE protocol, consisting of repeated exposure to drug cues combined with skills training, resulted in extinction to cocaine cues as suggested by decreased craving within and between sessions in both treatment conditions. All participants exhibited elevated heart rate with repeated exposures, demonstrating a potentiation in heart rate between sessions.

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Contributors: Drs. Brady, Saladin, McRae-Clark, Prisciandaro, and Santa Ana designed the study and wrote the protocol. Drs. Brady, Saladin, Santa Ana, and Prisciandaro managed the literature searches and summaries of previous related work. Drs. Nietert, Prisciandaro and Ms. Shaftman undertook the statistical analysis, and Dr. Santa Ana wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

FINANCIAL DISCLOSURES

The authors have no biomedical financial interests or potential conflicts of interest.

Keywords

cocaine; craving; cue exposure therapy; reconsolidation; D-cycloserine

Conclusions

50 mg of DCS may not be effective for extinguishing reactivity to drug cues for individuals with cocaine dependence.

Scientific Significance

Future studies examining the effect of DCS on facilitating extinction to drug cues should examine variations in cue exposure length, number of CE presentations, and timing of DCS dose administration prior to cue exposures, which may differentially impact drug cue reactivity.

INTRODUCTION

Characterized by periods of abstinence interspersed with episodes of drug use, cocaine (COC) dependence is a chronic relapsing disorder that is difficult to treat.¹ Conditioned responses to drug cues (e.g., drug paraphernalia) develop as a result of repeated pairings between stimuli and COC and have been found to play a critical role in eliciting craving,² drug-seeking behavior, and relapse.^{3,4}

One therapeutic approach to reducing reactivity to drug cues consists of repeated exposure to drug-related cues in the absence of the drug,⁵ which is presumed to attenuate cue-elicited responses via the gradual development of the inhibitory learning process of extinction.^{6,7} Pre-clinical investigations have shown that administration of D-cycloserine (DCS), a partial glutamate *N*-methyl-D-aspartate (NMDA) receptor agonist,⁸ enhances the learning that occurs during extinction training for appetitive-conditioned cues. Specifically, studies in rodents demonstrated a facilitative effect of DCS on extinction of cocaine-induced conditioned place preference⁹ and COC self-administration.^{10,11} The facilitative effect of DCS on extinction has been revealed through its ability to retard the reacquisition of COC self-administration following DCS-treated extinction training.^{12–13} These studies suggest the possibility that DCS may enhance the treatment potential of exposure-based therapy in humans with addictive disorders.

Despite promising outcomes in animal models, clinical studies investigating the effect of DCS on addictions-related exposure therapy are mixed. A double-blind, placebo-controlled pilot laboratory study in individuals with nicotine dependence showed that DCS combined with cue exposure plus skills training significantly attenuated within session craving and cue reactivity (skin conductance responses) to in-vivo smoking cues.¹⁴ In contrast, other studies have shown DCS to increase cue-induced craving in COC dependence,^{15–16} suggesting that DCS may augment reconsolidation of memories reactivated by COC cue presentations. In studies showing elevated COC craving in response to DCS, COC presentations were brief and participants were not instructed to employ skills designed to reduce craving in the presence of cues. Practice of such skills may serve to counteract the effects of DCS on

reconsolidation of cue-elicited memories while at the same time permitting DCS to enhance learning of strategies for managing the response to COC cues. Aside from its enhancement on exposure-based psychotherapies, such as acceleration of obsession-related distress reduction in patients with obsessive-compulsive disorder¹⁷, DCS has been shown to facilitate declarative learning with regard to enhancing rate of encoding of object-location associations (memorization of colored photographs),¹⁸ suggesting that DCS may have some potential for enhancing interventions involving skills acquisition. Thus, aside from conditioned cue effects, reactivity to drug cues may be influenced by cognitive mechanisms that impact the magnitude of response.¹⁹ Given this influence, teaching participants ways to counteract their experience with drug cues using cognitive strategies may reduce craving.²⁰

Thus, we sought to evaluate the combination of drug cue exposure and coping skills training for reducing craving in the presence of COC drug cues. In the current investigation, cocaine-dependent participants were randomized to receive either DCS or placebo (PBO) administered prior to extinction trials on two days of COC cue exposure sessions. Extinction procedures involved exposure to drug-cues plus skills training (e.g., cognitive skills designed to reduce reactivity to COC cues), referred to as cue exposure (CE). We hypothesized that the administration of DCS + CE would lead to a significant decrease in both drug craving and physiologic arousal (i.e., heart rate), both complementary and commonly assessed measures of reactivity to drug cues.

METHODS

Participants

Forty-seven men and women aged 18–65 who met Diagnostic and Statistical Manual of Mental Disorders²¹ criteria for COC dependence within the past three months and indicated COC as their drug of choice were recruited through media advertisements in the community and local substance abuse treatment clinics. Exclusion criteria included significant medical and psychiatric conditions. With exception to COC, nicotine, alcohol, and marijuana (due to the high comorbidity of these substances with COC), participants meeting current DSM-IV substance dependence were excluded from the study. Participants taking selective serotonin reuptake inhibitors were not excluded. A total of 45 individuals, who did not meet study eligibility, were excluded.

Materials

Descriptive and Demographic Assessment—The Mini-International Neuropsychiatric Interview²² was used to assess exclusionary psychiatric diagnoses. Demographics including age, race, gender, education, marital status, employment, smoking status and COC use history (e.g., years of use) were assessed using an in-house questionnaire.

Substance Use Assessment—Substance use disorders (SUD) were assessed using the SUD module of the Structured Clinical Interview for DSM-IV.²³ Quantitative COC and other substance use data for the past 90 days were assessed using a modified Time-Line Follow-Back (TLFB) method.²⁴

Subjective Craving Assessment—Subjective ratings evaluating the craving domain ‘do you crave cocaine?’ were assessed at 12 time points (twice at baseline, during each CE trial, once after CE trials and twice after completion of CE trials) using a modification of the Within-Session Rating Scale²⁵, a visual analog scale (from ‘0’ = “not at all” - ‘10’ = “extremely”) of subjective desire to use COC.

Heart rate assessment—Using a MP100 Biopac system and following manualized data collection guidelines (Biopac Systems, Inc., Goleta, CA), heart rate was collected for a 5-minute period twice at baseline and while handling drug cues during each of the CE trials via two electrodes placed on the participant’s right clavicle and along the bottom of the ribcage or inside the ankle. Craving and heart rate measures were repeated at session 3. Movement during CET trials was filtered as artifact and removed by trained research staff so that heart rate data was free of movement artifact.

COC Cues—COC cues consisted of a small bag of simulated crack cocaine, the subject’s preferred style of crack pipe, a lighter, and money (\$20 bill) for those who use crack cocaine. For powder or IV users, simulated cocaine, COC paraphernalia, and money were used. Simulated crack COC was prepared using a mixture of benzocaine, baking powder, water, and small amount of vanilla extract (to add slight brownish-yellow color). The odorless paste was then dried and broken into pieces.

Study Procedures—The study was approved by the Institutional Review Board of the Medical University of South Carolina and participants were compensated for participation. Following a phone or in-person screening, participants were scheduled with a screening visit where they were consented, received diagnostic assessments, and a medical history and physical exam were performed. During the screening visit, qualified participants were asked to think of a time when they craved COC and ended up using as well as a negative event surrounding COC use for inclusion in CE procedures (described below). Details surrounding the events were recorded and used to construct personalized imagery scripts.²⁶

Two outpatient CE sessions were scheduled, separated by one day, and were provided within the same week (typically Monday/Wednesday). Participants were required to maintain at least 72 hours of abstinence from cocaine, alcohol, and all other drugs of abuse prior to all CE sessions (sessions 1 through 3) based on breathalyzer, confirmatory urine drug screens (UDS), and self-report in order to minimize the impact of recent drug/alcohol use on cue reactivity. Given the prolonged detection time of marijuana in urine, participants were allowed to have a positive UDS for marijuana. Participants did not smoke cigarettes during CE sessions and were given the option to receive a nicotine patch to minimize nicotine withdrawal during CE sessions. Baseline assessments including subjective craving (at which time no cues were presented) and heart rate were administered during CE sessions and measured on two occasions, 15 minutes apart, prior to administration of the CE trials. Approximately 30 minutes prior to the first CE trial, participants were randomly assigned to receive either 50mg of DCS or matched placebo (see DCS administration below). Gender and age were used as stratification variables to ensure balance between the treatment conditions. Participants received the same medication before each of the two CE sessions. Medication was compounded and packaged by the Investigational Drug Services (IDS) at

the Medical University of South Carolina in identical capsules. Both study personnel and participants were blind to group assignment. Participants returned for a 1-week follow-up visit, hereafter referred to as ‘session 3’, within 5 to 12 days following the second CE session at which time they received the same CE procedures and completed assessments. A placebo capsule was given prior to session 3 CE trials to all participants so as to replicate the previous procedures without the confounding of DCS dosage, as the purpose of session 3 was to explore the durability of DCS facilitation of extinction.

Cue-Exposure Procedures—Participants in the COC and PBO groups were administered a manualized CE protocol (manual available upon request) developed for the study²⁷ during each of the two CE sessions, providing a series of four cognitive behavioral skills training interventions adapted from available sources^{28,29} (i.e., guided imagery, urge surfing, coping with automatic thoughts to use COC, and methods to distract oneself from using COC). While seated in a comfortable chair, participants listened to the four automated audio recorded coping skills interventions delivered in a graduated fashion similar to Monti et al.³⁰, with each skill being presented separately at approximately 20 minute intervals over noise-cancelling headphones. After approximately 10 minutes for learning each skill, participants were requested to apply each specific skill to manage their craving in the presence of COC cues during CE trials. The COC cues were placed on a table directly in front of the participant who was asked to inspect and handle the COC cues for 5 minutes while listening to audio recorded instructions to rehearse and practice the specific coping skill strategy that was presented immediately prior to COC cue presentation. Subjective craving and heart rate was recorded during CE trials. After heart rate assessment was initiated, participants used one hand for handling COC cues and for circling their craving rating on paper while they remained motionless in other areas of the body during the physiological assessment. Each complete CE study session lasted approximately 167 minutes in length. Table 2 presents the timeline and flow of CE session activities for sessions 1 through 3.

DCS Administration—Participants were randomly assigned to one of two treatment groups: 50 mg DCS or PBO administered prior to each of the two CE trials. The 50 mg dose of DCS was chosen based on previous laboratory work demonstrating this dose as effective in enhancing attenuation of physiologic and subjective response in individuals with anxiety disorders.^{31–32} Oral DCS is almost completely absorbed³³ with peak plasma concentrations 3 to 4 hours after administration. Thus, in the current study, DCS was administered approximately 30 minutes prior to the first CE trial in order to reach peak concentrations during the memory consolidation period. As described above, all participants received PBO before CE trials at session 3.

Data analytic approach—Standard descriptive statistics were summarized for the full sample and compared between treatment groups with Wilcoxon two-sample tests for continuous measures and Pearson’s Chi-Square test statistic for categorical measures. Craving and heart rate were modeled using multilevel mixed linear models in SAS 9.2 (SAS Institute, Cary NC) to appropriately account for nesting of individual craving and heart rate measurements within sessions. Within-subjects factors included measurement occasion, to

model ‘within-session’ extinction, and session, to model ‘between-session’ extinction. Between-subjects factors included medication status (i.e., DCS vs. PBO). All possible between- $\times$ within-subjects factor interactions were evaluated (i.e., DCS/PBO $\times$ measurement occasion, DCS/PBO $\times$ session). Baseline craving and heart rate, each computed by averaging the two baseline session 1 assessments, were included in their respective statistical models as covariates. In order to ensure that cue exposure methods were effective for enhancing craving, a Wilcoxon signed rank test was used to evaluate whether mean ranks differed between baseline craving, when no cues were presented, and the first CET session (E1; when cues were presented). Additionally, any demographic variables that significantly differed between medication groups were covaried in statistical models. Post-hoc analyses within and between sessions were conducted using Bonferroni corrections for multiple comparisons. To assist in the design of future studies where craving or heart rate might be outcomes, Cohen’s *d*-values and their 95% confidence intervals were calculated to quantify the potential magnitude of between and within-group differences in craving and heart rate during sessions.

RESULTS

Baseline

Forty-seven participants completed both CE sessions and were randomized to receive one of two treatment conditions; DCS ($n=23$) or PBO ($n=24$). Table 1 presents participant demographics and clinical characteristics. Forty-six participants completed assessments at session 3. With the exception of participants in DCS being older in age ($p = .03$; $M = 49.2$; $sd = 8.8$) compared to participants in PBO ($M = 44.4$; $sd = 8.7$), there were no significant differences on any other demographic or COC use history characteristic. Age was controlled in all subsequent statistical models.

COC cue exposure craving extinction

Figure 1 (top panel) presents COC craving data at baseline, following CE trials (within CE sessions 1 and 2), and at session 3. Differences between treatment conditions on craving at baseline were not significant for any CE session. There was no significant main effect for treatment condition on craving, $F(1, 43) = 0.1$; $p = .75$; Cohen’s $d = -0.07$; 95% CI = $-0.49, 0.35$). Similarly, there were no significant interactions between treatment condition and measurement occasion (i.e., within-session extinction, $F(9, 43) = 1.3$; $p = .26$; $d = -0.05$; 95% CI = $-0.47, 0.37$), nor treatment condition and session (i.e., between-session extinction, $F(2, 43) = 0.6$; $p = .57$; $d = 0.12$; 95% CI = $-0.31, 0.54$).

Participants in both treatment conditions exhibited significant decreases in mean craving across measurement occasions (i.e., within-session), $F(9, 43) = 3.3$; $p = .004$; $d = 0.49$; 95% CI = $0.07, 0.92$ and between sessions, $F(2, 43) = 14.5$; $p < .0001$; $d = 0.85$; 95% CI = $0.41, 1.29$). Post-hoc analyses demonstrated that craving scores in both groups declined significantly from session 1 to session 2, and again from session 2 to session 3. Additional post-hoc analyses showed that within sessions 1 and 3 (but not session 2), craving scores declined in both treatment conditions with differences becoming statistically significant from baseline (Trial ‘E1’ in Figure 1, top panel) at the 3rd (E3) and 4th (E4) CE trials.

Differences in craving from baseline to the first trial (E1) at CE 1 were significant ($z = 3.35$; $p = .006$, $d = 0.32$; 95% CI = 0.09, 0.55). During this time, 46.8% of participants ($n = 22$) exhibited increased craving between baseline and the first COC cue exposure trial, indicating a moderate level of craving in response to cues. A planned contrast revealed that craving was significantly lower at session 3 relative to the combined mean of sessions 1 and 2, across participants, ($t [43] = -5.4$; $p < 0.0001$; $d = 0.64$; 95% CI = 0.21, 1.07).

Heart rate cue exposure reactivity

Figure 1 (bottom panel) presents mean collapsed heart rate at baseline, following CE trials (within CE sessions 1 and 2), and at session 3. Differences between treatment conditions for baseline heart rate were not significant at any CE session. There was no significant main effect for treatment condition on heart rate ($F [1, 41] = 1.0$; $p = .50$; $d = 0.15$; 95% CI = $-0.27, 0.58$). Mean heart rate significantly varied between sessions ($F [2, 78] = 5.75$; $p = .005$; $d = -0.18$; 95% CI = $-0.61, 0.24$) for both DCS and PBO participants, with session 1 heart rate significantly lower than session 2 ($p = .001$) and session 3 ($p = .05$), but did not significantly vary across measurement occasions (i.e., within-sessions) ($F [9, 334] = 0.7$; $p = .72$; $d = 0.12$; 95% CI = $-0.30, 0.55$). A planned contrast revealed that heart rate at session 3 did not significantly differ from heart rate at sessions 1 and 2, $t [78] = 1.0$; $p = 0.68$; $d = -0.03$; 95% CI = $-0.46, 0.39$).

DISCUSSION

Contrary to our hypotheses, DCS did not significantly facilitate response abatement within or between sessions relative to PBO. In other words, adding DCS did not increase the benefit of CE in which participants learned skills designed to reduce their reactivity to COC cues, relative to PBO. However, in both treatment conditions, CE resulted in some attenuation of responding to COC cues as indicated by decreased craving among participants within and between CE sessions. Heart rate, nevertheless, indicated a potentiation from session 1 to sessions 2 and 3.

One explanation for the finding that DCS did not significantly facilitate extinction learning relative to PBO may be that DCS had no incremental benefit on extinction of craving above that of the effect of the CE protocol (floor effect). Our findings showing that craving ratings in both groups declined in the first session and stayed fairly low throughout the next two sessions provides some support for this. Of note, DCS + CE in the current investigation was not associated with an increased craving response, as has been demonstrated in prior studies,^{16–17} and there was no evidence of potentiation of conditioned cue-elicited memory.

Alternatively, our findings may be the result of memory reactivation and reconsolidation within the context of length and the number of CE sessions and trials selected for this investigation. In response to drug cue exposure, memories associated with drug use may be reactivated and then restabilized following reactivation.³⁴ In the current investigation, the skills training and the four CE trials were provided within approximately 60 minutes, although the exposure trials themselves lasted five minutes per trial. Given that preclinical studies suggest that greater than 60 minutes of non-reinforced exposure is necessary to facilitate COC cue extinction responses³⁵ and that 60 cue presentations demonstrated a

reduction in cue-induced reinstatement in rats,⁹ the length and number of CE trials in the current investigation may not have been sufficient to allow DCS to augment a newly formed extinction process in humans.

With regard to the optimal time point at which DCS should be administered, the largest effect size for enhancing extinction in anxiety disorders is immediately before or just after exposure/extinction,³⁶ while for addictive disorders in humans, optimal timing of DCS administration is unknown. In the current study, 50 mg of DCS was administered 30 minutes prior to the first CE trial based on studies showing that maximal effect of DCS is during the acquisition and consolidation phases of extinction learning.³⁷ In other studies that examined the effect of DCS on drug-related cues (e.g., alcohol and nicotine cues), DCS was administered 60 to 120 minutes prior to drug cue exposure,³⁸ with one study showing differential effects of DCS compared to placebo when it was administered 1 hour prior to extinction training.¹⁴ Thus, one recommendation is for future studies to examine the impact of DCS + CE in preventing reconsolidation of the drug memory by investigating various lengths of exposure therapy, length of time between DCS administration and cue exposures, and increasing the number of cue exposure trials³⁹.

Although results showing that craving decreased over time while heart rate increased with repeated exposure is contrary to our hypothesis, this paradoxical finding is not uncommon in the literature in that craving levels frequently do not correlate with physiological responses.⁴⁰ Both decreases and increases in heart rate have been associated with craving⁴¹ and an increase in cardiac activity in response to drug cues is not necessarily related to a motivation to use COC,⁴² suggesting the possibility that other factors may account for increased heart rate, such as efforts to cope with drug cues.^{40,42}

Some study limitations deserve comment. In the current investigation, exposure to COC cues during CE trials may have failed to result in sufficient craving in order to avoid a floor effect. Based on the visual craving scale utilized in our study for assessing subjective desire to use COC ranging from '0' = "not at all" to '10' = "extreme" craving, scores during the first CE trial averaged below the rating of '4' ($M = 3.3$; $SD = 3.1$). However, our analysis indicated a statistically significant increase in craving from baseline (when no COC cues were presented) to CE session 1 at the first trial (when COC cues were presented), suggesting that a sufficient response to the COC cues was present for a decreased response to the cues over repeated trials to be observed. Nevertheless, given that the proportion of COC cue exposure responders in our study appears lower relative to that of other studies⁴³, it remains undetermined whether the effect of DCS was dampened due to the limited craving response among participants and future studies should assess craving to COC cues prior to CE sessions. Lastly, while craving decreased within and between CE sessions for all participants, it is unclear whether this decrease was a result of the CE protocol including skills training, or simply repeated presentations of COC cues alone.

In summary, the results of this randomized, placebo-controlled trial failed to demonstrate that DCS facilitated extinction learning, which would have been demonstrated by significantly lower levels of cue-elicited craving in the DCS vs. PBO group. Extinction to

drug cues was observed for both treatment conditions between CE sessions as well as within CE sessions with regard to COC craving.

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Figure 1.

Top Panel A: Collapsed COC craving during baseline CET sessions, CET trials (within CET sessions 1 and 2), and at session 3. Scale indicators are '0' = "not at all" to '10' = "extremely" for subjective desire to use COC. **Bottom Panel B:** Collapsed heart rate during baseline CET sessions, CET trials (within CET sessions 1 and 2), and at session 3. BPM = beats per minute. Error bars represent standard errors.

Table 1

Demographic and Clinical Characteristics

Participant Characteristics	Overall N = 47	DCS N = 23	PBO N = 24	p-value
Demographic Characteristics				
Age (years)	46.7 ± 8.9	49.2 ± 8.8	44.4 ± 8.7	0.03
Male n (%)	40 (85.1)	19 (82.6)	21 (87.5)	0.64
Race n (% black)	38 (80.9)	18 (78.3)	20 (83.3)	0.66
High school or above n (%)	40 (85.1)	19 (82.6)	21 (87.5)	0.64
Married n (%)	9 (19.5)	4 (17.4)	5 (20.8)	0.76
Employed n (%)	12 (25.5)	7 (30.4)	5 (20.8)	0.45
Smoker n (%)	38 (80.9)	18 (78.3)	20 (83.3)	0.66
COC Use Characteristics				
Age at first COC use	24.5 ± 9.5	26.4 ± 10.6	22.4 ± 7.9	0.32
Total years of COC use	19.0 ± 7.4	19.1 ± 8.7	19.0 ± 6.7	0.99
% days COC use in previous 90 days	37.6	37.1	38.0	1.00
Days of COC use 2 weeks prior to session 1	0.94 ± 1.5	0.92 ± 1.6	0.95 ± 1.5	0.94
Use per using day (\$ amount)	78.3 ± 57.6	82.2 ± 61.0	74.6 ± 54.0	0.59
Currently enrolled in treatment n (%)	19 (40.4)	12 (52.2)	7 (29.2)	0.10
COC Craving at session 1 baseline	2.4 ± 2.5	1.9 ± 2.5	2.8 ± 2.5	0.19
Days between screening visit and session 1	21.9 ± 12.7	18.8 ± 9.6	25.4 ± 15.1	0.08

Table 2

Timeline and flow of activities in sessions 1 through 3

Time of activity	Activity
12:30	<ul style="list-style-type: none"> urine drug screen pregnancy test (for females) breathalyzer application of nicotine patch (if applicable) baseline craving ratings[‡] baseline heart rate assessments[*]
1:45	Medication administration (DCS or PBO)
2:15	Cognitive Behavioral Skill #1: Guided Imagery
2:24	COC Cue Exposure Trial #1 <ul style="list-style-type: none"> COC cue presentation/setting up COC cues Biopac heart rate assessment 5 minutes COC cue manipulation (with one hand)[‡]/guided imagery practice craving assessment
2:31	Cognitive Behavioral Skill #2: Urge Surfing
2:40	COC Cue Exposure Trial #2 <ul style="list-style-type: none"> COC cue presentation/setting up COC cues Biopac heart rate assessment 5 minutes COC cue manipulation/urge surfing practice craving assessment
2:48	Cognitive Behavioral Skill #3: Coping with Automatic Thoughts to Use COC
3:01	COC Cue Exposure Trial #3 <ul style="list-style-type: none"> COC cue presentation/setting up COC cues Biopac heart rate assessment 5 minutes COC cue manipulation/coping with automatic thoughts to use practice craving assessment
3:10	Cognitive Behavioral Skill #4: Methods to Distract One's self from Using
3:17	COC Cue Exposure Trial #4 <ul style="list-style-type: none"> COC cue presentation/setting up COC cues Biopac heart rate assessment 5 minutes COC cue manipulation/methods to distract one's self from using practice craving assessment

[‡]Craving assessments were assessed at 12 time points (twice at baseline, during each CE trial, once after CE trials, and twice after completion of the four CE trials)

^{*}Heart rate assessments were administered twice at baseline, 15 minutes apart

[†] COC cue manipulation with one hand continued throughout cue exposure trials after heart rate assessment was initiated

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