Enhancing disrupted reconsolidation: Impact on cocaine craving, reactivity & use

RESEARCH STRATEGY

1. Significance

A. The Problem of Cocaine Use

Cocaine is second only to marijuana as the most frequently used illicit substance. Recent estimates[1] indicate that approximately .6% of the US population or 1.5 million individuals reported current cocaine use (i.e., past month). Consistent with these national averages, .8% or 21,000 South Carolinians reported current cocaine use and an additional 1.5% or 49,000 reported cocaine use in the last year. High rates of cocaine use/abuse translate into well documented and prodigious health and social costs.[2-7] Cocaine addiction is often resistant to treatment as indicated by high rates of relapse.[8-10] There are no FDA-approved pharmacological treatments for cocaine dependence despite intense research efforts, and existing behavioral therapies have limited efficacy when applied alone.[10-14] Since the efficacy of medications and behavioral therapies are generally enhanced when they are combined,[14] it would appear that integrated pharmaco-behavior therapies may prove to be the optimal treatment development strategy. To this end, the proposed study seeks to build on the findings of a recently completed R21 that provided initial evidence for the potential development of a novel pharmaco-behavior therapy that targets modulation of drug-related learning/memory.

B. Pharmacological Memory Modulation and Implications for Addictive Behavior

The concept of memory consolidation refers to a post-learning process (or processes) whereby new information, initially persisting in a relatively fragile state, gradually consolidates or becomes more stable over time.[15-19] Reconsolidation refers to a process (or processes) during which retrieved memories can either be strengthened or otherwise altered by updating or integrating new information into long-term storage.[20-23] Generally, the memory retrieval process that defines reconsolidation is initiated by the presentation of cues that putatively elicit targeted memories.[24-26]

There is considerable evidence that the adrenergic system, likely via a number of cellular processes operating in the basolateral amygdala, is involved in memory reconsolidation.[21,25,27-29] It has been speculated that β-adrenergic receptor functioning impacts reconsolidation because it has a regulatory role in cAMP response element binding (CREB) phosphorylation which is essential for the protein synthesis on which reconsolidation depends.[30] The importance of the β-adrenoreceptor in reconsolidation has been demonstrated in basic neuroscience studies in which post-retrieval administration of the nonselective β-adrenergic blocker propranolol results in disrupted reconsolidation of fear memory as indicated by reduced fear to a conditioned stimulus (CS).[31] More recently, propranolol-mediated disruption of reconsolidation (DoR) has been demonstrated in several laboratory-based, human fear conditioning studies.[30,32-35] Propranolol's ability to serve as an effective DoR agent is not restricted to studies that target memories for aversive learning. In fact, several studies have demonstrated robust DoR effects on memories for learning involving drugs of abuse, including morphine[36-39], alcohol[40] and cocaine[41-44]. One of the cocaine studies, by Bernardi and colleagues, served as the impetus for our recently completed R21. This study showed that animals trained to prefer the cocaine-paired side of a two-sided place conditioning chamber no longer exhibited a place preference if they received propranolol immediately following brief exposure to the apparatus (i.e., cue-elicited retrieval). The findings of this and related studies prompted our research group to consider how propranolol might be used to target clinically important memory processes in cocaine addiction. Given that drug reinforced Pavlovian and instrumental learning processes contribute significantly to the development and maintenance of addictive behavior[45], it would seem possible that propranolol might be gainfully employed to disrupt reconsolidation of memories for these learning processes and thereby facilitate recovery from addiction. The results of our research group's recently completed proof-of-concept study (manuscript under review for publication in a special issue of Psychopharmacology on consolidation and reconsolidation) provide some encouraging preliminary findings regarding this possibility.

C. Results of NIDA-funded R21 (DA025155)

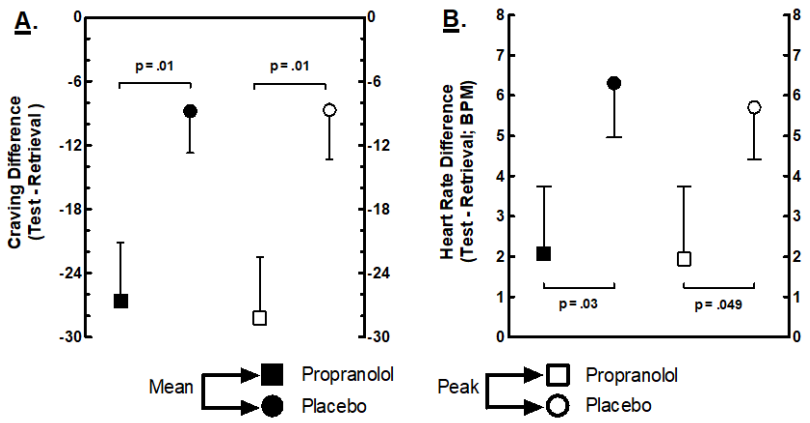
In this translational study, we employed cocaine cue exposure (CCE) to retrieve/reactivate memories that are presumed to underlie cocaine craving and cue reactivity in cocaine dependent (CD) individuals. The main hypothesis was that propranolol vs. placebo administration following cued reactivation could disrupt memory reconsolidation, the result of which would be attenuated craving and physiological responding (heart rate, blood pressure, skin conductance) to the cues during subsequent cue exposure. DoR would be expected because reconsolidation is presumed to be dependent on adrenergic functioning, which would be opposed by the pharmacological action of propranolol. The study also tested the secondary hypothesis that the postulated DoR

effect would be sufficiently robust to be evident (i.e., attenuated craving and physiologic reactivity) during a CCE one week later. Although the study was not powered to detect group differences in cocaine use, we did preliminarily examine cocaine use during the week preceding the follow-up CCE.

Study Design & Procedures. Non-treatment seeking cocaine-dependent (CD) individuals were recruited and randomized to receive either 40 mg propranolol (n=26) or a placebo (n=24) immediately following a "retrieval" session of CCE conducted in a controlled laboratory setting. In the retrieval CCE session, participants first viewed a 5 min 'video' depicting cocaine use and then handled 'in vivo' cocaine-related paraphernalia (e.g., simulated cocaine, $20 bill, mirror, lighter, etc.) for an additional 5 min. After a 10 min break, this video-in vivo cue sequence was presented a second time. Measures of craving, heart rate (HR), and blood pressure (systolic, SBP; diastolic, DBP) and skin conductance (SC) were obtained at baseline (30 min prior to the first CCE), immediately after each video-in vivo cue sequence, and 15, 30 & 60 min after the second cue sequence. One day after the retrieval CCE session, a "test" CCE session was conducted that was identical to the retrieval session except no medication was administered. This test session served to assess the acute effects of the medication on craving and cue reactivity elicited by same cues presented in the retrieval session. To prevent drug use between the retrieval and test sessions, participants remained overnight in the Medical University of South Carolina's Clinical and Translational Research Center (MUSC, CTRC). A third "follow-up" cue exposure session (identical to the test CCE session) was conducted one-week later.

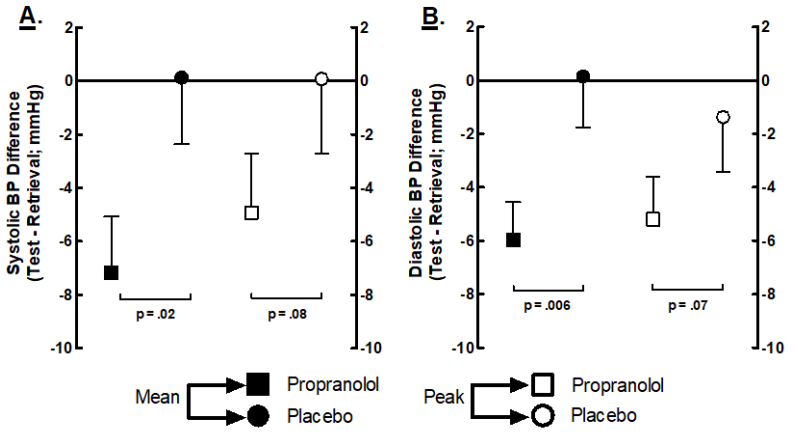
Study Results. Initial analyses compared the groups on important demographic (e.g., age, gender, race, education, etc.) and clinical variables (e.g., age at first cocaine use, dollar amount of cocaine use over 90 days preceding study participation, number of days using over 90 days preceding study participation, route of administration). The analyses failed to identify any group differences (all p's >.27). Finally, no group differences in baseline cocaine cue reactivity were detected on any primary outcome measure (all p's > .17; baseline measures were the measures obtained during retrieval CCE session before medication).

Figure 1



The present discussion will primarily focus on evaluation of the hypotheses using the main outcome measures (a) subjective craving (single-item 100 mm visual analog scale), (b) heart rate, (c) systolic and diastolic blood pressure, and (d) skin conductance. Since these measures were collected twice during the CCE, a mean and peak value was computed for each (in recognition of the possibility that medication effects could impact either the average or the maximum response, or both). These summary values were then used to compute difference scores for the mean and peak response by subtracting the mean/peak of the retrieval CE session from the mean/peak value obtained in the test CE session or the follow-up CE session. Therefore, negative difference scores would indicate a response decrement from the retrieval to the test or follow-up session whereas positive scores would indicate a response increment. Panel A and B of figure 1 depicts the mean (solid symbols) and peak (empty symbols) craving and heart rate difference scores, respectively, for propranolol (squares) vs. placebo (circles) treated groups. The figure shows and independent samples t-tests confirmed (all p values in figure) that (i) the propranolol treated group evidenced a greater decrement in mean and peak craving than did the placebo treated group, and (ii) the mean and peak heart rate increase evidenced by the propranolol treated group was significantly smaller than in the placebo treated group. Panels A and B of figure 2 depict the systolic (SBP) and diastolic blood pressure

Figure 2



(DBP) mean and peak difference scores, respectively, by group. Analyses confirmed that the mean SBP and DBP decreased significantly in the propranolol treated participants relative to the placebo treated individuals. Analyses also verified a trend towards a similar decrease in the peak responses on these measures. No group differences were detected for mean and peak SC (all p's > .4).

The same analyses were applied to the measures obtained at follow-up. Overall, the finding from the follow-up session suggest that the 'signal' detected in the test session had substantially dissipated. However, there were a number of observations that bear mention. First, the mean craving difference score of the propranolol treated individuals ($\overline{\times}$ = -32.0) trended towards being lower than that of the placebo treated individuals ($\overline{\times}$ = -21.3; t > 1.4, p < .08). Second, although not powered to detect differences in cocaine use, we preliminarily examined group differences on cocaine use status (self-report abstinence or use) at follow-up. Self-report data indicated that 43% of the propranolol group and 35% of the placebo group participants reported using cocaine, a difference that was not significant, $\chi^2(1) < 1$, p = .57. Given the possibility that amount of cocaine use may have differed between groups, we computed a difference score consisting of the participants mean dollar amount of cocaine used during the follow-up period ($\overline{\times}$ days = 9.0) minus their mean dollar amount of cocaine used during an equivalent number of days prior to study participation. The mean reduction, from pre-study levels, in dollar amount of cocaine used by the propranolol and placebo groups of $337 and $228, respectively, a difference that did not exceed statistical threshold, t(41) < 1, p = .23.

Since the difference scores indicate the magnitude of craving decrement from session 1 to session 2 was greater for propranolol-treated participants, the depicted findings are consistent with the hypothesis that pharmacological blockade of adrenergic activity after retrieval/reactivation of memories that support craving should disrupt memory reconsolidation and subsequently dampen craving and cue reactivity to the cocaine cues. The findings on the HR and BP measures are also consistent with the reconsolidation disruption hypothesis. Overall, the study findings are consistent with several basic neuroscience studies[41-43] documenting disruption of memories for learning previously established via cocaine reinforcement.

It should be noted that these findings cannot be explained by group differences in baseline or retrieval session cue-elicited mean or peak craving, HR or BP; statistical analyses failed to identify group differences on all measures (mean or peak craving, HR and BP at retrieval; all p's > .17). It is also unlikely that the R21 findings can be attributed to facilitated extinction. A number of recent infrahuman studies suggest that propranolol retards extinction of both aversive context conditioning[46] and appetitive sand maze learning.[47] The former of these two studies is of special relevance insofar as it indicates that a single administration of propranolol does not affect the rate of extinction, a finding that is in agreement with three previous studies.[48-50] Moreover, in a recent study by Kindt and colleagues[51] propranolol administration was found to have no effect on extinction as measured physiologically (i.e., startle reflex and skin conductance) whereas extinction at the cognitive level (i.e., participant expectancy of shock) was impaired. Taken together, the extant contemporary literature on the effects of propranolol on extinction suggests that propranolol either retards or has no effect on extinction learning. Lastly, it might be argued that if propranolol was biologically active at the time of the test session, then the HR and BP findings could have been a consequence of propranolol's known effects on these measures and that its anxiolytic properties might explain the group differences on the subjective measures, including craving. This explanation seems unlikely for several reasons. First, if decreased anxiety/arousal is what explained the lower craving, then one would expect the propranolol group would have evidenced a lower level of anxiety (we measured this with the STAI) at the test session; this was not the case as the groups were equivalent on state anxiety at both the retrieval and test CCE sessions. Second, because immediate release propranolol reaches peak plasma concentration in approximately 90 minutes[52,53] and has a half-life of 3-4 hours,[54-57] it seems unlikely that appreciable levels of propranolol would have been present 24 hours post-administration. Furthermore, a recent study[58] employing a sample of patients with liver cirrhosis reported that an 80 mg dose of propranolol had almost completely cleared (mean plasma propranolol concentration < 10 ng mL) when measured 24 hours post-administration. Since the participants in this study had normal liver function and received a 40 mg dose, it would seem very likely that propranolol had completely cleared in the 24 hours preceding the test session.

D. The proposed project: Augmentation of DoR

We believe the findings of the R21 are very encouraging but acknowledge that the therapeutic utility of DoR will depend on achieving a more robust effect on craving, cue reactivity and cocaine use behavior. There are at least two ways to achieve this signal augmentation. One would be to increase the number of medicated retrieval sessions and the other would be to increase the propranolol dose. There is no human data to appeal to in support of these manipulations having the desired effects, largely because so little human laboratory and/or clinical research has been done. However, there are a number of basic neuroscience studies that bear on these two methods. With regard to increasing the number of medicated retrievals, Fricks-Gleason and Marshall[42] reported

that one medicated retrieval produced a reduction in cocaine conditioned place preference (CPP) relative to placebo but did not diminish cocaine primed reinstatement; in contrast, multiple medicated retrievals (the number varied by subject as all had to meet a no preference criterion) accelerated the loss of the cocaine preference and, most importantly, eliminated cocaine primed reinstatement. Similar findings were reported in a study[59] of amphetamine CPP but the DoR agent was not propranolol (NMDA antagonist MK-801). Clinically, these findings suggest the possibility that multiple propranolol-medicated retrievals could help patients build resistance cue elicited craving that would persist after a brief lapse to use. In recognition of the likely possibility that increasing the number of medicated retrievals might augment DoR of cocaine memories, we are proposing to increase the number of medicated retrievals from one, as studied in the R21, to two (rationale for two medicated retrievals provided in the Alternative Design Considerations section below).

With respect to increasing dose, almost all studies of DoR employing human subjects have employed a propranolol dose of 40 mg[30,32,34,35,60,61] and there have been no attempts to compare this dose against a higher dose. Recently, two prominent research groups[62,63] in this area have noted the lack research efforts addressing this issue and have encouraged future research efforts to evaluate the ability of a higher dose to augment DoR. We concur with this recommendation and would add that the infrahuman literature provides some implicit support for the notion that a higher dose may very well achieve enhanced DoR. With little variation most animal (rat) studies of DoR have employed a dose of 10 mg/kg[31,41-43,64] which substantially exceeds the 40 mg dose typically used in most human laboratory/clinical studies. What is important here is that, broadly speaking, infrahuman studies tend to demonstrate DoR effects that are of a greater magnitude in that they are often sustained over longer periods of time and have been shown to be resistant to reinstatement. Thus, the animal literature can be broadly construed as suggestive that increasing the dose in studies with humans may yield a larger and more durable impact on behavior. While 10 mg/kg dosing regimens cannot be used with humans, it is certainly the case that a higher dose of this well-tolerated medication could be used safely. In the proposed study, we plan to contrast the 40 mg dose used in the R21 with an 80 mg condition (rationale for 80 mg dose is provided in the Alternative Design Considerations section below).

Clinically, the utility of any DoR-based treatment targeting cue-elicited craving and reactivity would be substantially enhanced if the treatment effects generalized to stimuli from the broader class of drug cues that were not encountered during retrieval. Soeter and Kindt,[35] employing their human differential startle fear-conditioning paradigm, recently reported that propranolol-induced DoR of conditioned fear was not restricted to retrieval cues but rather generalized to similar, category-related (picture) cues. These findings suggest that, at least under some circumstances, DoR effects in humans may very well impact memory for a broad network of related cues. Since our research group has developed and worked extensively with a broad range of cocaine related cues (video, in vivo and picture), a supplementary goal of the proposed study will be to examine generalization of DoR treatment effects to novel cocaine picture cues.

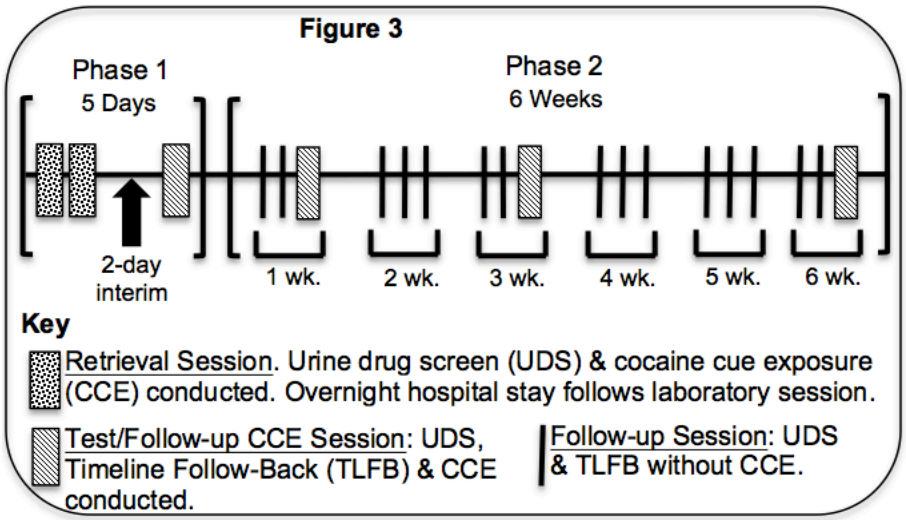
2. Innovation

The proposed study is innovative in that it challenges an existing paradigm in three ways. First, it focuses on altering memories of the "pathological" learning that subserve the maintenance of cocaine addiction[45] rather than seeking to establish new, extinction-based learning to oppose it (an approach that has had modest success). The overarching hypothesis is that attenuation of these memory processes should decrease cocaine craving, cue reactivity and use, thereby potentially enhancing outcomes for persons with this prevalent and intractable addiction. Second, the proposed research challenges the prevailing approach to pharmacotherapy. For example, current medications such as modafinil (non-amphetamine, psycho-stimulant) and baclofen ($GABA_B$ receptor agonist) require chronic administration to therapeutically impact the mechanisms of cocaine addiction, presumably by targeting the cocaine-induced neuro-adaptive changes in dopaminergic, GABAergic and glutamatergic functioning that underlie euphoria, craving and withdrawal.[13] The proposed study points to an alternative approach where medications are used acutely, and in concert with behavior therapy (e.g., CE), to produce relatively sustained changes in the network of memory, learning and motivational processes that support continued drug use.[45] Such an approach would have significant advantages over existing long-term medication treatments including reduced cost/time of administration, reduced likelihood of medication side effects, and increased likelihood of treatment compliance and retention. Since a highly efficacious mono-therapy for cocaine dependence has not been achieved, future treatment development may substantially benefit from focusing on the strategic integration of medication and behavioral interventions that yield better outcomes than either approach alone. Third, the generalizability of behavior therapy effects to novel stimulus conditions is widely viewed as desirable but rarely evaluated. The proposed study will employ novel picture cues in the test/follow-up CCE session to assess the extent to which any DoR effects generalize to cocaine cues not involved in the retrieval session treatments.

3. Approach

A. Design Overview

The proposed study has two primary goals and each goal has an associated study phase. The primary goal of **Phase 1** is to augment the effects of post-retrieval propranolol observed in the R21. To achieve this goal, participants will receive 40 mg propranolol, 80 mg propranolol, (immediate release) or placebo immediately following each of two, retrieval CCE sessions in which exposure to standardized cocaine stimuli will serve to retrieve/reactivate memories for learning that subserves cocaine craving and cue reactivity (see figure 3). The two retrieval CCE session will be completed 24-hours apart and will be followed, two days later, by a third unmedicated test/follow-up CCE session. This two-day interim period will allow for the complete clearance of propranolol; Participants will be compensated $75 to remain abstinent during this period. Multiple assessments of craving and physiological reactivity will be obtained at baseline and after stimulus presentations in all three CCE sessions (content and timing of stimulus presentation in each session are detailed below in the Procedure section below). Participants will remain in MUSC's CTRC on the evening of each of the propranolol treated retrieval sessions of Phase 1 to prevent drug use.



The primary goal of **Phase 2** will be to assess the effects of post-retrieval propranolol on indices of cocaine use obtained over a 6-week follow-up in which abstinence is no longer reinforced. Drug use will be retrospectively evaluated during weekly interviews using a calendar-based assessment and urine drug screens will be performed 3 times each week to provide an objective assessment of drug use/abstinence. At week 1, 3 and 6, laboratory-based test/follow-up CCE sessions (similar to identical to the test CCE session in Phase 1) will permit (a) continued assessment of the maintenance of treatment effects on craving and cue reactivity to cocaine cues, and (b) assessment of generalization of DoR effects to novel cocaine picture cues (detailed below in the procedure section).

B. Participants

A total of 180 non-treatment seeking, cocaine-dependent men and women (60 per treatment group), aged 18 or older, will be tested over a 54-month period (see Alternative Design Considerations section for a rationale pertaining to recruitment of non-treatment seekers). However, after getting close to the end of our recruitment we have found that 180 is not enough to collect the number of completers we need. We have increased enrollment to 200 in hopes to collect the number of completers we need to have significant power for statistical tests. This increase enrollment to approximately 67 per treatment group. Inclusion/exclusion criteria are detailed in the Protection of Human Subjects portion of this application.

Sample Size Estimation

Phase 1. In the proposed study, random effects ANOVA procedures will be used to assess differences among three treatment arms (placebo = PBO, 40 mg propranolol = 40PP, and 80 mg propranolol = 80PP). The over arching goal of the sample size estimation was to ensure the study will be sufficiently powered to adequately detect effect sizes that are both relevant to the study hypotheses and clinically meaningful. We restricted the Phase 1 estimation to the key outcome measure of subjective craving, as it has the largest standard deviation of all outcome measures. Drawing from the R21 results presented above, the subjective craving response following treatment with 40 mg of propranolol decreased 24.2 ± 24.7 points (mean ± SD, change on a 100 point scale) while the group treated with placebo was found to decrease 8.8 ± 19.9 points. This yields a Cohen's d of (15.4/22.3=) 0.69. In the proposed study, we want to be able to detect craving differences, should they exist, between the PBO and 40PP group and between the 40PP and 80PP group. Additionally, we will make the conservative assumptions that (a) the difference between the PBO and 40PP groups will be 10% smaller than observed in the R21; d = 13.9/22.3 = .62, and (b) the difference between the 40PP and 80PP groups will be substantially (30%) smaller than the difference observed in the R21; d = 11.6/22.3 = .52. Accordingly, assuming

a pooled SD of 22.3, an α = .05, and 60 participants randomized to each of three treatment groups, we will have 86% power to detect a d = .62 between the PBO and 40PP groups (i.e., craving difference of 13.9 units) and 80% power to detect a d = .52 between the 40PP and 80PP groups (i.e., craving difference of 11.6 units).

Phase 2. The phase 2 portion of the study was designed to assess group differences in cocaine use during the 6-week follow up. The previously completed R21 yielded an 86% follow up rate after a mean follow up time of 9 days. In the proposed study, we will conservatively estimate that there will be an 80% follow-up rate (n = 144 of randomized participants will be available for analysis), despite added reinforcement contingency for attending urine drug screen appointments and test/follow-up CE sessions. Although the R21 was not designed to assess the mean number of cocaine using days during follow-up and the number of days that each participant was followed was quite variable, we were able to estimate the standard deviation of the mean percent of using days to be approximately 11.3%. Therefore, assuming a similar common standard deviation in follow-up sample and with α = .05, a sample of 48 participants in each treatment group, we will have 80% power to detect a difference in the mean percent of cocaine using days of 5.6% (SD = 11.3%; Cohen's d = .50) between the propranolol treated (40PP & 80PP combined; n = 96) and placebo groups (n = 48). Additionally, assuming the same common standard deviation, α level, and group n, we would have 80% power to detect a mean percent cocaine using days difference of 6.5% between group 40PP and group 80PP. In either case, power will exceed 80% to detect differences that are both larger and more clinically substantive (e.g., 10%).

Recruitment

In the R21, we recruited two participants/month. In the proposed study, we plan to recruit 180 participants over a 54-month period, which represents a monthly recruitment rate of slightly more than three (3.3) participants/month. However, nearing the end of our study we have found that we need a higher enrollment to get the number of completers we need and to account for lost and withdrawn participants. We have increased our enrollment goal to 200 participants. In the R21, the recruitment goal was met by advertising in only one of four media outlets at a time (i.e., we would cycle through local area papers, radio, public transportation such as buses, and TV advertisements). To bolster recruitment in the proposed study, we plan to deploy advertisements in all four media outlets concurrently. We fully expect that this aggressive, media-intensive recruitment plan will allow us to randomize the targeted number of participants. Participants will also have the option of selecting text reminders for their appointments. Text messages sent to participants will be sent from the study's secured and encrypted email account.

C. Screening, General Assessment, Randomization, & Medication Procedures

Screening and Eligibility Assessment

Prospective participants will be screened by study personnel (by telephone or in person). A quick screening procedure will assess suitability for participation, inclusion/exclusion, psychiatric diagnoses, medical status, current medication regimen, etc. Interested participants will undergo a standard, IRB-approved consent procedure.

General Assessment

The Mini-International Neuropsychiatric Interview or MINI[65,66] is a semi-structured interview that permits diagnosis of current psychiatric disorders and SUDs using DSM-IV criteria and it will be used to assess psychiatric status/functioning as it pertains to the inclusion/exclusion criteria. Substance use in the three months prior to study involvement and over the course follow-up (Phase 2) will be assessed using a modified version of the Timeline Follow-Back (TLFB).[67] This is a calendar-based instrument used with specific probes to ascertain detailed information about amounts of substance use and will serve to determine frequency and dollar amount of cocaine and other drug use (this instrument will be used to assess the dollar amount of use pre-study for randomization purposes, as described above). A urine drug screen will be done to assess if the participant had used cocaine within the last 72 hours. As a component of the medical history and physical exam, electrocardiogram, blood chemistries and urine pregnancy test will be conducted to ensure that individuals are eligible to participate prior to admission to the CTRC. If the assessment visit could not be finished, participants will be asked to come back to complete the unfinished portion. After all inclusion criteria and no exclusion criteria have been satisfied, participants will be scheduled for the two retrieval CCE sessions to be conducted during a two day stay at the CTRC. If a participant has a positive cocaine urine drug screen, positive breathalyzer or fails to present for their scheduled CTRC stay, every attempt will be made to reschedule as quickly as possible.

Randomization

As in the R21, urn randomization will be used in assigning participants to the two propranolol groups (40PP & 80PP) and the placebo group (PBO)[68] while balancing treatment assignment on two variables. To maximize the power for a comparison of effect across gender and minimize confounding, gender will be balanced during the randomization. Dollar amount of cocaine use at baseline (pre-study involvement) is a likely prognostic factor on craving and other outcome measure and will be controlled during randomization. Specifically, the total dollar amount of cocaine use in the 3 months prior to study involvement will be determined (using the Timeline Follow-Back) and the following binary urn variable will be used: Participants with ≤ $1000.00 cocaine use pre-study involvement vs. participants with > $1000.00 cocaine use pre-study involvement. The effects of additional factors such as age and duration of use will be statistically controlled during the analysis (if necessary, see Data Analysis Plan below) since further stratification of the randomization could yield some stratum with very small expected sample sizes. This could lead to significant imbalance in the overall study.

Medication Administration

Immediately following the completion of the cue exposures in each of the first two retrieval CCE sessions (described below), one of three medications will be administered in accordance with randomization; 40 mg of immediate-release propranolol, 80 mg of immediate-release propranolol or a matching placebo will be administered. Medications will be compounded, packaged and dispensed by the MUSC Investigational Drug Service (IDS), who will also oversee the randomization procedures for the study and record the treatment assignment. The IDS provides 24-hour, seven-days-a-week, on-call availability to randomize, enroll, dispense medications and unblind as necessary.

D. Phase 1 Laboratory Session Procedures

Verification of Abstinence

Participants will be informed that they will be expected to remain abstinent from cocaine and other drugs for the 72-hour period preceding their CTRC admission in order to minimize the impact of recent drug/alcohol use on cue reactivity and minimize any potential for interaction between propranolol and cocaine/alcohol. Participants will be asked to come in the day before CTRC admission for a urine drug screen. If an individual tests positive for drugs or alcohol on admission day and/or the day before admission day, their admission will be rescheduled and they will not be compensated for that visit. If participant shows signs of intoxication/withdrawal (elevated blood pressure, diaphoresis, etc.), they will also be rescheduled. Individuals who test positive for substance use will be provided transportation to their residence (taxi service) if friends or relatives are unable to meet this need.

Session Preparation

Upon arrival at the CTRC at approximately 9:00 am, the participant will give breath and urine samples to assess abstinence for alcohol and other substances (as well as pregnancy for females). Observed urine drug screens in which a research assistant will monitor urine collection may be done at all required abstinence visits to minimize tampering with urine specimen. If the abstinence assessment is negative (see above, if positive), they will remain at the CTRC lounge until 9:30, at which time study personnel will escort them to the cue reactivity laboratory. Over the course of the two-day inpatient stay at the CTRC, nicotine patches will be provided to smokers, thereby reducing the risk of nicotine withdrawal during the cue exposure procedure. During the next half hour, a blood pressure cuff will be placed on the participant's arm and leads/sensors will be affixed, as described below, for the purpose of collecting HR and SC data. Participants will also complete a few assessments at this time (e.g., State Trait Anxiety Inventory or STAI, BDI, CSSA described below). Since all of these tasks will be accomplished in 5-10 min, participants will remain seated quietly for the remaining 20 min period. This waiting period serves to acclimate the participant to the laboratory setting (our research group has found acclimation to produce more stable baseline measures in several laboratory studies).

Cocaine Cue Exposure (CCE): Stimuli and Procedures

Video & In Vivo Stimuli: The combination of video and in vivo cocaine cues used in the R21 will also be used in the proposed study (see figure 4). These cues will be presented in all CCE sessions (unlike the picture-based novel CCE, described below, which occurs only in test/follow-up CCE sessions). The video cocaine cues will consist of a 5-min. video depicting cocaine use in a variety of settings. The in vivo cocaine cues will consist of a small bag of simulated crack cocaine, the participant's preferred style of crack pipe, a lighter, and money ($20 bill) for those who use crack cocaine. For powder or IV users, simulated powder cocaine, cocaine paraphernalia, and money will be used. During the in vivo cue presentation, the cocaine cues will be placed on the table directly in front of the participant and they will be asked to inspect and handle (with non-dominant hand) the cues for a five-minute period.

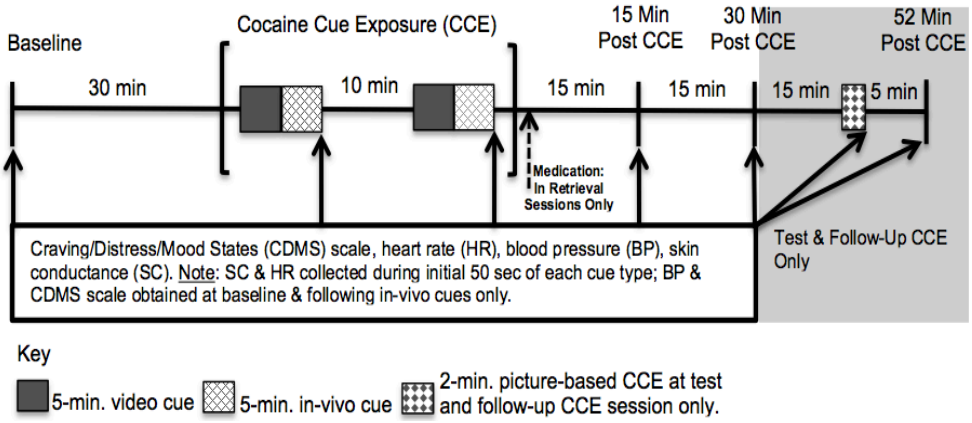
Picture Stimuli: A picture-based novel CCE will be administered at the end of all test/follow-up CCE session (described below) to determine if any observed DoR effects generalize to cocaine cues not previously experienced by the participants. The picture cues depict individuals of varied race and gender using crack or powder cocaine. The pictures will be categorized by route of administration and presented to participants according to their individual route of administration. A total of 12 novel pictures will be presented (10 seconds each) on a video screen located directly in front of the participant (the picture order will be counterbalanced across participants). Thus, the duration of the novel picture-based CCE will be 2 min. Heart rate and SC will be continuously measured for the first 50 sec of the picture presentation, as this is where the largest response is likely to occur. At the conclusion of the picture viewing participants will be prompted to complete the same assessments they completed following the video/in vivo CCE sequences (See Figure 4).

The pictures used in this exposure sequence will be derived from a library of 48 pictures (12 pictures will be presented in each test/follow-up CCE session; thus, participants will not see any picture more than once) that we have either developed or acquired from publically available sources.

Our research group has previously used this type of picture-based cue exposure procedure to successfully elicit craving in methamphetamine dependent individuals.[69,70] Additionally, previous research by our group has shown that these pictures (subset of 10) elicit greater cocaine craving and subjective arousal in cocaine dependent individuals (n = 27; craving $\bar{x}$ = 5.9 and arousal $\bar{x}$ =10.1) than in non-cocaine dependent controls (n = 28; craving $\bar{x}$ = .06 and arousal $\bar{x}$ = 5.3; both t's > 3.6, both p's < .001). Furthermore, the mean craving and arousal reported by cocaine dependent individuals in response to the cocaine pictures was greater than the mean craving and arousal they reported in response to a set of neutral comparison pictures (craving $\bar{x}$ = 1.0 and arousal $\bar{x}$ = 5.3; both t's > 4.5, both p's < .0001). Thus, we are confident these cocaine picture cues will serve as effective elicitors of craving and arousal in proposed study.

Procedure: At approximately 10:00 am, baseline subjective and physiologic outcome measures will be collected. Thirty minutes later, participants will receive the first sequence of CCE. Each sequence will consist of a 5-min video cocaine cue presentation followed immediately by in vivo cue presentation. Heart rate and SC data will be continuously collected during the first 50 sec of each cue type (video and in vivo). The CDMS Scale and BP will be obtained at the end of the in vivo cues. After the latter measures were obtained participants remained comfortably seated until the second, identical sequence of CCE commenced (approximately 5-10 min later). At the end of the CCE in the retrieval session, participants will receive their medication and complete all outcome measures. As indicated in figure 4, all dependent measures will be obtained immediately after CCE sequence and at 15 min. and 30 min. time points following termination of CCE. At the end of each retrieval session, research staff assisted the participant in removing the HR/SC leads and BP cuff. Participants will remain at the CTRC laboratory facility for an additional 60 min., at which time a blood draw will occur. The sample will be used to determine plasma concentrations of the propranolol so that the association between propranolol level and treatment effects can be assessed; the timing of the blood draw was based on the observation that peak concentrations of propranolol are reached 90-min post administration.[52,53] Also at this time, participants will be asked to complete a dual-item form that asks whether or not they thought they received propranolol or placebo and, for those who thought they received propranolol, at what dose level (this data will be used to assess the effectiveness of the blind). Research staff will then escort the participant to a research dedicated hospital room where they will remain overnight. The second retrieval cue exposure session, occurring the following day at the same time, will be identical to the first in all respects, including the overnight stay at the Institute of Psychiatry (IOP). Prior to discharge from the IOP the next day, research staff will schedule a test/follow-up CCE session, remind the participant that it is important to maintain abstinence during the interim period between their inpatient stay and the test/follow-up session and also remind them that a significant portion of the compensation (i.e., $75.00) available at the end of the test session will be contingent on a negative UDS. Our group has previously used a

Figure 4



modified version of the 'fishbowl' contingency management (CM)[71] procedure to successfully achieve an 80% rate of UDS verified cocaine abstinence over a 3-day period. Since the 'fishbowl' CM procedure only offered a small probability of earning the level of monetary compensation we plan to guarantee in the proposed study, we expect the abstinence rates during the 2-4 day interim period to exceed 90%.

The goals of the first test/follow-up session will be to evaluate the acute effects of dual medicated (either 40 and 80 mg propranolol) retrieval CCE sessions on craving and cue reactivity and to assess the generalization for these effects to novel cocaine cues picture cues. This session will be scheduled to occur no earlier than two days after inpatient discharge and no more than 4 days (this 2-4 days window will permit flexibility in scheduling to accommodate weekends and participant scheduling needs). The details of the first test/follow-up CCE session are identical to those described above for the retrieval sessions with the following exceptions. First, no medications will be administered. Second, UDS/breathalyzer assessment and Timeline Follow-Back will be administered to determine if the participant had maintained abstinence during the interim period (all participants, regardless of abstinence status, will be administered the CCE). Third, approximately 45 min after the CCE (i.e., 15 min after the 30 min post-CCE assessment; see shaded area in procedure Figure 4), the picture-based novel CCE procedure described above will be administered. At the end of the picture-based CCE, participants will complete 2 additional sets of post-cue measurements. Study staff will then remove the HR and SC leads and the participant will remain seated comfortably for 10 min. Prior to discharge, participants will be reminded that they are entering the follow-up phase (2) and that they are encouraged to remain abstinent from cocaine use but that abstinence will not affect the compensation that they receive for attending their scheduled follow-up sessions. In the event that a participant experiences elevated craving at the end of a CCE session (i.e., report a post-session craving score ≥ 20% above baseline), they will be asked to remain in the CTRC until their craving subsides. A member of the research staff will be available to discuss management of craving urges. Finally, study staff and the participant will schedule the three study visits that will occur over the ensuing week.

E. Phase 2 Follow-up Drug Use Assessments and Cocaine Cue Exposure (CCE) Sessions

Follow-up Assessment Sessions: The goals of the follow-up visits are to determine if (a) the effects of post-retrieval propranolol on craving and cue reactivity to both familiar and novel cocaine cues are sustained over the 6-week follow-up, and (b) the post-retrieval propranolol treatment(s) impact cocaine use (variously measured) during follow-up. There will be a total of 18 visits scheduled over 6 weeks, with three visits occurring per week. All follow-up visits will begin with a drug/alcohol assessment. Briefly, participants will meet research staff at MUSC's CTRC at approximately 9:00 a.m. on the pre-arranged day. At this time, a UDS and breathalyzer measurement will be obtained; cocaine, alcohol and other drug use status will be recorded. Next, research staff will perform a Timeline Follow-Back in order to ascertain the level of drug/alcohol use during the days since their last study visit. On follow-up visits that occur at the end of weeks 1, 3 and 6, participants will undergo a CCE session that is identical to the test session described above (test/follow-up CCE will follow drug/alcohol assessment). On these occasions, the cue exposures procedures will commence at approximately 10:30 a.m. to ensure that all study CCE sessions are being performed at approximately the same time of day (thereby serving to minimize the impact of circadian variation in sex and stress hormone levels on outcomes). Following CCE administration, the participant and staff will confirm the next appointment times and the appropriate level of compensation provided (see compensation plan below). At the end of each week, all appointments for the ensuing week will be scheduled. At the conclusion of the 6-week follow-up period, participants will be asked if they would like referrals for treatment

F. CCE Session Instruments and Related Measures

Self Report Measures

State-Trait Anxiety Inventory (STAI): The STAI is a 20-item self-report scale[72] employing a Likert-scale format with four responses per item (1-4). Ten of the STAI items measure feelings of stress and anxiety, while the remaining ten items measure feelings of relaxation.

Cocaine Selective Severity Assessment (CSSA): The CSSA is an 18-item interview-based measure[73] of cocaine withdrawal symptom severity (e.g., lethargy, sleep disturbances, lethargy). It will be used to assess the association between withdrawal symptom severity and treatment response.

Beck Depression Inventory (BDI): The BDI is a 21-item scale[74] that is a gold standard for the self-report assessment of depressed mood. The BDI will be administered at the screening visit and last study visit.

Adverse Events Form (AEF): We have used this instrument in many of our past to assess medication side effects/adverse events. The AEF will be administered at all study visits (i.e., end of inpatient stay and all test/follow-up visits).

Craving/Distress/Mood States (CDMS) Scale: This scale is a modified version of the Within Session Rating Scale[75,76] and was used in the R21 and in several past[77,78] and ongoing cue-reactivity protocols by our group. This self-report assessment contains thirteen, 100 mm visual analogue scales, with each being anchored by the adjectival modifiers "not at all" (left side of scale) and "extremely" (right side of the scale). The craving item asks the participant to rate the desire to use cocaine "right now". The remaining items assess other drug-related subjective states (withdrawal, anxiety, frustration, anger, depressed mood, etc.). Figure 4 shows the timing of administration of this scale within the CCE sessions.

Cocaine Craving Questionnaire- Brief (CCQ): The CCQ is a 10-item scale used to assess the participant's feelings and thoughts about using cocaine at that moment in time. This will be assessed at the end of CCE sessions.

Physiological Measures

Heart rate (HR), blood pressure (BP) and skin conductance (SC) were measured as indices of physiological arousal during each CCE session. Heart rate was collected via two electrodes, with one affixed to the right shoulder and the other on the bottom left side of the participant's ribcage. Blood pressure was measured using an intermittently inflatable cuff. Because this measure cannot be obtained unobtrusively, it will be taken at the same time as the CDMS is obtained (see figure 4 above). Skin conductance was recorded using Ag/AgCl electrodes attached to the skin over the metacarpal bone of the fifth digit, non-dominant hand. Since physiological arousal/reactivity was likely to be greatest in the earliest portions of a CCE sequence, HR and SC data will be continuously collected during the initial 50-second epoch of each video and in-vivo cue presentation and during the first 50-sec of the novel picture-based CCE (they also are collected at baseline and at 15-min and 30-min follow-up time points; see figure 4). The HR and SC signals will be amplified using the ECG 100c and GSR 100c Modules of the Biopac MP100 data acquisition system; the Biopac system will be interfaced with an Apple (MacBook Pro) laptop for data storage and subsequent reduction. While the HR, BP and SC measures obtained in the second medicated retrieval session may be impacted by the medication (not in the first retrieval session since the medication is administered after the CCE), it should be noted that these responses are not relevant to the evaluation of any hypothesis. Nonetheless, these responses will likely provide some measure/indication of the effects of the first medicated retrieval.

G. Participant Compensation

Participants will receive $50.00 for completing the initial assessment. There will be a $10.00 incentive if the participant shows up on their originally scheduled date and within 15 minutes of their scheduled time. The participant will be compensated $25.00 for the urine drug screen the day before admission to the IOP if they produce a negative urine drug screen. There will be $200.00 given to the participant for completing the inpatient portion of the study ($100.00 for each over night stay at the CTRC, including completion the retrieval CCE session). Compensation will only be provided in full when a participant completes the entirety of the overnight stays. Participants will not be able to collect a partial payment for completing only a portion of the overnight stays. Compensation for attending the test/follow-up session (2-4 days following discharge from the CTRC) will have three components; to encourage attending this session, $50.00 compensation will be provided; to increase the likelihood that cocaine abstinence since the time of their CTRC discharge is achieved, an additional $75.00 incentive will be available if participants provide a cocaine negative urine drug screen (UDS). Lastly, an additional incentive of $25 dollars will be contingent on their attending the test session on the scheduled day and time. Thus, the maximum compensation for Phase 1 participation is $435.00 ($60.00+$25.00+$200.00+$150.00). Compensation for these Phase 1 visits (the screening and these first three visits) will be provided at the end of the first test/follow-up session (visit 3). Compensation will only be provided in full for completion of all these sessions excepting in cases of medical withdrawal and not cases of violating protocol. Phase 2 (follow-up) of the proposed study will be 6-weeks in duration and will involve 3 visits to MUSC each week for a total of 18 visits. For each of the 15 visits that they are scheduled to provide a urine drug screen (UDS) and undergo a Timeline Follow-Back assessment (TLFB), they will be compensated $25.00. For each of the 3 visits they are scheduled to provide a UDS, TLFB and undergo CCE session, they will be compensated $75.00. Additionally, participants will receive a bonus payment of $50.00 at the end of each follow-up week if they have attended all 3 weekly visits as scheduled. Accordingly, the maximum compensation attainable in Phase 2 will be $900.00 [(15 x $25 = $375.00)+(3 x $75.00 = $225.00)+(6 x 50 = $300.00)]. The total maximum compensation for both phases of the study will be $1,335.00. If it is found that a

participant has provided false information regarding his or her identity, the PI has the right to withhold payment for their current visit and drop the participant from the study.

Respondent-Driven Sampling (RDS) will be used to enhance recruitment of the sample. The RDS sampling methodology is based on recruiting the eligible friends and acquaintances of each participant so that the sample "snowballs." Each eligible participant who is enrolled into the study, and agrees to take part in this recruitment assistance, will be given business cards and/or flyers to pass on to other potential participants. A referral will be instructed to call the site offices for screening and, if eligible, an appointment for further evaluation. The referral and the participant who made the referral must acknowledge the other party. If a referral completes the screening, overnight visits, and first follow-up visit, or phase 1 of the study, then the participant who made the referral will be compensated $20. Participant will receive cash payment at next visit or in person after the successful referral.

While this level of compensation may raise concerns that money earned from research participation could be used to purchase drugs or could be perceived as coercive, evidence from our prior studies (including the R21) as well as research by others[79] suggests that these concerns are not warranted. The details of these study finding are discussed in the Protection of Human Subjects section of this application.

H. Data Management and Data Analytic Plan

Research staff will perform data entry for self-report and ratings measure (under the supervision Mr. Baker, Co-I). Random data entry checks will both assess and enhance data integrity. Heart rate and skin conductance data will be acquired via specialized software and hardware (Biopac Systems, Inc.) interfaced with an Apple MacBook Pro computer. Standardized file formats will facilitate the rapid determination of summary values to be used for analysis purposes.

Outcome Measures

The main cue reactivity outcome measures for the Phase 1 are subjective craving and physiological reactivity. Summary mean and peak values for craving (and related subjective measures) will be computed for all CCE sessions administered over the course of the study (i.e., all retrieval and test/follow-up sessions). Outcomes for the physiological measures (heart rate, skin conductance and blood pressure) will be computed in a similar fashion. However, data reduction on the HR and SC measures will precede computation of the summary values. The main cocaine use outcomes in Phase 2 will be (1) latency (days) to first use, (2) number of cocaine using days during follow-up, (3) dollar amount of cocaine used during follow-up, and (4) proportion of positive vs. negative UDS. Summary values on outcome measures obtained during the first retrieval CCE session (i.e., before any medication is administered) will serve as baseline (cue-elicited) outcomes and will be used as covariates in the data analytic plan described below.

Data Analysis Plan

Baseline demographic and clinical measures will be compared across treatment groups using standard statistical methods. Categorical demographic/clinical variables will be analyzed using Pearson chi square tests of independence while continuous demographic/clinical variables will be compared using one-way ANOVA procedures.

Phase 1. The first component of hypothesis 1 is that participants receiving propranolol (40 mg and 80 mg) compared to placebo treated controls, will evidence significantly lower cocaine craving and physiological reactivity (HR, SBP, DBP) during the first test/follow-up CCE session. To test this a priori hypothesis, a generalized linear mixed effects model will be developed using model-based estimates to construct group level contrasts (40PP & 80PP combined vs. PBO). A separate contrast will be developed to test the second component of hypothesis 1 that relative to the group 40PP, the group 80PP will evidence lower levels of craving and cue reactivity. Since the expected response pattern characterized in both components of hypothesis 1 is expected to occur to the novel picture cues presented at the end of the test session, a similar analytic plan will be adopted to evaluate the secondary hypothesis.

Phase 2. The hypothesis (2) that propranolol treated individuals (40PP and 80PP combined), as compared to placebo treated controls, will evidence less cocaine use during the 6-week follow up will be assessed across a limited set of outcomes. Analysis of variance models will be used to assess the continuous outcomes such as the mean number of days reported using and dollar amount spent on cocaine during the follow up. The overall proportion of participants relapsing to cocaine usage will be assessed using logistic regression models to test if differences exist between the propranolol and placebo treated participants at the end of the follow up period. To test the latency to return to cocaine use, Cox proportional hazards regression models will be used to assess both time to first positive UDS/self reported cocaine use as well as time the to second positive UDS/self reported use.

In order to fully utilize the longitudinal data, additional analysis will test the pattern of positive UDS data over the entire course of the follow up (measured 3 x weekly for 6 weeks). These models will be developed through the use of generalized linear mixed effects models.[80,81] To test the hypothesis (3) that participants treated with propranolol (40PP and 80PP) vs. placebo will evidence less craving and cue reactivity to both familiar and novel cocaine cues presented during test/follow-up CCE sessions, linear mixed effects models will be developed. The models will explore the effects of treatment, time, cocaine use status, and the interactions of the factors on the craving and physiologic responses to cocaine cues presented during the week 1, 3 and 6 test/follow up CCE sessions.

Secondary Analysis. There are a number of secondary analyses of interest. First, it is possible that propranolol will begin affecting craving and cue reactivity as early as the second retrieval session. Therefore, we will use a linear mixed effects model to identify between group differences that develop in the second retrieval session. Second, it is expected that propranolol's ability to disrupt reconsolidation will be related to its bioavailability, which we will index using the plasma sample obtained approximately 90 min after each medication administration. We plan to use regression analyses to assess whether plasma concentrations of propranolol predict variation in the outcome measures (e.g., craving, cue reactivity and cocaine use) obtained across the test/follow-up CCE. Third, we plan to evaluate whether treatment impacts ambient or background craving and cue reactivity[82,83] (i.e., non-cue-elicited outcomes obtained a half hour before each test/follow-up CCE session) using linear mixed effects models. The models will also test the effects of time and cocaine use status. Fourth, since there is some evidence of gender differences in propranolol metabolism[84,85] and adrenergic functioning in emotional memory[86,87], we will examine associations between gender and treatment outcome. Fifth, we plan to evaluate the effectiveness of the participant blind. Specifically, responses obtained from the participants about which medication group (propranolol dose vs. placebo) they thought they were in will be contrasted with the medication condition to which they were randomized and analyzed via a Pearson chi square test of independence.

Missing Data. Since data for all medicated retrieval CCE sessions in Phase 1 will be collected while the participants are residing at the CTRC, missing data or study dropouts are not anticipated. Inevitably, over the 6-week follow up period, missing cue reactivity and cocaine use data will occur. The missing observations might be 'unit missing', which occurs when a participant does not present at one or more of the time points. The unit missing will be treated as though they are missing (completely) at random. Methods such as multiple imputations[88] using PROC MI and PROC MIANALYZE will be considered. With respect to the UDS data we will also perform a sensitivity analysis by treating any missing UDS as positive and reanalyzing the data.

I. Alternative Design Considerations and Potential Study Limitations

1. Propranolol Dosing: We considered three dosage increases for use in the proposed study; 60 mg, 80 mg and 120 mg. The decision to employ 80 mg dosage was based on the following rationale. An 80 mg dosage represents a doubling of the 40 mg used in the R21, which is conceptually congruent with the doubling of the medicated retrievals from one in the R21. From a pharmacokinetic perspective, it is known that the bioavailability of propranolol is rather modest (Approximately 25%) and variable[57] so it was important that the dosage increase be sufficiently large to ensure an appreciable increase in plasma concentration and therefore, increased availability in the brain. Accordingly, it seemed likely that the 80 mg dosage would, on balance, achieve a substantial increase in central availability without sizably increasing risk of sinus bradycardia or a hypotensive episode. Furthermore, there have been several human laboratory[89,90] and clinical studies[91] on single or dual administrations of 80 mg or more of propranolol with no reported adverse effects. These observations, together with the fact that participants will remain at the CTRC for both medication administrations, increased our confidence about the safety of using 80 mg while at the same time achieving a biologically significant increase in propranolol plasma concentrations.

2. Number of Medicated retrieval sessions. While it is reasonable to assume that multiple medicated retrieval CCE sessions may cumulatively interfere with memory reconsolidation, there are no human laboratory or clinical studies to guide decision-making regarding incremental utility of additional medicated retrievals. As noted above, there are two infrahuman studies[42,59] showing that 10 or more medicated retrievals achieve large DoR effects. However, these studies don't address the possibility that substantially fewer medicated retrievals may be all that is needed to achieve a significant augmentation of DoR. Moreover, high numbers of medicated retrieval sessions detract from the practical value and feasibility of DoR-based treatment. In the absence of any definitive empirical support regarding this decision, we have elected to double the number medicated retrievals employed in the R21. This decision represents an attempt to balance the goal of DoR augmentation with the increase in participant burden (i.e., more over night stays at CTRC), design complexity and difficulty interpreting the findings

(i.e., at what point does the amount of stimulus exposure require a transition from a reconsolidation to an extinction level of analysis[45]).

3. Non-treatment seeking sample. As in the case of the R21, non-treatment seeking cocaine dependent participants will be recruited for this study. We have elected to use non-treatment seekers because we have evidence from our previous laboratory studies[92] and from the R21 that non-treatment seekers essentially behave as though they are seeking treatment. That is, they often exhibit abstinence rates and reductions in cocaine use that are similar to levels observed in formal treatment outcome studies.[93-95] For example, 60-65% of the R21 sample reported no cocaine use at 1-week follow-up and their dollar amount of cocaine use decreased 85% from pre-study levels. Since main goal of the follow-up is to track individuals who have substantially reduced their cocaine use as they gradually return to substance use over a 6-week period and assess whether or not DoR retards the return to cocaine use, we believe that employing non-treatment seekers will permit attainment of this goal. Additionally, because the goal of the proposed study is to document the treatment potential of DoR, recruitment of treatment seekers seems premature.

J. Future Directions

Positive findings from the proposed study could lead to a phase III RCT in which a DoR treatment element is added to multi-component intervention to assess its incremental treatment utility. Because a DoR-based treatment component would be both brief and easy to integrate with other therapies, it would be relatively simple to evaluate it in the context of extant and new behavioral and pharmacotherapy combinations[96,97] as well as with the emerging cocaine vaccine.[98] Furthermore, since a DoR-based treatment targets the learning/memory processes underlying all forms of addictive behavior rather than a specific neurotransmitter system (i.e., GABA), it may have broader clinical utility and therefore be useful in treating addiction to a wide range of substances (e.g., cigarette smokers, opiate addicts, marijuana addicted young adults, etc.).

K. Operational Plan and Research Timetable

Since we have ongoing studies with a variety of substance using populations, an on-going FDA approval (IND) for propranolol, an aggressive media-based recruitment strategy and extensive experience using cue reactivity paradigms, we anticipate start up to occur in approximately 3-months. During this period, research staff will be hired and trained, the protocol will be IRB approved at MUSC and added to the existing IND application, and laboratory procedures and database(s) will be established. We will actively recruit participants for 54 months and plan to allow three months for final data cleaning/reduction, analysis and manuscript preparation (albeit manuscript preparation will begin sooner). Submission of a follow-up proposal will occur as soon as possible. At a recruitment rate of approximately 3-4 participants per month, we should have no difficulty in completing the study in the five-year timeframe. With regard to recruitment milestones, we anticipate being able to recruit approximately 30 participants in the 9-month recruitment period of years 1 and 5 and 40 participants during each of the 12-month recruitment periods of years 2 through 4.

L. Protection of Human Subjects

Drs. Saladin, Gray, McRae-Clark or Brady will monitor all study participants for psychiatric stability, and Drs. Gray and Brady will monitor for medical stability. The instrumentation used for physiological recordings meets all safety standards for non-invasive recordings, and participants are located out of reach of any AC-powered devices in the laboratory. All sessions will be conducted under the supervision of experienced personnel. If crisis intervention is necessary, senior research personnel will be available to evaluate the participant and provide an intervention or referral. If hospitalization is indicated, the patient will be hospitalized through the Center for Drug and Alcohol Programs (CDAP) at MUSC or an appropriate referral will be made. All participants will be fully informed that they may withdraw from the experiment at any time without penalty. All participant records will be kept in a locked filing cabinet, and confidentiality of all materials will be maintained. Offices will also be locked when not in use.

To ensure confidentiality, participant data will be number coded, and only the investigators will have access to the master lists of codes. All participant records will be kept in an office that will be locked at times when not in use. The research staff understands the importance of maintaining confidentiality. This method of maintaining confidentiality has been used for several years by our research group and has been effective.

Participants will be taught about potential side effects of propranolol and will be closely followed by either a MD (Gray/Brady), Pharm.D. (McRae-Clark) or other member of the research team. Propranolol administration will occur in a fully staffed clinical environment (CTRC), with emergency medications (i.e., IM diphenhydramine) and equipment available if necessary.

In the event that a participant experiences elevated craving at the end of a cocaine cue exposure session (i.e., report a post-session craving score ≥ 20% above baseline), they will be asked to remain in the CTRC until their craving subsides.

Inclusion Criteria

a) Participants must meet DSM-IV criteria for current cocaine dependence (within the past month). Participants may meet criteria for abuse, but not dependence, for any other substance with the exception of nicotine. Because of the high comorbidity of cocaine and nicotine dependence, excluding nicotine dependence would seriously compromise the feasibility of recruitment (nicotine patch will be provided to participants during the course of their involvement in the laboratory procedures). Although individuals who meet criteria for alcohol abuse will be accepted for study participation, anyone who has a measurable blood alcohol level on the day of testing will be excluded as acute alcohol intake can lower seizure threshold.
b) Participants must be able to provide informed consent and function at an intellectual level sufficient to allow accurate completion of all assessment instruments.
c) Use of one of the following methods of birth control by female participants: barrier methods (diaphragm or condoms with spermicidal or both), surgical sterilization, use of an intra-uterine contraceptive device, or complete abstinence from sexual intercourse.
d) Individuals must live within a 50-mile radius of our research program and have reliable transportation.
e) Individuals must consent to remain abstinent from all drugs of abuse (except nicotine) for 72 hours immediately prior to CTRC inpatient admission.
f) Individuals must consent to random assignment to one of three study groups (the two propranolol-treated groups or the placebo-treated group).

Exclusion Criteria

a) Women who are pregnant, nursing or of childbearing potential and not practicing an effective means of birth control.
b) Individuals with evidence of or a history of significant hematological, endocrine, cardiovascular, pulmonary, renal, gastrointestinal, or neurological disease including diabetes, as these conditions may affect heart rate or skin conductance measurement.
c) Individuals with significant liver impairment as propranolol is hepatically metabolized.
d) Individuals with current/active (untreated) psychotic disorder, current major depressive disorder, bipolar affective disorder or a severe anxiety disorder as these conditions may impact cue reactivity and would likely interfere with their ability to fulfill requirements for study participation (e.g., provide accurate interview data, complete study assessments, attend scheduled laboratory visits, etc.).
e) Individuals currently taking anti-arrythmic agents, psychostimulants or any other agents known to interfere with heart rate and skin conductance monitoring.
f) Known or suspected hypersensitivity to propranolol.
g) Individuals taking medications that could adversely interact with the study medication, including, but not limited to albuterol, insulin, or significant inhibitors of CYP2D6.
h) Individuals with bronchial asthma or chronic obstructive pulmonary disease, as the use of propranolol is contraindicated in these individuals.
i) Individuals with any physical condition or disability that would compromise optimal sensory processing of the cues (e.g., blindness).
j) Individuals who are currently using propranolol, as propranolol is the drug that will be administered during the retrieval sessions.
k) Individuals currently taking medications to treat chronic to severe pain as these drugs may effect cue reactivity.
l) Individuals that meet current criteria for high risk of suicide on MINI.