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Effects of a Context Shift and Multiple Context Extinction on Reactivity to Alcohol Cues

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Abstract

Cue exposure treatment (CET) attempts to reduce the influence of conditioned substance cues on addictive behavior via prolonged cue exposure with response prevention (i.e., extinction), but has received only modest empirical support in clinical trials. This may be because extinction learning appears to be context dependent and a change in context may result in a return of conditioned responding (i.e., renewal), although this has received only limited empirical examination. The current study used a four-session laboratory analogue of CET to examine whether a change in context following three sessions of alcohol cue exposure with response prevention would result in renewal of conditioned responding. In addition, this study examined whether conducting extinction in multiple contexts would attenuate renewal of conditioned responding. In a one-way between-subjects design, 73 heavy drinkers (71% male) were randomized to three conditions: 1) single context extinction (extinction to alcohol cues in the same context for three sessions followed by a context shift at the fourth session); 2) multiple context extinction (extinction to alcohol cues in different contexts each day for all four sessions); and 3) pseudo-extinction control condition (exposure to neutral cues in the same context for three sessions followed by exposure to alcohol cues at the fourth session). The results revealed the predicted cue reactivity and extinction effects, but the hypotheses that a context shift would generate renewed cue reactivity and that multiple contexts would enhance extinction were not supported. Methodological aspects of the study and the need for parametric data on the context dependency of extinction to alcohol cues are discussed.

Keywords

Alcohol; Cue Reactivity; Renewal; Conditioning; Craving; Translational Research

Although often overlooked, there is considerable evidence that classical conditioning plays a critical role in addictive behavior (Bouton, 2002a). Pavlov (1927/1960) originally reported that morphine acted as a powerful unconditioned stimulus (UCS), and it has been subsequently demonstrated that classical conditioning influences various aspects of addictive behavior, including tolerance, withdrawal, and craving (for a review, see Siegel & Ramos, 2002). With

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respect to craving, a large number of laboratory studies have demonstrated that individuals with a history of using a given substance exhibit potent increases in desire to use the substance when they are exposed to cues associated with the substance (Carter & Tiffany, 1999; Niaura et al., 1988), a procedure commonly termed the cue reactivity paradigm.

Evidence for the influence of such associative processes in addiction has prompted investigation into treatment to decrease the strength of these classically conditioned relationships. This approach is termed cue exposure treatment (CET) and involves exposing substance dependent individuals to cues for the problematic substance in settings that preclude use (i.e., exposure with response prevention [extinction]). This procedure putatively degrades the contingency between the conditioned stimuli (CSs) and the UCS (the substance), eventually extinguishing the conditioned responses (CRs), including craving. These CSs include visual, tactile, olfactory, and imaginal cues, as well as procedural aspects of use.

Cue exposure treatment has been tested in clinical trials for alcohol, nicotine, cocaine, and opiate dependence (e.g. Dawe et al., 1993; Drummond & Glautier, 1994; Niaura et al., 1999; O'Brien, Childress, McLellan, & Ehrmann, 1990), but a large proportion of the published clinical trials have been criticized for methodological problems. In a meta-analysis, Conklin and Tiffany (2002) found that only 9 of 23 published outcome studies on CET demonstrated sufficient methodological rigor for inclusion. Of the methodologically sound studies, the findings were mixed. Using Cohen's (1990) estimations, Conklin and Tiffany (2002) reported that effect sizes (Cohen's *d*) ranged from a large positive effect (+.7345) to a medium negative effect (-.4500), with an overall effect size of .0868, which was nonsignificantly different from zero. As a result of these findings, Conklin and Tiffany (2002) concluded that CET was not efficacious in treating addiction. Although this meta-analysis has some limitations (Drummond, 2002; Monti & MacKillop, 2007), the outcome data unequivocally fall short of the initial hopes for CET.

As a result, directives have been proposed to build on CET's promising foundation by applying findings from contemporary basic research on extinction (Conklin & Tiffany, 2002; Drummond, 2002; Havermans & Jansma, 2003). In particular, Bouton (2002b) has enumerated several aspects of extinction learning that have implications for therapeutic procedures that use the principles and methods of extinction to modify behavior. All emphasize the modern learning theory notion that extinction is not the erasure of learning (i.e., unlearning), but is new learning that reflects the multiple relationships that exist between stimuli. This in turn results in context-dependent learning, or the differential expression of behavior based on environmental context, and this has been demonstrated to take place under a number of conditions (Bouton, 2002b). Of particular relevance is the renewal of conditioned responding, or the recovery of the extinguished response when the context is changed after extinction. In this case, it appears that contextual stimuli acquire multiple meanings, signaling that the subject should respond one way in one context but another way in a different context. For example, if excitatory conditioning takes place in Context A and inhibitory conditioning takes place in Context B, when the organism returns to Context A, the initial conditioning will be expressed (Bouton & Bolles, 1979; Bouton & King, 1983; Bouton & Peck, 1989; Harris, Jones, Bailey, & Westbrook, 2000; Rauhut, Thomas, & Ayres, 2001). This is termed ABA renewal. Importantly, using the same example, if the organism is transferred to an entirely new context following extinction, the initial conditioning will also be expressed (Bouton & Bolles, 1979; Brooks & Bouton, 1993; Gunther et al., 1998; Harris et al., 2000). This is termed ABC renewal. In both cases, the primacy of initial acquisition learning over extinction learning is evident.

The implication of context-dependent learning on CET is clear: extinction-based efforts may poorly generalize beyond the setting in which they take place. For example, an alcoholic may experience decreases in cue-elicited urges in the clinical context where CET takes place, but

this may not necessarily extend beyond that specific treatment environment. By syllogism, it may be that for CET to be optimally effective, the treatment should attempt to minimize context-dependent learning and maximize generalization of extinction (Conklin & Tiffany, 2002; Havermans & Jansma, 2003).

Despite the extensive evidence from basic research and cogent speculation that CET may be limited by context dependent learning, there have been only a small number of direct studies on the context-dependency of extinction in humans and fewer still in reference to extinction to alcohol cues. Moreover, no studies to date have used procedures that parallel the provision of extinction in CET, leaving the probable degree of renewal in CET an open question. Therefore, the first goal of the current study was to use a laboratory analogue of CET to examine and characterize the magnitude of renewal as a result of changing contexts following three separate sessions of extinction to alcohol cues in the same context, as would typically take place in CET.

The second goal of the study was based on evidence from basic research that a number of procedures can reduce the context-dependency of extinction (e.g., Brooks & Bouton, 1993; Chelonis, Calton, Hart, & Schachtman, 1999; Denniston, Chang, & Miller, 2003; Gunther, Denniston, & Miller, 1998). For example, Brooks and Bouton (1993) demonstrated that a stimulus that was present both during extinction and in a novel context, termed an extinction reminder, attenuated renewal of conditioned responding. Subsequently, Collins and Brandon (2002) applied this finding to extinction to alcohol cues in heavy drinkers and also found that an extinction reminder attenuated renewal of cue-elicited craving. Similarly, two basic research studies have shown that conducting extinction in multiple contexts also reduces renewal. Using a conditioned suppression paradigm, Gunther, Denniston, and Miller (1998) found that rats for which the association was extinguished in three contexts showed attenuated responding compared to those receiving extinction in only one context. Similarly, Chelonis, Calton, Hart, and Schachtman (1999) used a conditioned taste aversion paradigm to demonstrate the same phenomenon: rats that received extinction training in three contexts showed an attenuated renewal of aversion to a sucrose solution when returned to the original context. Based on these studies, the second goal of the current study was to examine whether multiple context extinction would attenuate renewal of alcohol cue reactivity. As such, this study applied a translational research approach, attempting to leverage basic learning research to clarify the context-dependency of alcohol-related extinction learning.

To address these two goals, the study used a three-group design in a four day laboratory analogue of CET. There has been considerable heterogeneity in session spacing and other parameters in clinical studies of CET (Conklin & Tiffany, 2002) and the current study used spaced exposures across days and massed exposures within a given day. Unlike Collins & Brandon (2002), we elected to use spaced extinction sessions over four days because previous studies on both animals (e.g., Sangha, Scheibestock, Morrow, & Lukowiak, 2003) and humans (e.g., Rowe & Craske, 1998; Tsao & Craske, 2000) suggest spaced trials are more effective for extinction. In addition, CET is typically provided clinically in separate sessions. Each day, participants underwent massed exposures to either alcohol cues or neutral cues and this took place in either the same context as the previous day or a different context. Based on the existing literature, the study had four experimental hypotheses: (1) Initial exposure to alcohol cues on day one would elicit acute increases elevations in self-reported urge and salivation relative to a control exposure (i.e., evidence of alcohol cue reactivity); (2) Prolonged exposure with response prevention (ERP) would attenuate the initial reactions to alcohol cues and decrease subsequent reactivity to alcohol cues across sessions (i.e., evidence of extinction to alcohol cues); (3) ERP to alcohol cues in the same context during the first three days of the study followed by a context shift on the fourth day would result in a significant increase in cue reactivity (i.e., evidence of renewal of cue reactivity); (4) ERP in different contexts each day

of the study would result in significantly less renewal of cue reactivity on the fourth day (i.e., evidence of attenuation of the renewal effect via multiple context extinction).

Method

Participants

Participants were required to be at least 18 years old and heavy drinkers (i.e., 20+ standard drinks/week for males; 14+ for females). The heavy drinking criteria were used because they reflect drinking at $\geq 90^{\text{th}}$ %ile for four-year college students (Meilman & Presley, 1997) and samples recruited using these criteria have exhibited high levels of alcohol cue reactivity in previous studies (MacKillop & Lisman, 2005, 2007). In addition, because the alcohol cue exposures were generally oriented around beer stimuli, participants were required to indicate that they considered beer among their three favorite alcoholic beverages, that beer was among their three most frequently consumed alcoholic beverages, and that they rated the enjoyment of beer a 7 or greater on a 10-point Likert-type scale. Based on Staiger and White (1991), participants were asked their favorite brand of beer and were exposed to this brand during the exposure. In addition, participants were assessed for their most common reason for drinking from seven possibilities and received imaginal cues matched to their most common reason.

A power analysis (power = .80; $f = .40$; $\alpha = .05$; Faul & Erdfelder, 1992) based on effect-size differences in previous similar research (Collins & Brandon, 2002) indicated that a minimum sample size of sixty-six participants was necessary. Seventy-three participants (71% male; median age = 20) were recruited from the general population of Binghamton University (State University of New York) from November 2003 to May 2004 using posted flyers and classroom announcements. Participants typically described themselves as Caucasian (66%), with small proportions of Asian (11%), Hispanic (4%), and Ukranian (1%) individuals; 16% did not provide race/ethnicity. Participants reported consuming a mean of 30.5 ($SD = 14.78$; 98%ile among this cohort) standard drinks per week and participants' mean score on the Alcohol Dependence Scale (described below) was 11.7 ($SD = 4.84$), which approaches the 25th percentile in terms of alcohol dependence symptoms (Skinner & Horn, 1984). All participants were provided with either four research credits or \$40 for their participation, at their choice.

Experimental Design

The study used a one-way three-group between-subjects design (Table 1) in an experimental protocol that took place over four consecutive days with one session per day. Conditions were: 1) single context extinction (SC); 2) multiple context extinction (MC); and 3) neutral control (NC). The SC condition received prolonged exposure to alcohol cues with response prevention in the same context for days one, two, and three and received a context switch on day four; the MC condition received prolonged exposure to alcohol cues with response prevention in different contexts at each session of the study; the NC condition received prolonged exposure to neutral cues with response prevention in the same context for days one, two, and three, but underwent an exposure to alcohol cues on day four. The fourth day was the test trial for the effects of a context shift and multiple context extinction. The use of three different contexts was selected based on Gunther et al.'s (1998) experimental design, which demonstrated the attenuation of the renewal effect using three contexts. The NC condition was used to permit assessment of various baseline and habituation characteristics of participants, as recommended by Robbins and Ehrmann (1992). The NC condition was considered a pseudo-extinction control group because no significant initial reactions to the neutral stimuli were anticipated, meaning no subsequent decreases in those reactions would be evident.

Of note, the most common experimental preparations to study renewal are ABA renewal (acquisition in one context, extinction in a second context, testing in the original context; e.g.,

Bouton & King, 1983) and ABC renewal (acquisition in one context, extinction in a second context, and testing in a third context; e.g., Brooks & Bouton, 1993). To clarify the connection between this design and basic research on post-extinction renewal, the current study design was based on ABC renewal, albeit with some modifications. Unlike basic research, where all learning is *de novo*, previous translational research in humans on post-extinction renewal has typically focused on an individual's pre-existing conditioning history (e.g., Collins & Brandon, 2002; Mineka et al., 1999; Rodriguez et al., 1999). This was the case also in the current study. Specifically, for the SC condition, the acquisition context ("A") was considered the individual's previous alcohol-related conditioning history, the extinction context ("B") was the experimental room where extinction trials were conducted on days one to three, and novel context ("C") was the new experimental room on day four (test trial).

Paper-based Measures

Drinking Days Questionnaire (DDQ; Collins, Parks, & Marlatt, 1985)—The DDQ is a face-valid measure of an individual's average alcohol consumption per week that has adequate psychometric properties (Kivlahan et al., 1990).

Urge Report (UR)—Urge for alcohol was assessed using a single item measure, which is a commonly used assessment in laboratory settings (e.g. McGeary et al., 2006; Monti et al., 1999) and is useful in for minimizing assessment reactivity in studies using repeated craving assessment (Sayette et al., 2000). A 100-point Likert-type scale was used with four anchoring comments ("*I don't want a beer at all,*" "*I don't want a beer very much,*" "*I'd like a beer now,*" and "*I'd REALLY like a beer right now!!!*").

Alcohol Dependence Scale (ADS; Skinner & Horn, 1984)—Although participants were recruited based on quantitative and qualitative criteria related to alcohol consumption, the ADS, a continuous measure of alcohol dependence was included for descriptive purposes. The ADS is a 25-item measure of alcohol dependence symptoms that has been extensively previously validated (Skinner & Horn, 1984).

Demographics Assessment (DA)—A standard demographics measure was administered to assess racial/ethnic background, concurrent substance use, and other demographic variables.

Physiological Assessment

Salivation—Saliva was collected using the procedures described by Monti et al. (1987). Participants were asked to place three Crosstex® sterile cotton dental rolls in their mouths, two on the outside of their lower teeth (between the cheek and gums) and one behind their anterior lower teeth, beneath their tongue. Research Assistants (RAs) requested that participants open their mouths to verify that the dental rolls were placed correctly. Salivation was assessed to the nearest .001g by weighing the rolls using a Sartorius B 310 S scale prior to and following each assessment interval and by subtracting the pretest weight from the posttest weight.

Procedure

All procedures were approved by the Binghamton University Human Subject Research Review Committee and all participants underwent informed consent. During each session, the participants initially completed baseline measures and salivation assessment in a neutral laboratory room. During the first session, participants also completed the additional descriptive measures in this room. Following the baseline assessment, participants were escorted by an RA to a cue exposure room. Following the acute cue exposure (described in detail below), participants were then asked to again complete the urge report and their dental rolls were removed and weighed. Participants were then asked to insert fresh dental rolls and were

informed that they would spend the duration of the experiment in the cue room. In addition, they were informed that they were not permitted to drink the beverage under any circumstances. A 40-minute extinction period followed, based on previous CET clinical trials (Drummond & Glautier, 1994; Rohsenow et al., 2001). Throughout the extinction period, participants were assessed for urge and salivation every ten minutes. The procedure was completed for four days in a row (Monday to Thursday) at the same time each evening for each participant. Each session lasted one-hour, with the exception of the first, which lasted approximately 80-minutes due to the additional instructions and questionnaires. The study took place from 5pm to 10pm to maintain congruence with normative drinking hours and all subjects were run at the same time each night. RAs were different each day for all subjects across conditions. Participants were not prohibited from drinking between sessions, but drinking was assessed and examined in reference to the pertinent day four findings (see below). At the end of all four sessions, participants received a debriefing form and their compensation.

Alcohol and Neutral Cue Exposures

The multimodal alcohol cue exposure stimulus complex consisted of visual, auditory, olfactory, tactile, imaginal, and proprioceptive cues. Initially, participants were escorted by an RA to an experimental room (4'5" × 4'5" × 7'10") decorated with posters and other drinking paraphernalia and were left alone for 90-seconds to observe all of the relevant cues. The RA then returned and poured a beer that had been matched to the participant's reported favorite type of beer in the plain sight of the participant. The RA informed the participant that they would soon be asked to listen to a tape recording of a scenario related to drinking beer and would be asked to smell the beer from time to time. The RA then asked the participant to lift the beer up to their nose and take five deep breaths to establish the intended behavior during the imaginal scene. Participants were then asked to put on headphones and listen to an imaginal scene describing drinking the beer in a context matched to the individual's report on the screening. The imaginal scenes consisted of a narrative describing beer consumption in a situation related to one of seven reasons (happiness, tension, boredom, negative affect, anger, habit, and gustatory enjoyment) assessed during screening, as well as a detailed description of beer consumption. All imagery scripts were tape recorded, standardized for length, and read in a relaxing tone. On four occasions during the imaginal scene, the participants were asked by the narrator to lift the beer up to their nose and take five deep breaths, inhaling the aroma of the beer. This action provided regular exposure to the olfactory properties of the beer and mimicked the movements used to raise a glass when drinking, providing proprioceptive feedback. The neutral cue exposure was identical in every way but related to drinking water. The initial (acute) cue exposure periods lasted approximately 10 minutes and were followed by the 40-minute extinction period of exposure with response prevention and intermittent assessment.

Experimental Contexts

An important consideration for the experimental contexts was providing stimuli complexes that both mapped onto the participants' conditioning histories and were also sufficiently disparate to be identified as different contexts. To accomplish this, several approaches were used. First, in terms of visual cues, similar, but not identical, alcohol use paraphernalia (images of beer, individuals drinking, empty beer bottles and barroom table dressings) were used across contexts. Second, the same standardized imaginal scenes were used, but with different narrators. Third, each of the experimental rooms was designated as having an unobtrusive color theme. This included covering the exterior door with colored paper and a sign designating the color and using colored lights, lampshades, tablemats in the interior. Fourth, the five different experimental rooms (four alcohol cue exposure, one water cue exposure) were geographically distributed around the Department of Psychology at Binghamton University (State University

of New York). To minimize any effects of one specific experimental context or order, participants were counterbalanced by contexts and orders of contexts.

Manipulation Checks

To assess the adequacy of the experimental manipulations, following the final trial, participants were asked to fill out a questionnaire with open-ended items pertaining to various characteristics of the study during the first three sessions, such as whether they had been in one or several rooms, what the color-themes of the rooms they had participated in were, and whether the narrators were different on the tapes. In addition, a 7-point Likert-type scale was administered to assess how similar the imaginal scene was to the participants' regular drinking context during the first trial and, for each trial, how clearly they imagined the scene. Following the experimental procedures, a questionnaire was administered to examine participants' perspectives on the study.

Data Analysis

All baseline dependent variables were examined for distribution normality and outliers. Previous cue reactivity research has demonstrated that some individuals do not respond to substance cues (e.g., Avants et al., 1995; Monti et al., 1999; Rohsenow et al., 1992; Shiffman et al., 2004). Because an absence of cue reactivity would preclude detecting effects of extinction and context manipulations, non-reactors were identified and excluded from subsequent analyses. Non-reactors were defined as individuals who exhibited no change in urge in response to alcohol cues (Monti et al., 1999; Rohsenow et al., 1992), either on day one or day four depending on the condition. Mixed 3 (group) $\times$ 4 (day) analyses of variance were conducted on urge to drink each day to identify whether any cumulative effects on basal levels were evident, requiring nested analyses.

The principal analyses were focused on day one and the initial cue reactivity portions (the first 10-minutes of exposure) of days two, three, four, where the significant effects were predicted to be evident. On day one, initial reactions to alcohol cues and effects of extinction on urge to drink were examined using 2 $\times$ 6 mixed analysis of variance (ANOVA), with group (alcohol cues vs. neutral cues) serving as a two-level between-subjects independent variable and time serving as a six-level within-subjects independent variable (baseline, post cue exposure, extinction periods one to four [every 10-mins.]). The SC and MC conditions were collapsed for day one analyses because they received identical procedures on the first day of the study. For salivation, a 2 $\times$ 5 mixed ANOVA was conducted because salivation was collected across increments (i.e., five times per session). Where necessary, main effects and interactions were followed up with simple effects tests to clarify the relationships. Participants exposed to alcohol cues were predicted to initially exhibit significant increases in urge and salivation, and these effects were predicted to degrade over the course of extinction.

Effects of a context shift and extinction in multiple contexts were examined by conducting omnibus 3 (condition) $\times$ 4 (day) ANOVAs on the cue exposure change scores of the dependent variables (i.e., post cue exposure value minus baseline value) over the course of the four-day procedure. Main effects and interactions were followed by simple effects tests to clarify the relationships. Specific predictions were as follow: 1) the NC condition was predicted to exhibit a large difference in reactivity to cues on day four compared to day three, reflecting the differences in cues (day three = water; day four = alcohol); 2) the SC condition was predicted to exhibit significantly greater cue reactivity at day four compared to day three, reflecting the effect of the context shift between the two days; 3) the MC condition was predicted to exhibit significantly attenuated reactivity to alcohol cues compared to the SC condition on day four because of the preceding daily change in extinction context. Taken together, the topography of reactions to alcohol cues at day 4 was predicted to be NC > SC > MC.

For all analyses, statistical significance was set at $p < .05$ and effect size was calculated as partial eta-squared (η_p^2). All analyses were conducted using SPSS 14.0.

Results

Preliminary Analyses

At baseline, all data were adequately normally distributed, without outliers, and no data were missing. Initial examination of the data revealed that four individuals (two in the SC condition, two in the NC condition) did not react at all to alcohol cues and were excluded. For the remaining participants, no baseline differences were evident in urge to drink on the first day between groups ($F [2, 66] = 1.77, p > .14$). Analysis of baseline levels of urge over the course of the four days revealed no effect of condition or condition $\times$ time interaction ($ps > .10$), suggesting no cumulative effects on basal urge at the outset of the laboratory sessions.

Initial Cue Reactivity and Extinction

A 2 (group) $\times$ 6 (time) ANOVA on urge to drink revealed a significant main effect of group ($F [1, 66] = 11.42, p < .001, \eta_p^2 = .15$), a significant main effect of time ($F [5, 330] = 10.00, p < .0001, \eta_p^2 = .13$) and a significant interaction effect ($F [5, 330] = 6.83, p < .0001, \eta_p^2 = .09$). The interaction was clarified with individual t-tests at each time interval. As predicted, significantly greater urge to drink in the conditions receiving alcohol cues was evident following the alcohol cue exposure compared to the control condition ($p < .001$) and these differences successively became smaller over the course of extinction to the point of nonsignificance. These effects are depicted in Figure 1.

For salivation, there was a significant main effect of time ($F [5, 330] = 19.88, p < .0001, \eta_p^2 = .23$; initial $M = 4.71g [SE = .23]$, final $M = 3.31g [SE = .21]$), but no group effect ($F [1, 66] = 0.53, p > .45$) or interaction effect ($F [5, 330] = .47, p < .75, \eta_p^2 = .15$) was evident. Based on no differential levels of cue reactivity for salivation, no further analyses on salivation were conducted. A one-way three-group ANOVA indicated no differences in participant ratings of the similarity or clarity of imaginal stimuli between conditions during day one ($ps > .20$).

Renewal of Reactivity to Alcohol Cues and Effects of Multiple Context Exposure

A 3 (group) $\times$ 4 (day) ANOVA on change scores of urge to drink prior to and following the cue exposures each day (i.e., cue-elicited urge) revealed a significant effect of group ($F [2, 66] = 6.81, p < .005, \eta_p^2 = .17$), day ($F [3, 198] = 9.92, p < .0001, \eta_p^2 = .13$), and a significant interaction effect ($F [6, 198] = 11.49, p < .0001, \eta_p^2 = .26$). Follow-up univariate analyses were used to deconstruct these effects. Absolute values, change scores, and differences between groups for each of the four days are presented in Figure 2.

On day one, a significant group effect was evident ($F [2, 66] = 36.69, p < .0001, \eta_p^2 = .53$), with significantly greater cue-elicited urge in both groups receiving alcohol cues compared to the NC condition ($ps < .001$); this reflects the initial cue reactivity effect in the preceding section. On day two, a similar significant between-subjects effect was evident ($F [2, 66] = 8.58, p < .001, \eta_p^2 = .21$), reflecting the same differences between both the MC and SC conditions and the NC condition ($ps < .001$) and a decrease in magnitude of cue reactivity in the MC and SC groups of approximately 50%. On day three, a condition effect was no longer evident ($F [2, 66] = 1.31, p > .30$), reflecting further extinction to alcohol cues.

A one-way within-subjects ANOVA on change in cue-elicited urge in the NC condition from day three to day four revealed the predicted increase in cue-elicited urge on day four ($F [1, 21] = 16.35, p < .0001, \eta_p^2 = .44$). However, the same analysis of the SC condition revealed no significant increase in cue-elicited urge ($F [1, 22] = .16, p > .50, \eta_p^2 = .44$), suggesting no

renewal effect. A one-way between-subjects ANOVA on day four revealed a significant effect of condition ($F [2, 66] = 3.69, p < .05, \eta_p^2 = .10$), reflecting greater cue-elicited urge in the NC condition compared to the SC ($p < .05$) and MC conditions ($p = .10$), but, contrary to predictions, no difference was evident between the latter conditions ($p > .25$). In addition, the overall topography of urge to drink was $NC > MC > SC$ and did not conform to the predicted pattern. Taken together, although participants exhibited evidence of extinction over the course of the study, the results did not indicate renewal of cue-elicited craving as a result of a context shift or incrementally greater extinction via exposure in multiple contexts.

To further verify these findings, follow-up analyses were conducted using mixed ANOVAs (not change scores) on each day and including both reactors and nonreactors. All findings were the same. In addition, change scores for all three groups during the first exposure to alcohol cues (day one for SC and MC, day 4 for NC) were consolidated and analyzed to determine if there were any differences in initial cue reactivity using a one-way three group ANOVA, revealing no difference in reactivity between groups ($p > .10$). In terms of inter-session drinking, 56% of participants reported drinking at all between days one and three and did not take place disproportionately in any of the conditions ($p > .10$). The average number of standard drinks consumed over the three nights was 13.44 ($SD = 9.58$), or about four drinks per night. To examine whether inter-session drinking played a role in the results, the within-subjects day three to day four SC renewal analyses were reconducted using inter-session drinking as a covariate, but did this did not affect the findings. Likewise, including inter-session drinking as a covariate did not affect the day four between-subjects analyses.

Manipulation Checks and Post-experimental Data

Regarding the first three days of the study, 100% of the participants correctly endorsed whether they had been exposed to three different contexts (MC) or the same context (SC and NC). In terms of specifically identifying the colors of the contexts they experienced, 98.7% of the participants correctly selected the colors of the rooms in which they had been. In terms of identifying whether the narrators' voices were the same (SC and NC) or different (MC), 84% correctly identified whether the narrator was the same or different. Taken together, these data suggest that the participants recognized the experiment's context manipulations. In terms of participant perceptions of the procedure, 87% of participants stated that they would recommend participation in the study to their friends, suggesting that the procedures were not aversive.

Discussion

Robust findings from basic research have demonstrated the context dependency of extinction, potentially explaining the generally mediocre outcomes of CET for alcohol dependence. To further explore this possibility, the current study experimentally investigated whether a context shift following extinction would result in renewed reactivity to alcohol cues and whether multiple context extinction would attenuate this renewal. Consistent with predictions, participants initially exhibited robust initial increases in urge for alcohol and diminution of these responses via prolonged exposure with response prevention. This was evident both within the first session and over the course of the study. Contrary to predictions, however, at the test trial, there was neither evidence of renewed reactivity based on a context shift, nor evidence of significantly greater extinction due to extinction in multiple contexts. Indeed, qualitatively, the SC condition, which included extinction in the same context during the three preceding days, exhibited the most pronounced effects of extinction on the test day.

On one level, these findings can be interpreted in a positive light, indicating that extinction did generalize from one context to another and supporting the clinical promise of CET. Such generalization of extinction as observed in this study may in fact be responsible for the positive clinical effects of CET that have been reported (e.g., Drummond & Glautier, 1994; Monti et

al., 1993, 2001). However, the absence of a renewal effect was nonetheless in contrast to the predicted effects. This finding may be partially understood in the context of the larger translational literature connecting the animal and human findings on factors affecting extinction to alcohol cues. Only two studies have empirically investigated this area in human drinkers, with mixed results. Collins and Brandon (2002) found a renewal of urge and salivary reactions to alcohol cues, and also found attenuation of those reactions via an extinction cue. However, a recent study by Stasiewicz, Brandon, and Bradizza (2007) examined renewal and the effects of an extinction cue in a large clinical sample and found neither evidence of renewed reactivity, nor any effect of an extinction cue. The current study clearly converges with the latter.

Although the context dependency of extinction demonstrated in basic research is a highly plausible explanation for mediocre CET findings, the findings from Stasiewicz et al. (2007) and the current study could be interpreted as suggesting that extinction to alcohol cues does not appear to be context dependent. However, this seems unlikely given the extent of the basic scientific evidence on the nature of extinction (Bouton, 2002b). Rather, it seems more likely that extinction to alcohol cues is more or less generalizable based on various dimensions of the contextual conditions under which it takes place and is assessed, as has also been demonstrated by basic research (e.g., Brooks & Bouton, 1993; Gunther et al., 1998). Albeit only among three studies, the differences between the current study, Stasiewicz et al. (2007), and Collins and Brandon (2002) may provide insight into the conditions for observing renewal. Collins and Brandon (2002) differs from the two other studies in their use of massed trials in a single experimental session. Stasiewicz et al. (2007) used one extinction session and one test trial, and the current study used three consecutive extinction sessions and one test trial. In both cases, these multi-day procedures were implemented to more closely map onto the procedures used for CET (e.g. Drummond & Glautier, 1994; Monti et al., 1993). This parallel was intended to increase the robustness of the renewal effect in both studies, although paradoxically this was not the case. Stasiewicz et al. (2007) also differed from the current study and Collins and Brandon (2002) by using ambulatory alcohol dependent adults, as opposed to heavy drinkers, but this does not appear to have played a role in differences between studies.

Thus, renewal of alcohol cue reactivity effects may be more readily observable during single-session manipulations. This may be because participants perceive greater distinctions between contexts within a single session than in multiple sessions, where different contexts may be perceived as all simply being related to the study. However, this conclusion must remain speculative and it is hard to draw firm conclusions from only three studies, one positive and two negative. Given the importance of understanding extinction learning, identifying the conditions under which extinction of reactivity to alcohol cues does and does not generalize should be subject to systematic experimental investigation in future studies. It will be of high priority to determine not only the extent to which extinction observed in the laboratory (or clinic) renews in a novel context, but also in the drinker's typical drinking context. This question is at the heart of whether the limitations of CET are based on limited generalizability of extinction or other factors. Furthermore, consistent with a translational research approach, further clarification of the parameters of alcohol-related extinction learning may also contribute to an increased understanding of basic associative learning.

With regard to the effects of multiple context extinction, the interpretation that this approach did not attenuate renewal should be tempered by the fact that such a finding was predicated on evidence of a renewal effect in the SC condition. Because renewal was not evident in the SC condition, although the hypothesis was not supported, the current findings also do not contradict this possibility. Recent human studies investigating multiple context extinction to enhance the generalizability of extinction fear cues have reported mixed findings. Vansteenwegen et al. (2007) found positive effects of multiple context extinction in reducing

fear, but Neumann, Lipp, and Cory (2006) found no effect. At this point, the prospect of using multiple context extinction to enhance CET remains a possibility that is worthy of further pursuit. However, it is important to note that the use of multiple context extinction is but one of several promising strategies for extinction to alcohol cues, including other behavioral strategies (e.g., Denniston, Chang, & Miller, 2003), virtual reality (e.g., Lee et al., 2007), and pharmacological agents (e.g., Hofmann, 2007). In each case, if these approaches reliably enhance extinction, they may in turn enhance CET.

To recapitulate, although this study revealed the predicted findings with regard to cue reactivity and extinction, the hypotheses regarding the effects of a context shift and multiple context extinction were not supported. In reference to the small existing literature in this area, these findings diverge from those of Collins and Brandon (2002) but are similar to those of Stasiewicz et al. (2007). At this point, given the robust basic research and mixed human studies in this area, these findings suggest that systematic research is needed to clarify the parameters for understanding the context dependency of extinction to alcohol cues in humans, both for drinkers in general and those with alcohol use disorders receiving CET.

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Figure 1. Effects of alcohol cue exposure and extinction on urge to drink over the course of day one. Means and standard errors are presented. Conditions SC and MC are consolidated because they received identical procedures. Statistical significance reflects follow-up t- test tests; *ns* = nonsignificant, * $p \leq .05$, ** $p \leq .01$, *** $p \leq .001$.

Figure 2.

Differences in urge for alcohol during initial (acute) cue exposures on days one, two, three, and four. Panel A presents absolute means and standard errors across the three groups. Panel B presents differences in changes in urge between groups each day. All effects reflect individual comparisons between the experimental groups (SC and MC) and the control group (NC); no significant differences between the SC and MC groups were detected. Statistical significance reflects differences detected using univariate follow-up tests; † $p \leq .10$, * $p \leq .05$, ** $p \leq .01$, *** $p \leq .001$.

Table 1

Experimental design. Initial letters denote the type of cues used each day. Suffixes denote whether the context was the same or different for days two, three, and four; no suffix is used for the first day because it had no preceding day. On day one, the initial alcohol cue reactivity hypothesis was Control < Single Context = Multiple Context. At the test trial, the alcohol cue reactivity hypothesis was Control > Single Context > Multiple Context.

	Day One	Day Two	Day Three	Day Four (Test Trial)
Control	N	N-S	N-S	A-D
Single Context	A	A-S	A-S	A-D
Multiple Context	A	A-D	A-D	A-D

Notes: N = Neutral Cues, A = Alcohol Cues; for day two on, suffix of S = Same as preceding day, suffix of D = different from preceding day.