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Translation of Associative Learning Models into Extinction Reminders Delivered via Mobile Phones During Cue Exposure Interventions for Substance Use

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Abstract

Despite experimental findings and some treatment research supporting the use of cues as a means to induce and extinguish cravings, interventions using cue exposure have not been well integrated into contemporary substance abuse treatments. A primary problem with exposure-based interventions for addiction is that after learning not to use substances in the presence of addiction cues inside the clinic (i.e., extinction), stimuli in the naturalistic setting outside the clinic may continue to elicit craving, drug use, or other maladaptive conditioned responses. For exposure-based substance use interventions to be efficacious, new approaches are needed that can prevent relapse by directly generalizing learning from the therapeutic setting into naturalistic settings associated with a high-risk for relapse. Basic research suggests that extinction reminders (ERs) can be paired with the context of learning new and more adaptive conditioned responses to substance abuse cues in exposure therapies for addiction. Using mobile phones and automated dialing and data collection software, ERs can be delivered in everyday high-risk settings to inhibit conditioned responses to substance use-related stimuli. In this review, we describe how associative learning mechanisms (e.g., conditioned inhibition) can inform how ERs are conceptualized, learned, and implemented to prevent substance use when delivered via mobile phones. This approach, exposure with portable reminders of extinction, is introduced as an adjunctive intervention that uses brief automated ERs between clinic visits when individuals are in high-risk settings for drug use.

Despite the development of empirically-supported behavioral treatments for substance use, there remains room for improvement. A longstanding and primary problem in treatments for addiction is preventing relapse in high-risk contexts (e.g., Carroll, Rounsaville, & Keller, 1991; Marlatt, 1990; Marlatt & Gordon, 1985). High-risk contexts include settings and stimuli that have a high probability of eliciting conditioned responses proximally associated with subsequent drug use (e.g., craving, urges, drug-seeking behavior, etc.). Although avoidance of high-risk settings including people, places, and things associated with

substance use is a key principle used across many treatments, it is not always possible to avoid conditioned stimuli associated with addiction. Substance users need not only to avoid such cues, but also need to use a range of behavioral and cognitive strategies to reduce the probability of drug use in high-risk contexts.

Indeed, high rates of relapse in well-controlled studies suggest that even some of the best treatments for substance use may need to be enhanced, or that new more powerful treatments need to be developed. For example, in the NIDA Collaborative Cocaine Treatment Study, approximately 40% to 60% of all patients across treatment conditions used cocaine in the previous month at a 6 month follow-up post-treatment, and 40% to 50% of all patients had used cocaine in the last month at the 12-month follow-up (Crits-Cristoph et al., 1999). One potential solution to the problem of relapse is to develop behavioral interventions that directly train new conditioned responses to drug-related cues during treatment sessions (e.g., cue-exposure), and to use ambulatory computer-based technologies (e.g., mobile phones) to directly transfer these newly learned responses outside the clinic setting, in contexts where the probability of drug use is high. Newly learned responses to drug-related cues that emerge during treatment can be cognitive (e.g., rehearsing cognitive reappraisal in response to addiction cues), emotional (e.g., experiencing negative emotions without avoiding them), or behavioral (e.g., avoiding or escaping substance-related stimuli), and can be mediated by top-down (e.g., strategic processing, with awareness) or bottom-up (e.g., automatic, without awareness) neurobehavioral processes.

Novel interventions using technology to deliver both top-down and bottom-up approaches for addiction have recently begun being developed. Smartphone and internet-based interventions, for example, provide psychoeducation, cognitive, and behavioral strategies to help individuals in a top-down manner learn adaptive ways of thinking and behaving that may help reduce substance use (e.g., Bickel, Christensen, & Marsch, 2012; Marsch, 2012; McTavish et al., 2012; Whittaker et al., 2012). There are many possible ways to leverage technology to improve or develop new treatments for substance use, and several challenges are important to overcome as these treatment technologies advance. One common challenge for technology-based interventions is that they can be complex and time-consuming (e.g., using a computerized cognitive and behavioral coping skill training program), requiring that substance users self-initiate or engage in significant amounts of practice in order to learn new skills (i.e., therapy homework). Although this may not be problem for some individuals, interventions requiring significant cognitive processing, problem solving, motivation, or time may be inadequate in reducing substance use for other individuals. Another challenge is the need to develop technology-based interventions that can be used across substances of abuse and individuals, rather than developing and testing many different technologies unique in content and design for specific substances and/or populations.

Technological innovations for substance use treatments are needed that are: (a) simple, (b) brief, (c) able to be used across diverse substances and substance users, and that (d) provide automated interventions designed to elicit quick and automatic cognitive and behavioral changes concordant with abstinence. Exposure-based interventions that directly pair novel stimuli (e.g., tones) with the absence of conditioned responses (e.g., craving, drug use) in the

presence of drug-related conditioned stimuli (i.e., cues used in cue exposure interventions) and, subsequently, deliver these extinction reminders (ERs) via mobile phones may offer promise as a bottom-up approach to reducing relapse.

The primary aim of this paper is to outline how ERs can be conceptualized using associative learning models in order to be tested using mobile phones in adjunctive cue-exposure interventions for substance use. First, exposure therapies and extinction in the context of substance use are described. Second, processes underlying common threats to extinction which help explain relapse are outlined. Third, ERs delivered via mobile phones in naturalistic settings are suggested as a possible solution to problems with maintenance and generalization of extinction following exposure-based interventions. Fourth, technical accounts of contemporary associative learning models are detailed as candidate basic processes that may help explain mechanisms of ERs in relapse prevention. This translation of basic associative processes is intended to provide a framework for exposure with portable reminders of extinction as a novel behavioral intervention that includes controlled cue exposure in the therapeutic setting coupled with the delivery of ERs in high-risk naturalistic contexts using mobile phones to help reduce substance use. Finally, considerations are suggested for future research examining the use of ERs via mobile phones as a component of cue-exposure interventions.

Classical Conditioning Helps Explain How Responses to Drug-Related Cues are Acquired

In a classical conditioning paradigm, a neutral stimulus (e.g. tone) becomes a conditioned stimulus (CS) and elicits a conditioned response (CR, e.g. freezing) as a result of the stimulus being repeatedly paired with an unconditioned stimulus (US, e.g. shock). This process is known as “acquisition” (Pavlov, 1927), and is used to help understand the development of responses to cues in a wide variety of psychiatric disorders. For example, neutral stimuli or contexts that are present during panic episodes become associated with the panic response, and, subsequently, may trigger the panic episode next time the patient encounters these conditioned stimuli (Bouton, Mineka, & Barlow, 2001). A similar process plays a role in addiction. During the development of addiction, the drug (e.g., cocaine) acts as a US as it elicits an unconditioned response (UR; e.g., physiological responses) to compensate for the drug effects. Meanwhile, these effects become associated with neutral discrete and contextual stimuli present during drug exposure (e.g., people, places and things present during drug use). As a result, these contextual stimuli can become CS capable of eliciting CRs such as conditional compensatory responses that can occur even in the absence of the drug itself (Siegel, 2005). In addition to compensatory responses, the drug-associated stimuli can elicit craving for the drug when the person encounters these cues in the absence of the drug. Once CR to drug cues are acquired and reinforced with drug use, tolerance to the effects of the drug may increase, resulting in vulnerability to the development of addiction.

Exposure-Based Interventions and Extinction of Conditioned Responses

In contrast to acquisition, “extinction” refers to the process where the CS is presented alone in the absence of the US in order to decrease or eliminate the CR. The most commonly used behavioral therapies using extinction procedures are exposure therapies for anxiety disorders. There are a number of different specific exposure therapies for anxiety disorders (e.g., prolonged exposure, exposure and response prevention, etc.), and, collectively, these therapies are among the most well-researched evidence-based approaches across psychiatric disorders. Despite the differences in specific exposure therapy protocols, they share many similarities in underlying models of learning and treatment procedures. For example, all exposure therapies involve presenting CS (e.g., anxiety-related cues that are safe) to patients in a safe, structured, and controlled manner in order to elicit and extinguish CRs (e.g., anxiety, avoidance, etc.). When maladaptive CRs are extinguished (e.g., anxiety is decreased, etc.), new and more adaptive responses (e.g., approach behavior increases to safe but previously avoided cues) to CS can emerge and, over time, compete with the previous CR when subsequent CS are present, resulting in reduced anxiety.

Exposure therapies are rooted in classical and operant conditioning models of behavior change (e.g., Mowrer, 1960). The exact mechanisms of change are unknown in these therapies, though much research is occurring on this topic (e.g., McNally, 2007). However, for extinction training to occur, it is critical that repeated exposure to CS is not reinforced by previously learned and maladaptive CRs. For example, in exposure therapies for obsessive-compulsive disorder, exposure to cues that elicit obsessions are followed immediately by the inhibition of compulsive behavior (i.e., response prevention). This model has been extended to addiction. In previous studies, cues associated with substance use have been used to elicit CRs associated with drug use in the therapeutic setting, in order to extinguish responses to drug cues and reinforce new, more adaptive responses (for a meta-analysis, see Conklin & Tiffany, 2002).

Among a wide range of substance users, exposure to drug-related conditioned stimuli (e.g., seeing paraphernalia, watching others use) in a laboratory or clinic context is associated with increased desire to use and psychophysiological arousal (e.g., Childress et al., 1988; Johnson et al., 1998). Although there have been many laboratory studies using various different types of drug-related stimuli (e.g., videos of substances being ingested, paraphernalia, etc.) to induce cue reactivity, interventions designed to reduce substance use via cue exposure have demonstrated little efficacy as stand-alone interventions (e.g., Dawe et al., 1993; Drummond & Glautier, 1994; Monti et al., 1993; O'Brien et al., 1990; Powell et al., 1993). Indeed, in a meta-analysis of cue-exposure treatments for addiction, the overall effect size across nine studies was not significant ($d = .08$; Conklin & Tiffany, 2002).

During cue exposure for substance use, drug-related cues are repeatedly presented in the therapeutic setting by a counselor or therapist without being followed by immediate substance use. As with anxiety disorders, there are many different ways in which exposure can be conducted for addiction, including imaginal exposure (e.g., rehearsing imaginably a substance use-related situation), exposure to drug-related CS (e.g., lighters, money, videos depicting people using, etc.), or virtual reality-based exposure (e.g., Bordnick et al., 2008;

Saladin et al., 2006). Similar to exposure-based interventions for anxiety disorders, cue exposure for substance use can elicit and extinguish CRs (e.g., craving to use), and this process can be measured using subjective (i.e., self-reported urge to use) and/or biological measures (e.g., peripherally via psychophysiological responses, or centrally via neuroimaging). However, after craving or other CRs to addiction cues are extinguished in the clinic setting using any cue exposure protocol, a re-emergence of the originally conditioned response may occur. To understand how relapse may occur following exposure therapy, it is helpful to consider basic processes associated with extinction learning.

Extinction during cue exposure for substance use is a phenomenon wherein subsequent to the CS-US pairings, the CS (e.g., lighter) is presented alone in the absence of the US (e.g., cigarette) in order to decrease or eliminate the CR (e.g., smoking behavior) elicited by that CS. There are two basic hypotheses on the underlying mechanism of extinction. Some associative models (e.g., Rescorla-Wagner, 1972) suggest that the association between the CS and the US is unlearned. Alternative models (e.g., Konorski, 1948, 1967) proposed that the initially established excitatory CS-US associations are counteracted by a new inhibitory association. According to Larrauri & Schmajuk (2008), and supported by recent findings (Polack, Laborda, & Miller, 2012), during extinction the context becomes inhibitory (i.e., reduces the probability of the CR), counteracting the excitatory associations of the CS. Over time or in different (i.e., non-training) contexts, the CR to an extinguished CS may recover, indicating that extinction learning during exposure therapy should not be expected to indefinitely eliminate the CS-US association, but more likely inhibits the expression of these associations (e.g. Pavlov, 1927; Myers & Davis, 2007).

A Primary Problem with Exposure Therapies: Threats to Maintenance and Generalization

There have been criticisms of using exposure as an intervention in treatments for addiction (e.g., Drummond, Cooper, & Glautier, 1990; Tiffany, 1990). One important concern is that cue exposure may extinguish substance use-related CRs (e.g., craving) to relevant CS inside the clinic, but this extinction learning may not maintain over time or generalize across contexts *outside* the clinic, resulting in relapse. There are several common phenomena following extinction that contribute to relapse in exposure therapies: (1) spontaneous recovery, (2) reinstatement, and (3) renewal effects.

Spontaneous recovery refers to the recovery of the extinguished CRs elicited by the previously extinguished CS as a result of passage of time (Rescorla, 2004). For example, a patient whose urge to smoke crack cocaine is extinguished through cue exposure may re-experience the urge sometime after the therapy when encountering a stimulus that elicits memories of drug use (e.g., holding a lighter). Bouton has suggested that the excitatory associations acquired during conditioning generalized well across different contexts whereas the inhibitory associations learned during extinction are more sensitive to the changes in the context (Bouton, 1994). Therefore, any changes in the temporal or physical contexts may interfere with the retrieval process of the extinction memories. Consequently, the temporal delay following extinction results in a failure to retrieve the extinguished responses which could inhibit the CR (i.e., urge to use), because over time the extinction context cannot be

static and as a result of the dynamic nature of context over time, this “same” therapeutic setting is perceived as being different. Put differently, the memory of associations between the context and CS become inactive because the time when spontaneous recovery occurs is after the extinction training (e.g., Bouton, 1988, 1993). Therefore, when the extinguished CS (e.g., lighter) is presented in the same context after a delay, the extinction memory is not retrieved completely, resulting in recovery of the CR (i.e., urge to smoke). In line with this model, a discrete retrieval cue that functions as a reminder of the extinction context may reduce the amount of spontaneous recovery (Brooks and Bouton, 1993, 1994; Brooks, 2000). A retrieval cue (e.g., a neutral and novel stimulus) originally employed as a conditioned inhibitor in an extinction context can be considered an ER, and could be presented after training to reduce spontaneous recovery in the original extinction training context.

However, it is important to note that in exposure-based interventions for substance use, in vivo exposure to substance abuse cues outside the clinic is typically inappropriate (i.e., it may increase the probability of substance use), and, as such, the context of cue exposure is likely to be the clinic setting. Because the context for drug use is outside the extinction training context, ERs need to be conceptualized and learned to be used less as a way to reduce spontaneous recovery in the clinic setting and more directly in order to prevent relapse effects expected to occur in naturalistic high-risk settings for drug use. Both reinstatement and renewal effects are associated with exposure to substance abuse-related cues likely to be encountered in the natural environment.

Reinstatement refers to recovery of the extinguished CR as a result of subsequent exposures to the US after extinction (e.g., Rescorla and Heth, 1975). For example, reinstatement effects are thought to occur when, after urges to smoke crack cocaine are extinguished in the clinic setting through non-reinforced exposure to cocaine-related cues, the individual encounters the original US, in this case crack cocaine in his or her natural environment, and has strong urges to use again. According to Larrauri and Schmajuk (2008), the phenomenon of reinstatement demonstrates that making the extinction context neutral or excitatory eliminates the inhibition exerted by the context and therefore, the CR for the extinguished CS is recovered (e.g., Pavlov, 1927; Rescorla and Heth, 1975). Interestingly, if the reinstating US presentations take place in a different context than the original extinction context, the CR is less likely to be recovered in the extinction context (e.g., Bouton and Bolles, 1979; Bouton and King, 1983; Bouton, 1984; Baker, Steinwald, & Bouton, 1991; Wilson, Brooks, & Bouton, 1995; Frohardt, Guarraci, & Bouton, 2000). This suggests that reinstatement of the craving to the drug cues will be stronger if the patient uses drugs in or near the treatment setting (i.e., the extinction context) than if drugs are used in a different context removed from the treatment setting.

Renewal refers to the recovery of the extinguished CR when the CS is presented in a context that is different from the original extinction context (Bouton and King, 1983). Once the individual is outside the extinction context (e.g., they have left the clinic after cue exposure sessions and are in their natural environment), relapse may occur due to the differences between the training and naturalistic contexts. For example, a person whose urge to smoke crack cocaine triggered by holding a lighter is successfully extinguished in the therapy

context may feel the urge to smoke again when encountering the lighter outside the therapy setting (e.g., at home) in the absence of the inhibition provided by the therapy context. Renewal effects occur when CS-US pairings are first made in Context A (e.g., smoking at home) and CS alone trials are then presented in Context B (e.g., exposure to a lighter repeatedly without smoking inside the clinic setting). When exposed to the same CS back in the original acquisition Context A, the extinguished CR (e.g., urges to smoke) re-emerges as a result of returning to the acquisition context (e.g., Bouton and King, 1983). As outlined next, prevention of renewal may be made possible by pairing novel extinction reminders (i.e., ERs) with the extinction training context in which exposure therapy occurs. Another possibility is that ERs used both in the extinction and the acquisition contexts may help decreasing renewal by increasing the similarity between these two contexts. Therefore, extinction learning about the drug associated cues may be generalized from the therapy contexts to the home context through ERs and therefore, help to reduce relapse.

Introduction to a Possible Solution: Exposure with Portable Reminders of Extinction

In order to improve outcomes of exposure-based therapies for substance use, solutions need to be developed to address common threats to the maintenance and generalization of newly learned adaptive CRs. One solution may be to pair novel and neutral cues (e.g., sounds) with the context of extinction learning in exposure therapies within a clinic setting, and to deliver these extinction reminders (ERs) across relevant naturalistic contexts using mobile phones with automated delivery and data collection systems. This approach, exposure therapy with portable reminders of extinction, couples associative learning models with contemporary technologies in an effort to translate basic scientific findings into novel substance use interventions.

To deliver and evaluate ERs in order to prevent reinstatement effects, it may be useful to use mobile phones that can directly sample cravings to use and drug use in response to drug-related CS that cannot be avoided. This can be accomplished using software localized to a smartphone or connected remotely to a server at a treatment facility. A key advantage to using a remotely connected approach is the ability to use automated dialing or interactive voice recognition software to push calls out on a predetermined basis to individuals in treatment. This approach enables random and event contingent sampling of urges to use substances or risk for relapse. When individuals report being in a high-risk setting for relapse where reinstatement may occur (e.g., seeing drugs being used), they can be prepared to press a button on their phone (e.g., speed dial) in order to automatically hear the ER (or see it, if the ER is visual and presented on a smartphone) if the US is confronted. In this way, the mobile phone is used to provide a bottom-up reminder of the extinction training context, and data can be collected using the phone keypad to assess change in craving or other indices proximally linked to risk for drug use before and after the ER. In addition to using ERs to prevent reinstatement effects, portable reminders of extinction using mobile phones can be implemented to prevent drug use when the US is not present, but when the individual encounters CS associated with drug use (e.g., seeing a used needle in the trash) and renewal effects may occur.

As detailed below, the framework for portable reminders of extinction is rooted in animal and human learning research. For example, Bouton and Brooks (1993) used ERs in animal conditioning studies by pairing a novel cue with extinction training. After associating the novel cue with extinction, the ER was re-presented upon subsequent return to the original conditioning context in order to enhance extinction learning. Translating this model to a sample of social drinkers, Collins and Brandon (2002) similarly found that a novel ER (i.e., an unusual eraser) presented in the context where extinction to alcohol cues occurred reduced craving when alcohol cues were presented in a different (non-training) context containing the ER. To extend this research into clinical trials, it may be informative to consider underlying models of associative learning that can account for the effects of ERs. Indeed, the robust body of basic research on associative learning offers several primary explanations for the effects of ERs that can inform ways to optimize translational efforts to develop and test portable reminders of extinction as a way to directly intervene in the substance user's environment when risk for relapse is high but drug use has not yet occurred.

Basic Processes Underlying Portable Reminders of Extinction: Conditioned Inhibition of Discrete Stimuli

Because ERs may exert their influence by inhibiting previously learned responses to substance-related cues, they may function as conditioned inhibitors. Conditioned inhibition was defined by Pavlov (1927) as an inhibitory relationship between a stimulus (e.g. tone) and an unconditioned stimulus (food, US) which results in reduced or inhibited conditioned responses (e.g. salivation to tone which was previously paired with food, CR). Conditioned inhibition has been demonstrated in several different species and paradigms including, for example, fear conditioning (e.g. Zimmer-Hart & Rescorla, 1974), appetitive conditioning (e.g. Bower & Grusec, 1964), and drug self-administration (e.g. Kearns, Weiss, Schindler, & Panlilio, 2005) in rats, nictitating membrane response in rabbits (e.g. Marchant, Mis, & Moore, 1972), autoshaping in pigeons (e.g. Brown & Jenkins, 1967), fear conditioning (e.g. Neumann, Lipp, & Siddle, 1997; Grillon & Ameli, 2001) and causal learning (e.g. Kutlu & Schmajuk, 2012) in humans.

There are at least four ways to train a conditioned inhibitor (see Figure 1). One way is to pair a CS (e.g., a lighter), A, consistently with the US (e.g., cigarette) while presenting another CS (e.g., novel tones), X, consistently in the absence of the US. This method is called “differential inhibition” where consequently, with repeated exposure to X in the absence of US, X becomes a conditioned inhibitor. Another method is to present X “explicitly unpaired” with the US. This would include presenting X and the US negatively correlated in time where the CS and US presentations never coincide. A third method, known as “inhibition of delay” is to use a temporally long presentation of the CS where the US occurs at the end of the presentation of the CS. With training, it may be expected that the CR will decrease during the earlier presentation of the CS, which could decrease the probability that the CS would elicit the CR. Finally, the “conditioned inhibition” method occurs when A (i.e., the CS, in this case a lighter) is presented with the US (A-US trials) and the US presentation is omitted when A is paired with X (AX- trials). Following this method of

training, CRs are expected when A is presented but are expected to decrease when A is presented simultaneously with X.

According to the influential Rescorla and Wagner (1972) model, conditioned inhibition is a result of omission of the US when it is expected. In the conditioned inhibition paradigm (A-US, AX-NoUS), the model assumes that due to A-US trials A comes to predict the US but during AX-noUS trials the predicted US is absent and therefore, X forms negative (inhibitory) associations with the US. During exposure therapy, drug related cues (A) serve as the excitors and signal the presence of the drug (US). Consequently, ERs (X) presented during the therapy form inhibitory associations due to omission of the otherwise signaled drug. Similarly, the contextual cues during exposure therapy can acquire inhibition through the same mechanism. Thus, if the inhibitory ERs learned during the exposure therapy are presented in another drug-associated context (e.g. home) they may be able to reduce the probability of CR (e.g., craving, drug use).

The inhibitory strength of X, using any of the abovementioned training paradigms, can be examined in the laboratory using summation and retardation tests (e.g., Papini and Bitterman, 1993; Rescorla, 1969). A summation test consists of presenting the putative inhibitor, X, with a conditioned excitator with the expectation that the inhibitory CS would decrease the strength of the CR to the excitatory CS in comparison of the CR only to the excitator. In contrast, a retardation test consists of conditioning trials of the conditioned inhibitor with the expectation that the inhibitory CS takes longer to become excitatory than a neutral CS. As part of treatment development, laboratory-based tests of associative mechanisms underlying ERs can use summation and retardation tests to investigate whether ERs acquired inhibitory properties.

Basic Processes Underlying Portable Reminders of Extinction: Extinction Context as an Occasion Setter

Although associative learning models explain extinction and recovery effects based on the context becoming inhibitory during extinction, some studies have not observed direct inhibitory associations between the context and US during extinction (Bouton & King, 1983, Bouton & Swartzentruber, 1986, 1989). For example, Bouton and Swartzentruber (1989) showed that the extinction context failed to pass a summation test, suggesting it did not form direct inhibitory associations with a US. Because some attempts to demonstrate direct Context-US associations have failed, as an alternative to conceptualizing contextual ERs as conditioned inhibitors, Bouton (1993, 2004) has suggested that the extinction context may become a *negative occasion setter*, which controls the CS-US associations without forming direct associations with the US. That is, whereas simple conditioned inhibitors directly signal the absence of the US, occasion setters enable another CS to signal that the US will not occur.

Occasion setters have several characteristics that differentiate them from conditioned inhibitors and, in the context of exposure-based interventions for substance use, may have different implications for treatment. First, negative occasion setters for excitatory CS do not attenuate responding to a different excitatory CS. That is, occasion setters do not pass a

summation test (Morell & Holland, 1993). For example, if the therapy context is learned as a negative occasion setter for a specific CS (e.g., lighter), this context would not reduce craving for drug use initiated by a different excitatory CS (e.g., smelling cigarette smoke) for the same behavior. Second, occasion setters' ability to modulate a CS-US association is not affected when they are directly paired with the US. However, a negative occasion setter can inhibit the CS-US excitatory association rather than directly inhibiting the US. As such, when a negative occasion setter is separately paired with a US and tested with its original target again, it still reduces CRs to its target (Holland, 1989). Accordingly, contextual stimuli that function as negative occasion setters will elicit reduced urges to use substances when presented in the presence of CS, even if the therapy context itself becomes associated with subsequent drug use.

ERs may function as conditioned inhibitors for substance use when learned in a clinic setting to be directly inhibitory and as occasion setters by exerting inhibition without directly becoming inhibitory. Ross and Holland (1981, also Rescorla, 1985) found that a CS becomes a conditioned inhibitor if presented simultaneously with the excitor (simultaneous feature-negative discrimination) and becomes a negative occasion setter if it temporally precedes the excitor (serial feature-negative discrimination, see Figure 2). As discussed above, occasion setter ERs do not pass the summation test as they cannot be transferred to another excitatory CS unless the excitor is the target CS of another negative occasion setter (Morell & Holland, 1993, Holland, 1986, 1989). Therefore, ERs learned through occasion setting are only effective to a specific CS and cannot be used for different CS. In contrast, conditioned inhibitors can be transferred to other excitatory CS (i.e., other drug cues).

One way to use negative occasion setters would be to repeatedly pair these cues (e.g., tones) with a signal that an impending CS in the exposure protocol will not precede the drug-related US. After sufficient training, the negative occasion setter can be delivered via mobile phones as a preventive intervention before a US is present, and/or before any of a number of naturalistic CS are present. In this case, the individual would be trained clinically to call the clinic server to hear the ER when he or she was in a situation that did not yet contain substance-related cues but for which such cues could eventually become present (e.g., driving through a neighborhood with many drug-related CS that cannot be easily avoided).

Considerations for Research Testing ERs

In sum, basic research on spontaneous recovery, renewal, and reinstatement effects suggest that extinction during cue exposure for substance use does not lead to the unlearning of CS-US associations. Instead, these associations are likely masked by inhibitory associations of the extinction context. In the absence of these inhibitory effects from the extinction context, excitatory CS-US associations are likely to be expressed and the CR is recovered. In substance use treatments using exposure-based interventions, this means that repeated exposure to substance-related cues in a controlled and safe setting (i.e., the clinic) is unlikely to be sufficient as a stand-alone intervention in preventing relapse. Extinguished CRs such as craving or drug-seeking behavior in the presence of drug-related cues likely will occur: (a) later in time within the same extinction context due to spontaneous recovery, (b) upon re-exposure to the drug-related US due to reinstatement, or (c) in the naturalistic settings of

everyday life outside the clinic due to the distinct differences between the clinic and real-world contexts. Bouton (1993) suggests that these phenomena may be due, in part, to a failure in the retrieval of memories associated with extinction training. For example, after leaving the therapeutic setting and returning to the naturalistic context in which drug use occurs, the individual may recall a memory of conditioning following drug use, not extinction, and subsequent drug use may be more likely to occur.

For cue-exposure interventions to be efficacious, strategies are needed to reduce relapse that thoughtfully account for these basic behavioral phenomenon. One way to prevent relapse outside the clinic may be to leverage the process of conditioned inhibition occurring in the clinic setting during extinction learning. As described above, portable reminders of extinction include cue-exposure interventions that use novel ERs paired with the extinction context which are used on an *ad hoc* basis in an automated manner via mobile phones to reduce drug use in naturalistic settings, either preventatively as occasion setters or to directly inhibit CRs as conditioned inhibitors.

We have described associative mechanisms underlying relapse following cue exposure interventions for substance use, and suggest that mobile phones can be used as a technology platform to deliver ERs learned inside the clinic in order to generalize the effects of extinction learning outside the clinic. Mobile phones have advantages over discrete physical stimuli as ERs. They are found across all segments of the U.S. population, and have recently been utilized in the treatment of substance abusing patients (e.g., Gustafson et al., 2011; Whittaker et al, 2012). Mobile phones continue to become less expensive with more functions, and can be used to measure peripheral psychophysiological data (e.g., heart rate), global positioning (i.e., GPS), behavioral movements and expression (e.g., speed of typing, vocal expressions) in naturalistic settings. Mobile phones with connected software can provide a wealth of data to treatment centers about substance use, cravings, and other measures of daily functioning germane to treatment planning. In short, there is great potential in the use of mobile phones as a technological platform for substance use interventions.

The relative absence of human clinical data on ERs provides ample opportunities for future research in this area to translate basic behavioral findings into portable reminders of extinction as an efficacious treatment approach. Many parameters of portable reminders of extinction in general and ERs specifically need to be investigated. For example, it is unknown how to optimize the presentation of ERs in order to obtain the most durable effects over time. Additionally, it is unknown what specific formal or functional properties of ERs are necessary and sufficient to help reduce drug use. Novel and neutral ERs should be effective when they are paired with the extinction context and no other learning contexts. However, it is an empirical question whether, for some individuals, ERs may be optimized when they are paired with a previous learning history before treatment. Similarly, it is unknown whether ERs should be highly arousing or neutral in emotional valence.

ERs used as part of portable reminders of extinction need to be carefully investigated before it is understood how to optimally translate them into clinical protocols. Studies examining the effects of ERs are needed both inside and outside the extinction context. Because most

research on ERs has been conducted within the laboratory, it is necessary to begin translating the extant basic animal and human learning research out of the laboratory and into novel adjunctive interventions. Indeed, when testing for the efficacy of ERs in preventing reinstatement, evaluations in the extinction context (i.e., the therapeutic setting) may overestimate the effects of ERs compared to what might be expected in the natural settings where US are confronted. In addition, the acceptability of ERs on mobile phones has yet to be characterized, and research is needed to investigate how to deliver ERs when individuals have used substances after being presented ERs.

Although strategies for reducing relapse in high-risk contexts vary across the most promising treatments for addiction, (e.g., *avoid* high-risk situations, develop cognitive and behavioral coping skills, include sober significant others as community reinforcement for abstinence; e.g. Higgins et al., 2000; Mercer & Woody, 1999), the general approach across drug counseling, contingency-based reinforcement, coping skills training, and relapse prevention training programs is relatively consistent. Each of these treatments includes stimulus control, analysis of antecedents and consequences of drug use, awareness of high-risk contexts, behavioral skills, and lifestyle changes. In conventional treatments using talk therapies, direct relapse prevention interventions only occur *during* treatment sessions. Between sessions, behavioral homework is assigned, and it is hoped that individuals will implement relapse prevention skills successfully to reduce drug use. Automated dialing with or without interactive voice recognition software can be used to send phone calls randomly to assess drug use risk, and to offer opportunities to receive ERs. When individuals are at-risk for substance use, this approach allows them to use a mobile phone on an ad hoc basis to receive the ER in order to prevent drug use. With portable reminders of extinction as an adjunctive intervention, it may be possible to offer individuals a bottom-up, brief, automated way to remind themselves of their therapeutic experiences inside the clinic in order to decrease the probability of substance use.

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Figure 1.

Four methods to produce conditioned inhibition. A: Differential Conditioning (A-US/X-NoUS). B: Explicitly Unpaired procedure (X-NoUS/US). C: Inhibition of Delay (X-US with a short CS-US overlap). D: Conditioned Inhibition (A-US/AX-NoUS)

Figure 2. Simultaneous and Serial Feature-Negative Discrimination. A: Simultaneous feature-negative discrimination in which the feature and the target CS presentations overlap during no US trials. B: Serial feature-negative discrimination in which the feature CS precedes the target CS during No US trials.