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Modeling Relapse Situations in the Human Laboratory

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Abstract

It is well known that alcoholism is a chronic relapsing illness. While stress significantly impacts alcoholism risk, there is also evidence that increasing levels of alcohol use affect peripheral and central stress and reward pathways thereby setting up a reciprocal relationship among the effects of alcohol consumption of the development, course of and recovery from alcoholism. This chapter reviews our efforts in assessing the integrity of stress pathways in alcoholism by examining whether altered responses of the stress pathways play a role in relapse risk. Using validated human laboratory procedures to model two of the most common situations that contribute to relapse risk, we review how such models in the laboratory can predict subsequent alcohol relapse. Empirical findings from human laboratory and brain imaging studies are reviewed to show that specific stress-related dysregulation accompanies the alcohol craving state in alcohol-dependent individuals, and such dysregulation along with increases in alcohol seeking are predictive of increased alcohol relapse risk. Finally, the significant implications of these findings for the development of novel treatment interventions that target stress processes and alcohol craving to improve alcoholism relapse outcomes are discussed.

Keywords

Relapse precipitants; Human laboratory models; Stress; Drug cues; Drug craving; Relapse risk

1 Introduction

The last two decades have seen tremendous growth in neuroscience with significant advances in understanding the cellular and molecular correlates of addiction. Basic science research has identified novel molecular and cellular factors associated with addiction. Neuroadaptations in stress pathways and their interaction with reward and motivational circuits have been identified as critical in perpetuating the chronic relapsing nature of addictive disorders (Koob et al. 2004; Kreek and Koob 1998; Sinha 2001, 2007). With these advances in neuroscience, there is greater impetus to examine these mechanisms in humans and in the clinical context. This chapter describes the efforts of my laboratory in modeling real-world situations in the laboratory and assessing their contribution to alcohol relapse risk. Human laboratory studies have been used often to model drug effects, drug self-administration and desire, craving and urges for substances. In the human laboratory, our goal has been to provoke relapse risk situations and assess whether we can induce hallmark features of alcohol seeking and consumption and assess its subsequent effects on relapse susceptibility. An additional goal is to translate previously identified preclinical (animal and human) mechanisms of the alcohol disease state in the laboratory so as to provide a methodology for the development and testing of novel treatment interventions in humans.

2 The Challenge of Modeling Alcohol Relapse Risk in the Laboratory

2.1 Studying Stress, Cues and Alcohol Craving in the Laboratory

Environmental stimuli previously associated with drug use, or internal cues such as stress responses, negative affect and withdrawal-related states associated with alcohol and drug abuse, can function as conditioned stimuli capable of eliciting craving (Stewart et al. 1984) which can increase relapse risk. Classical conditioning is one mechanism by which neutral environmental cues paired with drug acquires emergent stimulus effects in contrast to stimuli paired with placebo drug (Foltin and Haney 2000; O'Brien et al. 1998). These data are consistent with many human laboratory studies documenting that exposure to external drug-related stimuli, which may include people and places associated with alcohol and drug use such as beer cans, bars, smoking cigarettes and drinking alcohol, seeing drinking buddies and other alcohol-related situations that involve drinking, can result in increased drug craving and physiological arousal related to the drug itself (Carter and Tiffany 1999a). Exposure to negative mood or withdrawal-related distress has also been associated with increases in drug craving and cue reactivity (Childress et al. 1994; Cooney et al. 1997) and our early laboratory studies showed increased alcohol and drug craving and arousal with exposure to personalized stress in the laboratory (Sinha et al. 2000; Sinha et al. 1999; Sinha and O'Malley 1999). While interoceptive cues may become paired with drug effects and increase drug craving and physiological reactivity, the possibility that stress activation may directly affect craving and compulsive seeking and that conditioned emotional responses associated with drug cues may activate additional emotional motivational circuits that in turn affect craving and relapse processes was a possibility worth exploring in laboratory studies. Thus, laboratory studies were needed to understand the similarity and differences in different types of relapse situations and to examine how stress- and cue-related mechanisms may affect alcohol craving and relapse susceptibility in humans.

There is a growing literature that alcohol and drug abusing individuals show greater cue reactivity than recreational users of alcohol and drugs (Glautier et al. 1992; Greeley et al. 1993; Kaplan et al. 1985; Pomerleau et al. 1983; Willner et al. 1998). While social drinkers report increases in cue-induced alcohol craving, findings on behavioral and physiological responses to cues in social drinkers are weak and quite mixed in the literature (Carter and Tiffany 1999b; Litt and Cooney 1999). In other evidence, severity of alcohol use has been shown to affect the magnitude of cue reactivity, compulsive alcohol seeking and stress-related changes, including alcohol-related morbidity (Fox et al. 2005; Grusser et al. 2006, 2007; Rosenberg and Mazzola 2007; Sinha 2008a, b; Yoon et al. 2006). These data are consistent with large population-based studies indicating that with greater amounts of weekly or daily alcohol and drug use, there is greater risk of alcohol-related problems, addiction and chronic diseases (Dawson et al. 2005; Rehm et al. 2009; Room et al. 2005). Thus, with increasing levels of alcohol and drug use, there appears to be greater craving responses. Whether such increases in craving and 'wanting' are mediated by neuroadaptations in stress and motivational systems that drive craving, compulsive seeking and drug use behaviors, notions that are consistent with recent incentive sensitization and allostasis models of addiction (Koob et al. 2004; Robinson and Berridge 1993), remains to be fully established in human studies. Human laboratory models provide a unique opportunity to test these hypotheses in humans and translate the understanding of the association between stress, craving and relapse susceptibility from basic science models of relapse into the clinical context.

2.2 Chronic Alcohol-Related Changes in Emotion, Stress and Motivational Systems

There is now solid evidence that regular and chronic alcohol use is associated with stress-related symptoms and changes in mental state which may include increased anxiety and

negative emotions, changes in sleep and food intake, aggressive behaviors, alterations in attention, concentration and memory and desire/craving for alcohol (Sinha 2001, 2007). Stress-related symptoms are most prominent during early abstinence from chronic alcohol use, but some of these changes have also been documented during active use of specific drugs. Growing evidence from basic science studies and further corroboration from human neuroimaging indicate that chronic alcohol abuse alters reward and motivational responses, including alterations in dopaminergic activity, and that such changes are associated with increases in alcohol craving (Cleck and Blendy 2008; Gilman and Hommer 2008; Heinz et al. 2004, 2005; Koob and Kreek 2007; Koob et al. 2004; Martinez et al. 2007; Volkow 2004).

In other evidence, it has long been known that alcohol stimulates the hypothalamic-pituitary-adrenal (HPA) axis and initially stimulates the autonomic systems by provoking sympathetic arousal followed by depressing such activation (Ehrenreich et al. 1997; Lee and Rivier 1997). Dramatic adaptations of the HPA axis akin to tolerance has also been demonstrated with regular and chronic alcohol abuse in animals (Zhou et al. 2000; Richardson et al. 2008) and in humans (Adinoff et al. 1998, 2005; Wand and Dobs 1991). Similarly, chronic alcohol-related changes in autonomic responses, particularly in parasympathetic vagal tone has also been documented in non-human primates (Shively et al. 2007) and in humans (Ingjaldsson et al. 2003; Rechlin et al. 1996; Thayer et al. 2006). These data are consistent with changes in peripheral stress pathways which parallel other basic science findings of alcohol-related adaptations in the extrahypothalamic corticotrophin releasing factor (CRF) systems and the noradrenergic pathways that are consistent with an upregulated central CRF and noradrenergic pathways (Rasmussen et al. 2006; Cleck and Blendy 2008; Koob and Kreek 2007; Koob 2009; also see Heilig et al. 2010 for review). These data document specific dysregulation in emotion, stress and motivational systems in alcoholics, and raise the question of whether these measures contribute to the high levels of emotional distress and the pathophysiology of alcohol craving and compulsive alcohol seeking associated with relapse susceptibility.

2.3 Modeling Relapse Situations in the Laboratory

There are many challenges to studying relapse situations and compulsive alcohol seeking in the laboratory. A key challenge is the ecological relevance of the provocation method, especially when studying psychopathological populations where the specific psychiatric illness is itself seen as a chronic distress state (Brady and Sinha 2005). For example there are widespread individual differences in relapse situations (McKay et al. 1995, 1996) and hence using experimental-derived standard provocateurs may not capture drug-related associations that are likely involved in craving-and relapse-related motivational processes. Another challenge is that as relapse situations often involve drug, drug-related, emotional or stressful and such stimuli invoke arousal of stress pathways, there is a need to address the well-known alterations in the 'normal' stress responses. Of course, one way to address these issues is by designing laboratory experiments with adequate within-group control conditions and/or between-group controls such as inclusion of non-addicted healthy controls or social drinkers. In our studies, we have increasingly added both in the experimental designs so that we can examine changes in motivational state as a function of exposure to relapse situations and changes in biological stress and arousal measures in comparing to healthy non-addicted individuals using comparable methods in the laboratory. Finally, an additional consideration is that of stress and craving measurement. Ensuring sensitivity in measurement of basal stress responses to detect adaptation pertaining to disease state could relate it to changes in motivation state and craving associated with provoked or challenge responses.

3 Developing a Valid Laboratory Model of Relapse Situations

In order to develop a validated method to study relapse situations in alcoholics and drug abusers in the laboratory, the method needs to achieve four objectives as outlined in our previous review (Sinha 2009). The method should (a) consistently reproduce a hallmark disease symptom, such as craving, in the laboratory setting, thereby providing internal validity; (b) provoke the particular disease symptom which in turn, should be associated with alcoholism severity; (c) be predictive of alcohol use behaviors and real-world clinical outcomes; and finally (d) be responsive to interventions, i.e., making the disease worse or better.

In the clinical context, alcoholic patients entering outpatient substance abuse treatment report high levels of stress and an inability to manage distress adaptively, thereby increasing the risk of succumbing to high levels of drug craving and relapse to drug use (Sinha 2007). While patients are often successful in learning cognitive-behavioral strategies in the clinic, relapse rates remain high (Brandon et al. 2007), suggesting difficulties in applying and accessing these strategies in real-world relapse situations. The focus of our laboratory studies became the development of an ecologically relevant method that models such relapse risk in real-world situations in order to understand the biobehavioral mechanisms underlying relapse susceptibility. One key feature of our method was to provoke two of the most common relapse situations, namely emotionally stressful situations and drug-related situations in order to develop a comparable method of provoking stress- and the drug-related craving state. A second key aspect was to build in an experiment control condition to account for the non-specific aspects of the experimental procedures.

3.1 Emotional Imagery Methods

Emotional imagery paradigms have been widely used in behavioral and neuroimaging research to understand the pathophysiology of mood and anxiety disorders, including major depression, panic disorder, obsessive compulsive disorder and post-traumatic stress disorder (Cook et al. 1988; Foa and Kozak 1986; Mayberg et al. 1999; McNeil et al. 1993; Orr et al. 1993, 1998; Pitman et al. 1987; Shalev et al. 1993; Teasdale et al. 1995). They have also been used for anger provocation to assess anger effects on markers of cardiovascular disease (Nelson et al. 2005). There is also a body of research using imagery procedures to study the effects of affect and cues on nicotine craving in the laboratory (Cepeda-Benito and Tiffany 1996; Drobles and Tiffany 1997; Maude-Griffin and Tiffany 1996; Tiffany and Drobles 1990; Tiffany and Hakenewerth 1991). While the mood and anxiety disorders literature had moved to the use of individualized script scenarios, the work of Tiffany and colleagues was primarily based on standard and generic scripts for induction of nicotine cue reactivity.

The emotional imagery method has been developed by Lang and colleagues based on the premise that emotional imagery activates the same physiological, subjective and behavioral responses as emotions in real life, thus being a potent, ecologically valid research procedure to study emotional experiences. According to Lang (1977, 1979), emotions are represented as networks in memory and include three kinds of information: (a) information about the specific stimulus context, (b) information about verbal, physiological and overt behavioral responses, and (c) interpretive information about the meaning of the stimulus and response elements of the structure. Activation of any network “node” or component would activate the full network and produce the emotional experience in question. In developing and validating this method in studies on the psychophysiology of fear and anxiety, Lang found that the more the number of stimulus aspects as well as physiological, behavioral and emotion consistent cognitive responses that were included into the imagery induction script, the stronger the activation produced by the imagery procedure (Lang et al. 1980, 1983). He and his colleagues also found that when the imagery scripts were based on *personal* fear

scenarios compared to standard fear, anger and anxiety scripts, subjects showed stronger physiological and subjective responses (Cook et al. 1988; McNeil et al. 1993; Miller et al. 1987). In our earlier studies on the psychophysiology of emotions, we reported significant physiological responses associated with specific emotion states in healthy volunteers, using individualized scripts for the primary emotions of fear, sadness, anger, fear, joy and neutral-relaxed states (Sinha et al. 1992; Sinha and Parsons 1996). On the basis of this previous theoretical and empirical knowledge on provocation of emotions, we developed a standardized method to elicit individualized real-world relapse situations from subjects that involved emotional stress, drug-related scenarios and a neutral-relaxing scenario as a control situation.

3.2 Individualized Emotional Imagery Procedures

Individualized guided imagery procedures involve an initial imagery script development session, standardized script generation and audiotaping, followed by a habituation and imagery training session that precedes the experimental sessions [full description of procedures is provided in Sinha (2001 Manual for imagery script development procedures. Unpublished manuscript) and Sinha and Tuit (2011)]. The experimental method involves development of scripts for stress, emotions and/or alcohol-related stimuli along with a non-specific control script, each based on the subject's individual experiences. Below is a sample script development session, lasting approximately 1 h, which involves developing a single script from a stressful situation, an alcohol-related craving and consumption situation and a neutral-relaxing situation. The conditions are presented in random order and counterbalanced across subjects. Subjects remain blind to the order and type of condition until the presentation of audiotape, while the experimenters remain blind to the order and content of each audiotape during laboratory sessions.

3.2.1 Imagery Script Development Session—In a session prior to the laboratory sessions, scripts for the guided imagery induction are developed. The *stress imagery script* is based on subjects' description of a recent event that the subjects experienced as "most stressful". Stress is defined for each subject as a situation that made them "sad, mad or upset and in that moment they were not able to change the situation". Subjects individually calibrate the situation by rating their perceived stress experienced in that particular situation on a 10-point Likert scale where "1 = not at all stressful" and "10 = the most stress they felt recently in their life". Only situations rated by the subjects as 8 or above on this scale are accepted as appropriate for script development. This procedure ensures that each stress script is individually calibrated for the level of subjective stress across subjects. Traumatic situations or stressful situations that involved drug-related stimuli, such as being arrested for possession of drugs or being caught in a police chase, are not allowed. Examples of acceptable stressful situations include breakup with significant other, a verbal argument with a significant other or family member or unemployment-related stress, such as being fired or laid off from work.

The *alcohol-related script* is developed by having subjects identify a recent situation that included alcohol-related stimuli and resulted in subsequent alcohol use (e.g., buying alcohol, being at a bar, watching others drink alcohol; getting together with alcohol-using drinking buddies). Alcohol-related situations that occurred in the context of negative affect or psychological distress are not allowed, i.e., going to a bar after a marital conflict, or feeling depressed and calling a drinking buddy. A *neutral-relaxing script* is developed from the subjects' commonly experienced neutral-relaxing situations. Neutral-relaxing events that involve drugs, people associated with drugs or those involving high arousal are not allowed.

A ‘script’ or description of each situation (script length varies based on the aim of the study and the associated methodological issues), is developed using Scene Development Questionnaires [SCQ, adapted from Lang et al. (1980), presented in Sinha R (2001 Manual for imagery script development procedures. Unpublished manuscript)] which obtain specific stimulus and response details, including specific physical and interpersonal context details, verbal/cognitive attributions regarding the situation, and physiological and bodily sensations experienced for the situation being described. While the scripts include individual context information and are therefore personalized, they have standard style that is replicated across all scripts. Table 1 presents sample scripts for each condition from alcohol-dependent individuals. The three scripts for each subject are then recorded on an audio-tape as stimuli for guided imagery in the experimental sessions.

3.2.2 Manipulation Check for Script Development—All three scripts are also rated on a Likert scale from 1 to 5 on a standard rating form (Independent Rating Scale) by two objective independent raters for stressful and emotional content. If a stress imagery script scores below a rating of 3 for stressful content on a 5-point rating scale the subject will be asked to develop a new script at the next appointment prior to the laboratory sessions. On the other hand, if the alcohol-related script scores above a “3” for stressful or emotional content, the subject will develop a new alcohol-related script at the next appointment. These procedures ensure that the stress- and alcohol-related scripts are equated in intensity and content. It further ensures that differences in stress reactivity are not due to differences in intensity and emotional content of the stressor.

3.2.3 Imagery and Relaxation Training—Although all individuals are able to imagine situations especially from their own lives, imagery ability varies across individuals and it has been found that imagery and relaxation training increase the emotional responses during imagery provocation (Miller et al. 1987). Thus, subjects are provided with relaxation training followed by general imagery and physiological response training (fully described in the imagery training procedures manual; Sinha, 2001 Manual for imagery script development procedures. Unpublished manuscript). The imagery training involves subject visualizing some commonplace scenes as they are presented to them. The scenes are neutral and non-emotional in content, such as reading a popular magazine. Following the imagery, the subject is asked questions about the visualization and given pointers regarding the process of imagining the scene. The subject also imagines scenes that are non-emotional but physically arousing in nature, such as doing sit-ups in gym class. With these scenes subjects are asked whether they notice any changes in their physiological response, such as change in heart rate or change in breathing. Once again, pointers in regard to imagining the situation “as if” they were really present in the situation are presented. The relaxation and imagery training procedure takes approximately 1 h and was developed to ensure that all subjects are trained on the method of generating an image and maintaining it for 2–3 min.

4 Provocation of Relapse Situations in the Laboratory

In developing a validated laboratory model for relapse situations, we targeted alcohol and drug craving as a primary outcome measure that is both a common feature of alcoholism and substance abuse and is also known to relate to the disease state. In our initial studies, we compared a commonly used standard social stress task, giving a speech in front of a video camera with the potential for a monetary reward, and compared that method to 5-min individualized guided imagery exposure of subjects’ own recent stressful scenarios. We found that in addicted individuals, stress imagery elicited multiple emotions of fear, sadness and anger as compared to the stress of public speaking, which elicited increases in fear but no anger and sadness. In addition, individualized stress imagery resulted in significant increases in drug craving while public speaking did not (Sinha and O’Malley 1999). In the

next study, we examined stress-induced and drug-related craving and physiological responses using individualized scripts of comparable length and style for stress-, drug- and neutral-related situations. Significant increases in heart rate, salivary cortisol levels, drug craving and subjective anxiety were observed with imagery exposure to stress and non-stress drug cues as compared to neutral-relaxing cues in cocaine-dependent individuals (Sinha et al. 2000). Using these methods, we have been able to reliably induce alcohol and drug craving in multiple groups of treatment engaged cocaine-, alcohol- and opiate-dependent individuals and increase desire for drug in healthy social drinkers (see Fig. 1) (Chaplin et al. 2008; Fox et al. 2007; Hyman et al. 2007; Sinha et al. 2003). In addition, mild to moderate levels of physiological arousal and subjective levels of distress were found to accompany the alcohol/drug craving state (see Fig. 2).

4.1 Provoked Alcohol and Drug Craving and Severity of Disease State

In the second criteria for validated models of relapse situations, it is specified that the key outcome measure associated with alcoholism disease state should vary as a function of severity of disease state. We hypothesized that if drug craving and associated stress dysregulation are indeed factors affected by chronic alcohol and drug abuse, then severity of alcohol and drug abuse should affect craving and stress dysregulation. We examined severity of cocaine and alcohol use among addicted individuals by dividing the cocaine and alcohol addicted sample (all of whom met dependence criteria) into those who were using alcohol and drugs at a high frequency, i.e., greater than 3 times per week, prior to inpatient admission for research, versus those who used drugs at a lower frequency of less than 3 times per week and assessed whether individuals with higher severity of drug abuse showed greater drug craving, anxiety and more stress dysregulation. Findings indicated that addicted individuals using cocaine and alcohol four or more days per week showed greater drug craving, anxiety and associated cardiovascular and HPA response to both stress and alcohol/drug-cue exposure as compared to those using 3 days or less per week (Fox et al. 2005). Thus, consistent with epidemiological and clinical studies cited earlier, the emotional imagery-based laboratory method was found to be sensitive to severity of disease state in both drug craving and associated anxiety and in level of stress dysregulation.

4.2 Stress Dysregulation and Enhanced Drug Craving in Addicted Individuals

In the previous sections, we summarized the findings where laboratory studies reliably induced stress- and cue-induced alcohol and drug craving in multiple groups of addicted samples, and with evidence of stress-related physiological changes with stress and with drug cue exposure as compared to neutral imagery exposure. Initial evidence of the effects of disease severity on these responses was also observed. We also investigated whether these responses are altered or dysregulated in early abstinent alcoholics in comparison to non-addicted, social drinking controls. One potential drawback of standard laboratory stress provocation tools has been that patients may not find methods such as a public speaking or a math problem meaningful and relevant to their lives which could differentially affect participation in the stress provocation between addicted samples and controls. In contrast, individualized emotional imagery procedures account for potential differential effects of stress provocation by individually calibrating the level of stressfulness among subjects. Thus, there are no differences between controls and patients on stressfulness ratings of their stress scenarios. Comparability across alcohol-related scenarios is not problematic as these situations are elicited for presence of alcohol and drug-related stimuli, leading to wanting alcohol and subsequent alcohol use itself.

We compared 4-week abstinent alcoholics to matched social drinkers (drinking less than 25 drinks per month). The recovering alcoholics at 4-week abstinence showed greater levels of basal heart rate and salivary cortisol levels compared to control drinkers. Upon stress and

alcohol cue exposure, they showed greater subjective distress, alcohol craving and blood pressure responses, but a blunted stress-induced heart rate and cortisol responses compared to controls (Sinha et al. 2009). Furthermore, alcoholic patients showed a persistent increase in alcohol craving, subjective distress and blood pressure responses across multiple time-points as compared to social drinkers, suggesting an inability to regulate the high alcohol craving and emotional stress state. These data indicate greater allostatic load in abstinent alcoholics accompanied by dysregulated stress responses and high levels of craving or compulsive seeking for the preferred drug.

Together, these data indicate that stress responses are altered in alcoholics and these alterations also include an enhanced susceptibility to stress- and cue-induced alcohol seeking which is not seen in healthy non-addicted individuals (see Fig. 1). Furthermore, there are basal alterations in peripheral markers of stress, indicative of stress-related dysregulation in the CRF-HPA axis and in autonomic responses as measured by basal salivary cortisol and heart rate responses; these high basal responses are associated with lower or blunted stress-related arousal, similar to other high and chronic distress states (Li et al. 2007; Sinha et al. 2000; Steptoe and Ussher 2006). It is important to note that these alterations were not accounted for by the smoking status or lifetime history of anxiety or mood disorders and therefore appear to be related to the history of chronic alcohol abuse. The persistence of emotional distress and alcohol craving induced by stress and alcohol cue exposure suggests a dysfunction in emotion regulatory mechanisms. As HPA axis responses and autonomic-parasympathetic responses contribute to regulating and normalizing stress responses and regaining homeostasis, dysfunction in these pathways and their related central mechanisms may be involved in perpetuating alcohol craving and relapse susceptibility.

5 Neural Correlates of Stress and Drug Craving in Addiction

With the emergence of functional neuroimaging technology in the last 15 years, effective experimental methods to assess drug craving, emotions and stress within the confines of neuroimaging procedures have been developed. Using a variety of cue induction procedures, many studies have examined brain regions associated with craving in addicted individuals. Exposure to drug cues is known to increase craving increases activity in the amygdala and regions of the frontal cortex (Childress et al. 1999; Grant et al. 1996; Kilts et al. 2001). Gender differences have also been reported in cue-related activation in the amygdala and frontal cortex in cocaine-dependent individuals (Kilts et al. 2004; Li et al. 2005). Cue-induced craving for nicotine, methamphetamine and opiates also activate regions of the prefrontal cortex, amygdala, hippocampus, insula and the Ventral Tegmental Area (VTA) (see Sinha 2007). Having successfully modeled stress-induced craving experimentally in the laboratory, we also examined brain activation during stress and neutral imagery in a functional magnetic resonance imaging (fMRI) study. Although healthy controls and cocaine-dependent individuals showed similar levels of distress and pulse changes during stress exposure, brain response to emotional stress in paralimbic regions such as the anterior cingulate cortex, hippocampus and parahippocampal regions was observed in healthy controls during stress while cocaine patients showed a striking absence of such activation (Sinha et al. 2005). In contrast, patients had increased activity in the caudate and dorsal striatum region during stress, activation that was significantly associated with stress-induced cocaine craving ratings. Similarly, stress, alcohol cue and neutral imagery exposure was assessed in social drinkers and robust and similar activation of corticolimbic striatal regions were seen with stress and alcohol cue exposure. Alcohol cue-induced ventral and dorsal striatal activity correlated with alcohol cue-induced craving in men (Seo et al. 2010a).

Recent studies using Positron Emission Tomography (PET) have also shown significant positive correlations between the dorsal striatum and drug cue-induced cocaine craving

(Volkow et al. 2006; Wong et al. 2006). These findings are consistent with imaging studies with alcoholic patients showing increased association between dorsal striatum regions and alcohol craving in response to presentation of alcohol-related stimuli (Grusser et al. 2004; Wrase et al. 2002). Using PET imaging with alcoholics and cocaine patients, research has shown a significant association between dopamine D2 receptor binding in the VS and drug craving as well as motivation for self-administration (Heinz et al. 2004; Martinez et al. 2005, 2007). On the other hand, neuropsychological and imaging studies examining prefrontal executive functions, including impulse control, decision making and set shifting, have shown executive function deficits and hypo-frontal responses in addicted individuals compared to control volunteers (Ersche et al. 2005, 2006, 2008; Hester and Garavan 2004; Kaufman et al. 2003; Li and Sinha 2008; Noel et al. 2007; Paulus et al. 2006). Together, these data show a distinct pattern of findings indicating that increased stress- and cue-induced craving and compulsive drug-seeking states in addicted individuals are associated with greater activity in the striatum, but decreased activity in specific regions of the cingulate and prefrontal cortex and related regions involved in controlling impulses and emotions (Li and Sinha 2008).

6 Laboratory Response to Relapse Situations and Subsequent Alcohol Relapse

An important aspect of modeling hallmark addictive symptoms such as alcohol craving in the laboratory is to understand its related mechanisms and also to demonstrate the validity of the model by examining whether it shows predictive power with regard to actual drug use behaviors and/or real-world clinical outcomes. Because our laboratory studies described earlier were conducted with treatment engaged alcoholics and drug abusing samples who were inpatients at a treatment research unit, we were able to add a careful assessment of relapse once patients were discharged. This allowed us to examine specific markers of the stress and craving states that are predictive of relapse outcomes. Thus we followed inpatient treatment engaged alcohol-dependent individuals in our studies after discharge following completion of 5 weeks of inpatient alcohol treatment, for 90 days to assess relapse outcomes. Face-to-face follow-up assessments were conducted at 14, 30, 90 and 180 days after discharge from the inpatient unit. Our follow-up rates for these assessments have been 96, 89, 92, and 86% respectively.

Our initial evidence from assessing whether laboratory responses to stress- and alcohol-related stimuli exposure are predictive of alcohol treatment outcomes were positive. We found that stress-induced alcohol craving in the laboratory during inpatient treatment was predictive of number of days of alcohol used and total number of drinks consumed during the 90-day follow-up period (Breese et al. 2005). These data corroborate our findings in cocaine abusers showing that stress-induced cocaine craving and HPA arousal are associated with earlier relapse and more cocaine use at follow-up (Sinha et al. 2006). More recent data indicate that both stress and alcohol cue-induced craving are associated with time to alcohol relapse (Sinha et al. 2011). Furthermore, blunted or low levels of stress-induced ACTH and heart rate responses, but higher cortisol/ACTH ratio at baseline and for stress and neutral condition are each predictive of shorter times to relapse (Sinha 2008a, b; Sinha et al. 2011). These data are consistent with some earlier reports of stress system involvement in relapse outcomes in alcoholics. Negative mood and stress-induced alcohol craving and blunted stress and cue-induced cortisol responses have been associated with alcohol relapse outcomes (Breese et al. 2005; Cooney et al. 1997; Junghanns et al. 2003). Thus, for alcoholic samples, as in the cocaine group, it appears that the drug craving state marked by increasing distress and compulsive motivation for drug (craving) along with poor stress regulatory responses (altered HPA responses or increased noradrenergic arousal) results in an enhanced susceptibility to addiction relapse.

Findings from our neuroimaging study that modeled stress and alcohol cue exposure in a functional MRI study, found hyper-responsivity of the ventromedial prefrontal cortex (VmpFC) and ventral striatum during neutral relaxed imagery and blunted responses of these regions during stress and alcohol cue exposure (Seo et al. 2010b). Higher activation of the VmpFC during the neutral condition and blunted response during stress and alcohol cues significantly predicted the level of stress-induced and alcohol cue-induced craving and concomitant anxiety during stress and alcohol cue exposure. Both hyper-responsivity of the ventral striatum and VmpFC during neutral relaxed states and blunted response during stress states were associated with a greater propensity to relapse (Seo et al. 2010b). Normalization of these regions that are critical in integration of emotional-motivational function would therefore be an important target of recovery and treatment of alcoholism.

7 Specific Responses as Targets for Treatment Development

The previous sections describe our approach to modeling relapse situations in the laboratory in alcoholics and summarized the evidence thus far, on whether stress and alcohol cue-related craving and stress dysregulation are predictive of alcohol relapse outcomes. The findings indicate that both stress and alcohol cue-induced provoked craving could serve as markers of relapse susceptibility. Altered HPA activity, especially cortisol/ACTH ratio as a marker of adrenal sensitivity was also found to be associated with relapse. Among brain imaging responses, altered stress-related activity in the VmpFC was also a sensitive measure of relapse. While anxiety and negative emotions such as anger, fear and sadness ratings were not predictive of relapse, they were significantly correlated with stress- and cue-induced alcohol craving and may serve as secondary target measures, which in conjunction with alcohol craving, could provide useful indicators of change in emotional distress associated with alcohol craving. All of these could serve as outcome measures for further experimental testing of novel pharmacological and behavioral treatment interventions to prevent stress- and cue-related alcohol relapse.

8 Implications for Treatment Development to Prevent Stress- and Cue-Related Relapse

Having validated a human laboratory model with effective provocation methods and reliable measures of stress and drug craving, we have recently begun to test novel pharmacological agents that may decrease stress- and cue-induced alcohol craving and normalize stress regulation using agents that have shown promise in basic science models and/or in the clinical setting. One of the key advantages of using human laboratory models for this purpose is that they provide a cost-effective and efficient way to assess new approaches prior to undertaking large-scale clinical trials.

Several animal models of relapse have shown that overactive brain CRF, noradrenergic and glutamatergic systems along with underactive dopamine and GABA systems contribute to the high craving states and the chronic relapsing nature of addiction (Goeders 2002; Kalivas and Volkow 2005; Koob et al. 2004; O'Brien 2005; Shaham et al. 2003; Vocci et al. 2005; Weiss 2005). For example, using animal models of drug self-administration and reinstatement, preclinical studies have shown CRF antagonists and α -2-adrenergic agonists to be efficacious in reducing stress-related drug seeking in addicted laboratory animals (see Shaham et al. 2003; Weiss 2005 for review). Similarly, α 1-adrenergic antagonists such as Prazosin have been found to decrease alcohol withdrawal symptoms, alcohol consumption and stress-induced relapse in animal models (Gilpin et al. 2009; Rasmussen et al. 2006; Walker et al. 2008) and in a pilot clinical study of alcoholics (Simpson et al. 2009).

We have previously tested whether the α -2-adrenergic agonist, lofexidine, is effective in decreasing emotional stress, physiological arousal and stress-induced drug craving in opiate-dependent individuals in naltrexone treatment. Although naltrexone, an opiate antagonist, is approved in the treatment of opioid addiction, it is not used widely because of poor compliance and high relapse rates. Thus, it provided a good model to conduct proof of concept studies to assess whether stress-related relapse can be decreased with lofexidine. In an initial small laboratory study, we demonstrated that naltrexone-treated opioid-dependent individuals showed high levels of stress- and cue-induced drug craving, physiological arousal and emotional distress when compared to neutral relaxing stimuli (Hyman et al. 2007). In a second study, lofexidine was found to significantly decrease stress-induced opiate craving and anger ratings while also decreasing basal heart rates and improving opiate relapse outcomes in a small study of naltrexone-treated opiate-dependent individuals (Sinha et al. 2007). Most recently in treatment engaged alcoholics, we have found that stress and alcohol cue-induced alcohol craving, anxiety and stress dysregulation were each decreased relative to neutral responses with Prazosin and not in placebo-treated alcoholics (Fox et al. 2011). These studies provide initial support for the use of the human laboratory model to study relapse risk especially as a tool for testing novel pharmacological interventions.

9 Limitations and Caveats

It is important to acknowledge that modeling relapse situations in laboratory settings remain a challenge in the field. Several caveats about the emotional imagery methods and procedures used to provoke relapse situations in the laboratory need to be highlighted. First, while the emotional imagery method is effective and has been used in the study of mood and anxiety disorders and in cardiovascular disease, our adaptation of these methods is manualized, technically rigorous and therefore time-consuming and resource intensive. For example, individual script development sessions are conducted and then scripts for each condition per subject are developed. Only highly trained research staff who have completed a structured script development training and are certified for script development should be developing such stimuli for laboratory situations. Our procedures have been tested in treatment-engaged addicted patients and healthy individuals and hence its effectiveness in non-treatment seeking and actively using individuals are not known.

While this review described the specific methods used in our laboratory studies, there are other experimental factors that are important to consider in studying relapse situations. For example, duration of the exposure to relapse situations may significantly affect strength of response. For example, in the laboratory studies, our script length is 5–6 min while in the brain imaging session they are 2 min long. Furthermore, in a medication study currently underway, we are using 10-min exposure periods with two scripts for each condition. Other factors, such as aversiveness of the relapse situation, its intensity and controllability are all factors that impact laboratory responses and ultimately affect the ability to detect individual differences in the laboratory, especially in clinical samples, with respect to clinical outcomes.

10 Summary

This paper describes the development and validation of a human laboratory model to assess chronic alcohol-related neuroadaptations in abstinent alcoholics. As alcohol-related neuroadaptations specifically affect the stress and reward pathways, the particular challenge of studying the most common relapse triggers, such as, stress and alcohol cues and associated alcohol craving is discussed. Four criteria for development of a valid human laboratory model for alcohol-related adaptations and assessing relapse risk is outlined. Evidence from human laboratory and neuroimaging studies that show specific neuroadaptive

changes in stress pathways and whether such changes alter subjective affect, alcohol craving and relapse risk is presented. Specific responses that are predictive of alcohol relapse risk are identified, and their use to screen novel pharmacological agents that show promise in reducing stress and cue-induced alcohol craving and normalizing stress dysregulation is discussed. Availability of such valid human laboratory models provides an important step towards development of new treatment targets to decrease alcohol relapse risk and improve clinical outcomes in the future.

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Fig. 1.

Mean and standard errors for peak drug craving and anxiety ratings during exposure to stress, drug cues and neutral imagery conditions in separate groups of alcoholic-, cocaine- and opioid-dependent individuals and healthy social drinkers combined across three studies (Fox et al. 2008; Hyman et al. 2007; Sinha 2008a, b). **a** Peak craving during stress and drug cue conditions is significantly higher in abstinent alcoholics-, cocaine- and naltrexone-treated opioid patients compared to social drinkers ($P < 0.0001$ for both conditions). **b** Peak anxiety ratings is significantly higher in abstinent alcoholics-, cocaine- and naltrexone-treated opioid patients compared to social drinkers in both stress and drug cue conditions (stress: $P < 0.005$; drug cue: $P < 0.0001$)

Fig. 2.

Mean and standard errors for: **a** basal heart rate measured at baseline prior to imagery exposure over several time points across three separate days of experimental testing in alcoholic (AD) and cocaine (COC) patients compared to social drinkers (SD) ($AD > COC > SD$, $P < 0.01$); and **b** basal salivary cortisol averaged for two baseline assessments across three separate testing days ($AD > SD$, $p < 0.01$; $COC > SD$, $P < .11$); **c** peak heart rate responses in the stress (S), drug cue (D) and neutral (N) conditions: SD group shows $S > N$, $P < 0.0001$; $D > N$, $P < 0.02$; $S > D$, $P < 0.04$), while AD group only shows increases response in $D > N$, $P < 0.01$; and no differences between conditions in the COC group; **d** average salivary cortisol responses to stress (S), drug cue (D) and neutral (N) conditions: SD group shows $S > N$, $P < 0.05$, AD group shows $D > N$, $P < 0.05$, and COC group shows no differences between groups in responses [combined data averaged from Fox et al. (2008) and Sinha (2008a, b)]

Sample individualized scripts

Table 1

Stress	It is Saturday night about 5:00 p.m. R. picks you up at your apartment and you are on your way to the bowling alley. As you get in the car, you ask her, "Do you love me or not?" She wants to talk to you about this tonight. Your heart beats faster. She drives the car and you press her to tell you what's on her mind. There is silence in the car. You feel tense all over your body. You are not sure what's going on, but it doesn't sound good. She stops the car in the parking lot. Your face is tight. Gritting your teeth, you ask her to tell you right now. She starts by saying, "we are always fighting, and I really need to focus on school". Your stomach is in a knot. She blames you for acting too much like her father. You feel hot all over. You can't believe she is saying this, and you dread what's coming next. She doesn't want to see you any more! You feel choked up. You try to explain to her you have always tried to help and be there for her. She says she doesn't like you when you get moody, loud and upset at her. Blood rushes to your head. How come she never said anything before. You start to wonder if she has been seeing other people. Your jaws are clenched. You want to scream and strike someone. You feel betrayed and alone. You want to say so much but no words come out. Tears come to your eyes and you just want to go home.
Drug-related script	It is the morning of July 4. You are at the Lighthouse Beach for the first picnic of the summer. Your eyes glance up at the cloudless blue sky. You see the barbecues all set up. You feel a sense of being more alive. You watch the flames are burning high. You feel pumped up. There are coolers spread out all over the beach. There are over 50 people here already, and the party is finally getting started. Almost everyone has a drink in their hands already. There are butterflies in your stomach. Now you really want a drink. You want to get all nice. You eyes glance over to one of the coolers. You flip the lid and take a look inside. Your heart beats faster. You see bottles of Beer, Gin, Scotch, Vodka, and Rum. You are breathing faster. You reach into one of the coolers and bury your hand in the ice. Your hand feels cold and wet. There is a tingling sensation inside you. You grab onto a can of beer and pull out your arm. You give it a shake to remove some of the excess water. You wet your lips as you crack it open. You raise the beer to your mouth and tilt it back. It feels ice cold against your lips. There is a rush of excitement inside you. You let the beer flow into your mouth and slide down your throat. There is a warmth inside you. Now you have a taste for it. You are ready for another big swig.
Neutral-relaxing script	You are sitting on the beach on a bright summer day. You breath in deeply as you notice a red kite against the cloudless blue sky. Your eyes trace the path of the kite as it whips up and down in spirals with the wind. The sun glares at you from behind the kite and makes the white sandy beach sparkle with reflection. You tense the muscles in your forehead and around your eyes, squinting to block out the bright sunlight. You follow with your eyes the long white tail, which dances from side to side beneath the soaring kite. You take in a few deep breaths of the fresh ocean air, noticing the smells of the fish and the salt water. The warm sun beats down against your skin and a light gentle breeze blows over you. You listen to the soothing sound of the ocean waves, roaring and splashing as it comes onto the sand, and quiet as the water goes back out to sea. You relax the muscles in your arms, back and legs as you lay back on the sand, feeling the soft fine granules of sand between your toes and fingers. The tension from your body goes down and you feel comfortable and at ease. Your breathing slows down and the worry thoughts seem to fade away. There is a sense of lightness and you want to hold time and capture this moment. A feeling of peace overcomes you.