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Modeling stress and drug craving in the laboratory: implications for addiction treatment development

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Abstract

Addiction is a chronic relapsing illness affected by multiple social, individual and biological factors that significantly impact course and recovery of the illness. Stress interacts with these factors and increases addiction vulnerability and relapse risk, thereby playing a significant role in the course of the illness. This paper reviews our efforts in developing and validating laboratory models of stress and drug cue-related provocation to assess stress responses and stress-related adaptation in addicted individuals compared with healthy controls. Empirical findings from human laboratory and brain imaging studies are presented to show the specific stress-related dysregulation that accompanies the drug-craving state in addicted individuals. In order to adequately validate our laboratory model, we have also carefully examined relapse susceptibility in the addicted individuals and these data are reviewed. The overarching goal of these efforts is to develop a valid laboratory model to identify the stress-related pathophysiology in addiction with specific regard to persistent craving and compulsive seeking. Finally, the significant implications of these findings for the development of novel treatment interventions that target stress processes and drug craving to improve addiction relapse outcomes are discussed.

Keywords

Addiction; addiction treatment; drug craving; human laboratory models; relapse susceptibility; stress

INTRODUCTION

The last two decades has led to a 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 (Kreek & Koob 1998; Koob *et al.* 2004; Sinha 2007). With these advances in neuroscience, there is greater impetus to examine these mechanisms in humans and in the clinical context. Human laboratory studies have been used often to model drug effects, drug self-administration and desire, craving and urges for substances. This paper describes our approach to modeling stress, drug craving and compulsive seeking in the laboratory and to assess their effects on relapse susceptibility. The goal was to develop a valid and reliable laboratory model that would allow us to achieve the following objectives: (1) to understand how stress increases drug seeking and relapse susceptibility by identifying the pathophysiology of stress and compulsive seeking in addiction; and (2) to provide translation of identified pre-clinical mechanisms of disease to the

development and testing of novel treatment interventions in humans. Achieving these objectives in laboratory studies would contribute to identifying clinical markers of stress- and craving-related pathophysiology that could then be targeted for treatment development. This approach is a cost-effective and efficient way to facilitate both understanding the mechanisms underlying stress, craving and relapse and to identify promising treatment targets for development.

THE CHALLENGE OF MODELING STRESS AND CRAVING IN ADDICTED INDIVIDUALS

It is well documented that regular and chronic drug use is associated with stress-related symptoms and changes in mental state that 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 drug (Sinha 2001, 2007). Stress-related symptoms are most prominent during early abstinence from chronic drug use, but some of these changes have also been documented during active use of specific drugs. Basic science and human neuro-imaging studies have demonstrated alterations in stress and reward pathways, namely, the extrahypothalamic and hypothalamic corticotrophin-releasing factor (CRF) systems and the noradrenergic pathways as well as alterations in dopaminergic activity with chronic drug use (Kreek & Koob 1998; Koob *et al.* 2004; Volkow *et al.* 2004; Martinez *et al.* 2007; Porrino *et al.* 2007; Cleck & Blendy 2008).

Human laboratory manipulations of stress have also shown altered stress responses in addicted individuals as compared with control volunteers. Acute withdrawal states are associated with increases in CRF levels in cerebrospinal fluid, plasma adrenocorticotrophic hormone (ACTH), cortisol, norepinephrine (NE) and epinephrine (EPI) levels (Adinoff *et al.* 1990, 1991; Vescovi *et al.* 1992; Tsuda *et al.* 1996; Ehrenreich *et al.* 1997; Koob & Le Moal 1997; Mello & Mendelson 1997; Kreek & Koob 1998). Early abstinence is associated with high basal cortisol responses, and a blunted or suppressed ACTH and cortisol response to pharmacological and psychological challenges in alcoholics and chronic smokers, whereas hyper-responsivity of hypothalamic-pituitary adrenal (HPA) hormones in response to metyrapone have been reported in opiate and cocaine addicts (Kreek 1997; Schluger *et al.* 1998; Contoreggi *et al.* 2003; Ingjaldsson, Laberg & Thayer 2003; Adinoff *et al.* 2005). Furthermore, withdrawal and abstinence from chronic alcohol is also associated with altered sympathetic and parasympathetic responses (Rechlin *et al.* 1996; Ingjaldsson *et al.* 2003; Rasmussen, Wilkinson & Raskind 2006), and altered noradrenergic responses to yohimbine challenge in early abstinence from cocaine has also been observed (McDougle *et al.* 1994). These data document specific stress-related dysregulation in addicted individuals, and raised the question of whether these measures contribute to the high levels of emotional distress and the pathophysiology of drug craving and compulsive drug-seeking associated with relapse susceptibility reported by addicted patients in clinical settings.

Environmental stimuli previously associated with drug use, or internal cues such as stress responses, negative affect and withdrawal-related states associated with drug abuse, can function as conditioned stimuli capable of eliciting craving (Stewart, de Wit & Eikelboom 1984). 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 (O'Brien *et al.* 1998; Foltin & Haney 2000). 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 drug use or drug paraphernalia such as needles, drug pipes, cocaine powder or beer cans, and *in vivo* exposure to drug itself—can result in increased drug craving and physiological reactivity (Carter & Tiffany 1999). Exposure to negative affect, stress or withdrawal-related distress has also been associated with increases in drug craving

and cue reactivity (Childress *et al.* 1994; Cooney *et al.* 1997; Sinha & O'Malley 1999; Sinha, Catapano & O'Malley 1999; Sinha, Fuse & Aubin 2000). Whereas 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 contribute to the conditioning effects on craving and drug-use behaviors needs to be further explored. Thus, laboratory studies are needed to understand the similarity and differences in stress- and cue-related mechanisms affecting craving and relapse susceptibility in humans.

There is a growing literature that addicted individuals show greater cue reactivity than recreational users of drugs (Pomerleau *et al.* 1983; Kaplan *et al.* 1985; Glautier, Drummond & Remington 1992; Greeley *et al.* 1993; Willner *et al.* 1998). Whereas social drinkers report increases in cue-induced alcohol craving, findings on behavioral and physiological responses to cues in social drinkers is weak and quite mixed in the literature (Carter & Tiffany 1999; Litt & Cooney 1999). In other evidence, severity of alcohol use has been shown to affect magnitude of cue reactivity, compulsive alcohol seeking and stress-related changes, including alcohol-related morbidity (Fox *et al.* 2005; Grusser, Morsen & Flor 2006; Yoon *et al.* 2006; Grusser *et al.* 2007; Rosenberg & Mazzola 2007; Sinha 2008b). These data are consistent with large population-based studies indicating that with greater amounts of weekly and daily alcohol and drug use, there is greater risk of addiction and chronic diseases (Rehm *et al.* 2003; Dawson *et al.* 2005; Room, Babor & Rehm 2005). Thus, with increasing levels of 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 (Robinson & Berridge 1993; Koob *et al.* 2004) 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 to the clinical context.

THE CHALLENGE OF STUDYING STRESS AND DRUG CRAVING IN LABORATORY MODELS

There are many challenges to studying stress, drug craving and compulsive seeking in the laboratory. Ecological relevance of the provocation methods is among the more important of these factors, especially when studying psychopathological populations where the specific psychiatric illness is itself seen as a chronic distress state (Brady & Sinha 2005). Indeed, widespread individual differences in what is considered 'stressful' and in stress responses have been well documented (Cohen, Kessler & Gordon 1995; Lazarus 1999). These factors become more significant if the goal of the studies include assessing alterations from the 'normal' responses and include healthy non-addicted individuals. Of course, one way to address these issues is by designing laboratory experiments with adequate within-group control conditions. As one focus of our research has been to understand stress and drug craving, it became important to develop a method that allowed us to compare stress-related drug craving with the more common cue-induced drug-craving responses using comparable methods in the laboratory. This was a particular methodological challenge and few studies had directly compared both types of provocation in the same experiments. Finally, an additional consideration was that of stress and craving measurement, and ensuring sensitive measurement of basal stress responses to detect adaptation pertaining to disease state and relate it to provoked or challenge responses.

DEVELOPING A VALID LABORATORY MODEL TO STUDY STRESS AND DRUG CRAVING

On the basis of previous human laboratory studies in stress and drug craving, we determined that to develop a laboratory method to study stress and drug craving in addicted samples with the goal of understanding the mechanisms linking these phenomena and validating its relevance to clinical phenomena, the procedures should achieve four objectives. The method should: (1) consistently reproduce a hallmark disease symptom in the laboratory setting, thereby providing internal validity; (2) produce stress and drug-craving responses that are associated with disease severity; (3) be predictive of drug-use behaviors and real-world clinical outcomes; and finally, (4) be responsive to interventions—i.e. making the disease worse or better.

In the clinical context, addicted 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). Although patients are often successful in learning cognitive-behavioral strategies in the clinic, relapse rates remain high suggesting difficulties in applying and accessing these strategies in the real-world context. The focus of our laboratory studies became the development of an ecologically relevant method that models the real-world emotional stress and drug-related responses in order to understand the bio-behavioral mechanisms underlying stress and drug-related craving, compulsive seeking and relapse susceptibility. The key features of the method were to develop a comparable method of provoking stress and the drug-related craving state and to build in an experiment control condition to account for the non-specific aspects of the experimental procedures.

Emotional imagery methods

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

The emotional imagery method was developed by Lang (1977; 1979) and was based on the basic 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: (1) information about the specific stimulus context; (2) information about verbal, physiological and overt behavioral responses; and (3) 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). They also found

that when the imagery scripts were based on personal fear scenarios compared with standard fear, anger and anxiety scripts, subjects showed stronger physiological and subjective responses (Miller *et al.* 1987; Cook *et al.* 1988; McNeil *et al.* 1993). In our early 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, Lovallo & Parsons 1992; Sinha & Parsons 1996). On the basis of this previous theoretical and empirical knowledge on provocation of emotions, we developed a standardized method, described in the following section, to elicit individualized emotional stress and drug-related situations from subjects.

Individualized emotional imagery procedures

The individualized guided imagery procedures involves an initial imagery script development session, standardized script writing and audio-taping, followed by a habituation and imagery training session that precedes the experimental sessions (full description of procedures is provided in Sinha (unpublished manual). The experimental method involves development of scripts for stress, emotions and/or drug-related stimuli along with a nonspecific control script, each based on the subject's individual experiences. In the following section is a sample script development session, lasting approximately 1 hour, which involves developing a single script from a stressful situation, a drug-related craving and consumption situation and a neutral-relaxing situation. The conditions are presented in random order and counter-balanced across subjects. Subjects remained blind to the order and type of condition until the presentation of audiotape, whereas the experimenters remained blind to order and content of each audio-tape during laboratory sessions.

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 could not do anything 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 level of 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 drug-related script is developed by having subjects identify a recent situation that included drug-related stimuli and resulted in subsequent drug use (e.g. buying alcohol, being at a bar, watching others drink alcohol or smoke crack/drug; getting together with drug-using buddies). Drug-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 (adapted from Lang *et al.* (1980), presented in Sinha (unpublished manual),

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. Although the scripts include individual context information and are therefore personalized, the script has a standard style that is replicated across all scripts. Table 1 presents sample scripts for each condition. The three scripts for each subject are then recorded on an audio-tape as stimuli for guided imagery in the experimental sessions.

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 five-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 drug-related script scores above 3 for stressful or emotional content, the subject will develop a new drug-related script at the next appointment. These procedures ensure that the stress and drug 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.

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 increases 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 unpublished). The imagery training involves subjects' 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 hour and was developed to insure all subjects are trained on the method of generating an image and maintaining it for 2–3 minutes.

INDUCTION OF STRESS AND DRUG CRAVING IN THE LABORATORY

In our initial studies, we compared a commonly used social stress task, giving a speech in front of a video camera with the potential for a monetary reward, to the 5-minute 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 with 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 whereas public speaking did not (Sinha *et al.* 1999; Sinha & 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-related 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 with neutral-relaxing cues in cocaine-dependent individuals (Sinha *et al.* 2000). Using these methods, we have been able to reliably induce drug craving in multiple groups of

treatment-engaged cocaine, alcohol- and opiate-dependent individuals and increase desire for drug in healthy social drinkers (Sinha *et al.* 2003; Fox *et al.* 2007; Hyman *et al.* 2007; Chaplin *et al.* 2008). In addition, mild to moderate levels of physiological arousal and subjective levels of distress were found to accompany the drug-craving state.

In a more comprehensive assessment of the biological stress response in recently abstinent cocaine-addicted individuals we reported that brief exposure to stress and to drug cues compared with neutral relaxing cues activated the HPA axis (with increases in ACTH, cortisol and prolactin levels) as well as the symphoadrenomedullary systems, as measured by plasma NE and EPI levels (Sinha *et al.* 2003). Furthermore, we found little evidence of recovery or return to baseline in ACTH, NE and EPI levels even over an hour after the 5-minute imagery exposure, suggesting the persistence of a dysregulated stress and drug-craving state with exposure to stress and to drug-related stimuli.

Although we have yet to fully examine individual differences in the mentioned responses and in the factors that contribute to high drug craving and compulsive-seeking states, we examined severity of cocaine and alcohol use among addicted individuals to assess 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 4 or more days per week showed greater drug craving, anxiety and associated cardiovascular and HPA response to both stress and drug-cue exposure compared with those using cocaine and alcohol 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 specific biobehavioral alterations associated with severity of recent drug use in addicted individuals.

STRESS DYSREGULATION AND ENHANCED DRUG CRAVING IN ADDICTED INDIVIDUALS

The previous sections summarized findings from laboratory studies that reliably induced stress and cue-induced 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 with neutral imagery exposure. Initial evidence of the effects of disease severity on these responses was also observed. We then investigated whether these responses were altered or dysregulated in comparison with non-addicted samples. One potential drawback of standard laboratory stress provocation tools has been that patients may not find the standard stress methods of public speaking or a math problem meaningful and relevant to their lives that could differentially affect participation in the stress provocation between addicted samples and controls. In contrast, the 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 drug-related scenarios were not problematic as these situations were elicited for presence of drug and drug-related stimuli, leading to wanting drug and subsequent drug use itself. The non-addicted group included light to moderate social drinkers who consumed less than 25 drinks per month.

We first compared abstinent, treatment-engaged, cocaine-dependent individuals to a demographically matched group of healthy social drinkers using individually calibrated, personally emotional stress- and drug/alcohol-cue related imagery compared with neutral imagery. Findings indicated that cocaine patients showed enhanced levels of emotional distress and physiological arousal and higher levels of drug craving to both stress and drug-cue exposure compared with controls (Fox *et al.* 2008). On the other hand, social drinkers showed increased cue-induced drug craving, albeit at lower levels than patients, but minimal levels of

stress-induced drug craving. However, we have since reported sex differences in these responses in social drinkers, with socially drinking men but not women showing a positive correlation between emotional distress responses and drug craving in the stress condition (Chaplin *et al.* 2008). Interestingly, the men reported greater levels of alcohol consumption than women, and it may be possible that an increased level of alcohol exposure even in the light-to-moderate group led to greater stress-related drug craving.

In another study, we also compared 4-week abstinent alcoholics to matched social drinkers. The recovering alcoholics at 4-week abstinence showed greater levels of basal heart rate and salivary cortisol levels compared with control drinkers. Upon stress and alcohol cue exposure, they showed greater subjective distress, alcohol craving and blood pressure responses, but blunted stress-induced heart rate and cortisol responses compared with controls (Sinha *et al.* 2008). Furthermore, alcoholic patients showed a persistent increase in alcohol craving, subjective distress and blood-pressure responses across multiple timepoints as compared with social drinkers, suggesting an inability to regulate the high drug craving and emotional stress state. These data indicate greater allostatic load in abstinent alcoholics that is accompanied by a dysregulated stress responses and high levels of craving or compulsive seeking for the preferred drug in order to alter hedonic state and achieve short-term homeostasis.

Together, these studies indicate that stress responses are altered in addicted individuals and these alterations also include an enhanced susceptibility to stress and cue-induced drug seeking that 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 (see Fig. 2a,b) and these high basal responses are associated with lower or blunted stress-related arousal (Fig. 2c,d), similar to other high and chronic distress states (Steptoe & Ussher 2006; Li *et al.* 2007). It is important to note that these alterations were not accounted for by smoking status or lifetime history of anxiety or mood disorders and therefore appear to be related to history of alcohol and drug dependence and dependence severity. The persistence of emotional distress and drug craving induced by stress and drug-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 drug craving and relapse susceptibility.

NEURAL CORRELATES OF STRESS AND DRUG CRAVING IN ADDICTION

With the emergence of functional neuro-imaging technology in the last 15 years, effective experimental methods to assess drug craving, emotions and stress within the confines of neuro-imaging 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 known to increase craving increases activity in the amygdala and regions of the frontal cortex (Grant *et al.* 1996; Childress *et al.* 1999; Kilts *et al.* 2001) and with gender differences observed in amygdala activity and frontal cortex response 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 (see Sinha & Li 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 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 (ACC), hippocampus and parahippocampal regions, was observed in healthy controls during stress, whereas 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.

Recent positron emission tomography (PET) studies 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 (Wrase *et al.* 2002; Grusser *et al.* 2004). Using PET imaging with alcoholics and cocaine patients, research has shown a significant association between dopamine D2-receptor binding in the ventral striatum 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 hypofrontal responses in addicted individuals compared with control volunteers (Kaufman *et al.* 2003; Hester & Garavan 2004; Ersche *et al.* 2005, 2006, 2008; Paulus *et al.* 2006; Noel *et al.* 2007; Li *et al.* 2008; Li & Sinha 2008). 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 & Sinha 2008).

PREDICTION OF STRESS AND CUE-INDUCED DRUG RELAPSE

It is well known that drug abusers and alcoholics often cite stress and negative affect as reasons for relapse to drug use (Ludwig & Wikler 1974; Litman, Eiser & Rawson 1977; Marlatt & Gordon 1980, 1985; Litman *et al.* 1983; Bradley *et al.* 1989; Wallace 1989; McKay *et al.* 1995). This has led to the inclusion of coping skills as an integral component of the empirically validated behavioral treatments for addiction (Shiffman 1982; Marlatt & Gordon 1985; Monti *et al.* 1989; Cohen & Lichtenstein 1990; Brewer *et al.* 1998). However, despite the efficacy of several behavioral interventions in addiction treatment (Miller *et al.* 1992; Budney & Higgins 1998; Carroll 1998), it is well known that relapse rates in addiction remain high, and that stress and drug-related stimuli are potent factors contributing to the high rates of addiction relapse (O'Brien *et al.* 1998; McKay *et al.* 1999; Sinha 2001). An important aspect of modeling hallmark addictive symptoms such as drug craving in the laboratory is to understand its related mechanisms and also to demonstrate the validity of the model by examining if 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 addicted samples who were in-patients 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. We followed the in-patient treatment-engaged, cocaine- and alcohol-dependent individuals in our studies after discharge following completion of 3–5 weeks of in-patient substance-abuse treatment, for 90 days to assess relapse outcomes. Subjects returned initially for one follow-up interview at 90 days; and more recently, follow-up assessments are conducted at 14, 30, 90 and 180 days after discharge from the in-patient unit. Our follow-up rates for these assessments have been 96, 89, 92 and 86%, respectively. For outcomes in the cocaine group, we found that stress-induced cocaine craving in the laboratory significantly predicted time to cocaine relapse. The data showed that the higher the stress-induced drug craving in the laboratory, the shorter the time to relapse after in-patient treatment, with every point increase in overall stress-induced cocaine craving leading to a 31% increased risk of relapse to drug use (Sinha *et al.* 2006). Furthermore, although stress-induced ACTH and cortisol responses were not associated with

time to relapse, these responses were predictive of amounts of cocaine consumed during follow-up. Interestingly, although in this study we did not find that drug cue-induced craving was predictive of relapse, there was a high correlation between stress-induced and drug cue-induced craving and in stress and drug cue-induced HPA responses. These data suggest that at least in the case of cocaine dependence, stress and drug cue-induced distress states produce a similar compulsive drug-seeking state that is associated with relapse vulnerability.

Our initial evidence from assessing whether laboratory responses to stress and alcohol-related stimuli exposure are predictive of alcohol treatment outcomes have also been positive. We found that stress-induced alcohol craving in the laboratory during in-patient 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). More recent data suggests that both stress and alcohol cue-induced craving is associated with time to alcohol relapse. Preliminary analyses also indicate that blunted or low levels of stress-induced ACTH and heart rate responses is predictive of shorter times to relapse (Sinha 2008a). These data are consistent with some earlier reports of stress system involvement in relapse outcomes in alcoholics and smokers. Negative mood and stress-induced alcohol craving and blunted stress, and cue-induced cortisol responses have been associated with alcohol relapse outcomes (Cooney *et al.* 1997; Junghanns, Backhaus & Tietz 2003; Breese *et al.* 2005). Nicotine-deprived smokers who were exposed to a series of stressors showed blunted ACTH, cortisol and blood pressure responses to stress but increased nicotine withdrawal and craving scores, and these responses were predictive of nicotine relapse outcomes (Al'absi, Hatsukami & Davis 2005). Thus, for alcoholic and smoking 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.

Finally, we've also conducted initial analyses to assess whether brain responses to stress in cocaine-dependent individuals is predictive of relapse outcomes. We found that altered responses in the rostral ACC was predictive of time to cocaine relapse and also number of days of cocaine used during follow-up in cocaine-dependent individuals (Sinha & Li 2007). These data provide early evidence that altered response to stress in the medial prefrontal cortex/ACC contributes to relapse susceptibility. Follow-up studies are underway to further confirm these findings in larger sample sizes and to assess the role of dorsal striatum, amygdala and the dorsal ACC during stress and drug-cue exposure and their relationship to relapse outcomes.

SPECIFIC RESPONSES AS TARGETS FOR TREATMENT DEVELOPMENT

The previous sections described our approach to modeling stress and drug craving in the laboratory in addicted individuals and summarized the evidence thus far on whether the stress and drug craving responses are predictive of addiction relapse outcomes. The findings indicate that both stress and drug cue-induced provoked craving could serve as markers of relapse susceptibility. Altered HPA activity, and in some instances altered heart rate, was also found to be associated with relapse. Among brain imaging responses, altered stress-related activity in the medial pre-frontal cortex/rostral ACC was also a sensitive measure of relapse in one study. Although 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 drug craving and may serve as secondary target measures, which in conjunction with drug craving, could provide useful indicators of change in emotional distress associated with drug 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 addiction relapse.

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 drug craving and normalize stress regulation using agents that have shown promise in basic science models. 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 gamma-aminobutyric acid systems contribute to the high craving states and the chronic relapsing nature of addiction (Goeders 2002; Shaham *et al.* 2003; Koob *et al.* 2004; Kalivas & Volkow 2005; O'Brien 2005; Vocci, Acri & Elkashef 2005; Weiss 2005). For example, using animal models of drug self-administration and reinstatement, preclinical studies have shown CRF antagonists and alpha-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). Although our laboratory data indicating a high stress and drug-craving profile supports the use of CRF antagonists to ameliorate such effects, these agents are not available for testing in addicted patients. We therefore began with testing whether alpha-2-adrenergic agonists such as lofexidine are effective in decreasing emotional stress, physiological arousal and stress-induced drug craving. The first set of studies was conducted in opioid-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 with neutral relaxing stimuli (Hyman *et al.* 2007). In a second study, lofexidine was found to significantly decrease stress-induced opiate craving and anger ratings, at the same time also decreasing basal heart rates and improving opiate relapse outcomes in a small study of naltrexone-treated opiate-dependent individuals (Sinha *et al.* 2003). These studies provide initial support for the use of the human laboratory model described in this paper as a tool for testing novel pharmacological interventions.

LIMITATIONS AND CAVEATS

It is important to acknowledge that induction of stress and drug craving in laboratory settings remains a challenge in the field. Several caveats about the emotional imagery methods and procedures used to induce stress and drug craving in the laboratory need to be highlighted. First, although 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 senior research staff (those with masters in a clinical/counseling or related field), postdoctoral fellows and faculty level individuals are allowed to conduct the sessions and generate scripts. Our procedures have only been tested in treatment-engaged addicted patients and healthy individuals and hence then effectiveness in non-treatment seeking and actively using individuals are not known.

Although this review described the specific methods used in our laboratory studies, there are other experimental factors that are important to consider in studying stress and drug craving.

For example, duration of the exposure to stress or to the drug-related stimuli significantly affects strength of response. For example, in the laboratory studies, our script length is 5–6 minutes whereas in the brain imaging session it is 2 minutes long. Furthermore, in a medication study currently underway, we are using 10-minute exposure periods with two scripts for each condition. Another example of extending the exposure period is the well-established Trier Social Stress Task (Kirschbaum, Pirke & Hellhammer 1993), a standard social stress test that includes a combination of two types of stressors—a speech test and a challenging math task that lasts anywhere between 10 and 15 minutes in its various adaptations. Such a long exposure likely contributes to its ability to produce robust cortisol responses. On the other hand, a very brief but highly arousing stressor is the cold pressor task that can last up to 90 seconds and can increase sympathetic arousal but has low levels of HPA axis activity. Other factors, such as aversiveness of the stressor, 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, and their potential impact on clinical outcomes.

CONCLUSION

In summary, this paper described our efforts in provoking stress and drug craving in the laboratory in order to assess alterations in stress responses, drug craving and compulsive seeking and addiction relapse susceptibility. We have reliably induced emotional distress and drug craving in addicted samples, shown alterations in hedonic state during drug cue-exposure and dysregulation of stress responses peripherally and in corticostriatal-limbic responses. Furthermore, several of the laboratory responses were found to be predictive of clinical relapse outcomes thereby validating the model in its ability to prospectively predict drug-use behaviors and relapse susceptibility. Initial positive results have also been seen when using the method to test pharmacological agents to decrease stress and drug craving. Several studies testing additional behavioral and pharmacological manipulations to assess their effects on stress dysregulation and drug craving in addicted samples are currently underway. Further development of the model in terms of examining individual differences factors such as the impact of specific genetic polymorphisms and early and chronic stress factors on basal and response measures of stress and level of drug craving would be useful in identifying individuals who are most susceptible to stress-related neuroadaptation in addiction, and those most susceptible to high levels of stress and cue-induced drug craving and compulsive seeking. Such research would be of clinical benefit both in the assessment of relapse susceptibility and also in matching individuals specifically vulnerable to stress-related neuroadaptations and drug craving to interventions that are specific to these addictive processes.

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Figure 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 (Hyman *et al.* 2007; Fox *et al.* 2008; Sinha *et al.* 2008). (a) Peak craving during stress and drug-cue conditions is significantly higher in abstinent alcoholics, cocaine- and naltrexone-treated opioid patients compared with social drinkers ($P < 0.0001$ for both conditions). (b) Peak anxiety ratings are significantly higher in abstinent alcoholics, cocaine- and naltrexone-treated opioid patients compared with social drinkers in both stress and drug-cue conditions (stress: $P < 0.005$; drug cue: $P < 0.0001$)

Figure 2.

Mean and standard errors for (a) basal heart rate measured at baseline prior to imagery exposure over several timepoints across three separate days of experimental testing in alcoholic (AD) and cocaine (COC) patients compared with social drinkers (SD) ($AD > COC > SD$, $P < 0.01$); and (b) basal salivary cortisol averaged for two baseline assessments across three separate testing days ($AD > SD$, $P < 0.01$; $COC > SD$, $P < 0.11$); (c) peak heart rate responses in the stress (S), drug cue (D) and neutral (N) conditions: SD group shows $S > N$, $P < 0.0001$; $D > N$, $P < 0.02$; $S > D$, $P < 0.04$), whereas 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; Sinha *et al.* 2008)

Table 1
Sample individualized scripts.

Stress

It is Saturday night about 5:00 PM. 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 4th. 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 breathe 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.