The Role of Stress in Addiction Relapse

Rajita Sinha, PhD

Corresponding author
Rajita Sinha, PhD
Department of Psychiatry, Yale University School of Medicine,
34 Park Street, Room S110, New Haven, CT 06519, USA.
E-mail: rajita.sinha@yale.edu

Current Psychiatry Reports 2007, **9:**388–395
Current Medicine Group LLC ISSN 1523-3812

Stress is an important factor known to increase alcohol and drug relapse risk. This paper examines the stress-related processes that influence addiction relapse. First, individual patient vignettes of stress- and cue-related situations that increase drug seeking and relapse susceptibility are presented. Next, empirical findings from human laboratory and brain-imaging studies that are consistent with clinical observations and support the specific role of stress processes in the drug-craving state are reviewed. Recent findings on differences in stress responsivity in addicted versus matched community social drinkers are reviewed to demonstrate alterations in stress pathways that could explain the significant contribution of stress-related mechanisms on craving and relapse susceptibility. Finally, significant implications of these findings for clinical practice are discussed, with a specific focus on the development of novel interventions that target stress processes and drug craving to improve addiction relapse outcomes.

Introduction

It has long been known that stress increases the risk of drug abuse and relapse [1]. Initially, the basis for this association comes from clinical observations, surveys, and epidemiologic studies. However, the mechanisms by which stress exposure increases drug use and relapse risk have been elusive until recently. The last two decades have seen a dramatic increase in preclinical and clinical research to understand neural circuits associated with stress and those underlying addictive behaviors. Evidence suggests that the neural circuits involved in stress overlap substantially with brain systems involved in drug reward. Chronic use of drugs can result in neuroadaptive changes in brain stress and reward pathways that in turn can alter a dependent individual's response to stress, particularly with respect to the perpetuation of addictive behaviors and relapse [1,2•]. Clinical observations and patient description of stress-related situations that have led to drug use and relapse situations in addicted individuals in early recovery are presented.

Patient vignettes

Stress situation

This situation was rated as a 9 for "highly stressful" on a 10-point Likert scale in which 0 is "not at all stressful" and 10 refers to "highly stressful—most you've felt recently" and was narrated by a female patient addicted to alcohol and cocaine and in recovery for 6 weeks.

"It was late at night in the spring. I was at my sister's place. I remember her saying, 'You are so smart … why are you wasting your life?' I remember she said, 'I have been around drugs, I should have been the drug user, but I didn't, and why did you turn out a loser?' She didn't know how it was making me feel. I felt I had to leave. I could not handle those emotions in that period of my life. I was withdrawing. I was trying to leave. I told her, 'I don't want to talk about this; I can't talk about this in this condition.' I was sad; I was very sad. I was sad because I had no answers for her … you know … I didn't know what to tell her. I went and got the telephone and I called for a ride. I remember I had dropped the cordless phone and um … she yelled at me. 'You bitch, you're a crackhead; you can't buy me another phone.' I'll never forget that statement … and um … I ran out of the house. I was very, very distraught, I was crying, and I wanted to use so badly. As a matter of fact, there was a bar right around the corner. It had to be around 1 AM, because I remember I went to that bar and I would say it was a little after 1 AM when I drank till it closed at about 2 AM. I felt disgusted … just thinking of it … I can remember … I almost felt like nauseous … anxious … very anxious … I had to … it's a terrible feeling … I don't even like to think about it … but I had to have a drink. Like I said, all I can remember is feeling nauseous, like an upset stomach. I would have to say I felt tense, like in my shoulders and all over. My heart was racing, and I felt like I was burning up. I just had to get out of there, and all I could think of was having a drink."

Drug-related situation

"It would have been in the afternoon on a fall day. I believe that I had just woken up … you know, I was partying all night, sleeping all day, and this particular afternoon

I woke up and I wanted to get high really bad. I was in my bedroom when I woke up. I was so used to people coming over, around that time or before, to get me high, and nobody was showing up … and I was like (gestures shock), 'Where is everybody?' (laughs) … you know what I mean. I was waking up to it … that's all I did was get high all day, and this particular morning no one was showing up. I went downstairs to see if I saw anybody. So I starting thinking about how am I going to get my hands on some crack. So I called up a couple of dealers, but of course they wouldn't give me any. By now I really have to get high—like I have to have it now. It's a whole body thing, you know, your whole body gets tense, your head is not feeling right, and it was just a real intense, powerful craving. I was angry. I was sweating and snapping at people. I was very mean to everyone. It just wasn't me, and I didn't like it because I realized how I was acting, and I did not like it. But I couldn't stop it. I could not get myself out of it. I know I wasn't going to get out of it until I got high."

These patient descriptions illustrate several points about stress and drug-seeking behavior that are relevant from a clinical perspective. The first vignette is a fairly typical description of interpersonal stress situations described by patients when discussing stress precipitants to relapse. Although patients are less likely to divulge specific details of craving situations in a clinical context, the second vignette illustrates that drug cues and increased craving states in which drug access is limited can also increase anxiety and stress-related arousal in addicted individuals. These clinical situations raise many questions about the role of stress in drug seeking and in relapse susceptibility. The first point to establish is whether stress and drug cues establish similar drug-craving states that may be targeted in treatment. Second, they also raise the issue of whether the response to stress- and drug-related stimuli is different in addicted patients and whether stress responses and managing stress are altered as a function of chronic drug use. Although these vignettes provide anecdotal evidence, the question of whether craving and stress-related arousal are predictive of relapse outcomes and whether stress causes relapse also need to be addressed. Finally, if stress plays an important role in both stress- and cue-related relapse, what types of interventions would be helpful, and how can a clinician use the stress and craving responses to better address the treatment needs of the addicted individual? The sections to follow address each of these questions to illustrate the role of stress in addiction relapse.

Psychobiological Changes Associated with Chronic Use of Psychoactive Drugs

Increases in irritability, anxiety, emotional distress, sleep problems, dysphoria, aggressive behaviors, and drug craving are common during early abstinence from alcohol, cocaine, opiates, nicotine, and marijuana [3–6]. Recent conceptualizations of drug dependence emphasize the establishment of a withdrawal-related "negative affect" or psychologically distressed state during abstinence in addicts that is associated with neuroadaptations in brain reward circuits and stress pathways [7–10]. Severity of the previously described abstinence symptoms is known to predict treatment outcome among smokers, cocaine addicts, heroin-dependent individuals, and alcoholics [5,11–16]. In general, findings indicate that the greater the dependence and abstinence severity, the greater the susceptibility to relapse and poor treatment outcome.

Also, a growing body of evidence documents alterations in the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, autonomic nervous system changes, and alterations in brain dopaminergic and emotion and motivational systems of addicted individuals. Research has shown that both acute and protracted withdrawal from psychoactive substances are associated with overactivity of the corticotropin-releasing factor (CRF) systems as documented in preclinical studies [8] and in clinical studies showing CRF-HPA disturbances in alcoholics, opiate addicts, and cocaine-addicted individuals [2•,7,17,18]. Autonomic and noradrenergic abnormalities also have been well documented, with overactivity of these systems during acute and protracted withdrawal from opiates, alcohol, and cocaine [2•,19–23]. These findings indicate that the CRF and the autonomic/noradrenergic systems are dysregulated during acute withdrawal. In addition, mild to moderate alterations may exist past acute withdrawal during protracted abstinence, at least with the 4- to 12-week period, which may contribute to the behavioral responses to stress and its link to relapse susceptibility.

In addition, findings from human brain imaging studies have reported short- and long-term changes in the dopaminergic system in humans. Reduced glucose metabolism, especially in frontal regions, during both acute and protracted withdrawal (up to 3–4 months) from cocaine has been observed (see [9] for review). Alcoholics and cocaine abusers show a significant reduction in dopamine D_2 receptors as compared with healthy controls, particularly in frontal-striatal regions [9]. Some evidence also suggests increased density of dopamine and noradrenergic transporter binding sites in the striatum with chronic cocaine abuse [24–26], a finding that has been replicated in rhesus monkeys chronically exposed to cocaine [27,28]. Thus, these data point to alterations in frontal and striatal regions of the dopaminergic and noradrenergic pathways that exist past acute withdrawal and may be associated with difficulties in regulating emotions, stress, and problems in selecting of goal-directed adaptive responses, as opposed to the selection of habitual, maladaptive responses.

Effects of Stress on Drug Craving and Arousal in Addicted Individuals

Drug craving or "wanting" for drug is a hallmark feature of addiction. It is an important component in mainte-

nance of addictive behaviors [29–33], and preclinical data indicate that sensitization processes resulting from neuroadaptations in brain reward pathways due to chronic drug abuse underlie this excessive "wanting" or drug-seeking state. They suggest that these neuroadaptations lead to an increase in the incentive salience of drugs. That exposure to drugs and drug-associated stimuli then results in an excessive "wanting" or craving, thereby increasing the susceptibility to relapse. To the extent that subjective craving in addicts and drug-seeking behavior in animals represents a measure of "wanting," there is growing research on examining the neural and psychobiological substrates underlying these states.

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 [34–36]. Foltin and Haney [37] demonstrated that classical conditioning is one mechanism by which neutral environmental cues paired with cocaine smoking in cocaine abusers acquire emergent stimulus effects in contrast to stimuli paired with placebo cocaine. These findings validate a host of 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 physiologic reactivity [38]. Exposure to negative affect, stress, or withdrawal-related distress also has been associated with increases in drug craving and cue reactivity [39–42].

One line of research in my laboratory has focused on examining the effects of stress- and drug-related cues on drug craving in alcoholics; cocaine-dependent individuals; and naltrexone-treated, opiate-dependent individuals in recovery. We examined drug craving and reactivity in treatment-engaged, abstinent, addicted individuals who were exposed to stressful and nonstressful drug cue situations and neutral-relaxing situations, using personalized imagery procedures as the induction method (Sinha, Unpublished manual). Our initial findings indicated 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, imagery of personal stressors produced significant increases in cocaine craving, whereas public speaking did not [41,43]. Significant increases in heart rate, salivary cortisol, drug craving, and subjective anxiety also were observed with imagery exposure to stress and nonstress drug cues as compared with neutral-relaxing cues in cocaine-dependent individuals [42]. More recently, we have shown that stress- and alcohol-/drug-related stimuli similarly increase craving, anxiety, negative emotions, and physiologic responses in abstinent alcoholics and in naltrexone-treated, opiate-addicted individuals [44,45]. On the other hand, recently abstinent alcoholics and smokers consistently show a blunted HPA response as measured by cortisol to stress compared with nonsmokers [46,47].

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 as compared with neutral-relaxing cues activated the HPA axis (with increases in adrenocorticotropic hormone [ACTH], cortisol, and prolactin levels), as well as the sympthoadrenomedullary systems as measured by plasma norepinephrine (NE) and epinephrine (EPI) levels [48]. Furthermore, we found little evidence of recovery or return to baseline in ACTH, NE, and EPI levels even more than an hour after the 5-minute imagery exposure. These data provided some indirect evidence of a dysregulated stress response during exposure to stress and to drug cues. However, I elaborate on the direct evidence of alterations in the stress- and reward-related responses in addicted individuals compared with controls in the next sections.

Brain-imaging studies with drug abusers have shown that exposure to drug cues known to increase craving resulted in activation of the amygdala and regions of the frontal cortex [49–51]. Gender differences in amygdala activity and frontal cortex response in cocaine-dependent individuals also have been reported [52,53]. Amygdala nuclei are also essential in the acquisition of Pavlovian fear conditioning [54], and stress exposure is known to increase dopamine release in the basolateral amygdala [55]. As stress also increases drug craving, we examined brain activation during stress and neutral imagery in a functional MRI 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 (an area important in emotion regulation), hippocampus, and parahippocampal regions was greater in healthy controls during stress, whereas cocaine patients showed a striking absence of such activation [56••]. 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. In a recent positron emission tomography study, Volkow et al. [57•] have also reported significant positive correlations between the dorsal striatum and drug cue-induced cocaine craving. These findings are also consistent with functional MRI data on alcoholic patients showing increased association between dorsal striatum regions and alcohol craving in response to presentation of alcohol-related stimuli [58,59]. Together, these findings indicate that specific regions of the cingulate cortex, striatum, and amygdala are involved in the increased responses to stress- and cue-induced drug craving ratings and that this circuitry may be dysfunctional in addicted individuals.

Altered Stress Responsivity and Enhanced Drug Craving in Addicted Individuals

Whereas stress- and drug-related stimuli similarly increase subjective distress and drug craving in recently abstinent addicted individuals, there is specificity in physiologic and HPA axis responses to stress by primary drug of abuse. Our group recently compared abstinent 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 an enhanced sensitivity to emotional distress and physiologic arousal and higher levels of drug craving to both stress and drug cue exposure compared with controls [60••]. Similarly, we also compared 4-week abstinent alcoholics to matched social drinkers. The recovering alcoholics at 4 weeks abstinence showed greater levels of basal heart rate and salivary cortisol levels compared with control drinkers. Upon stress and alcohol cue exposure, they showed persistently greater subjective distress, alcohol craving, and blood pressure responses but blunted pulse and cortisol responses compared with controls [61].

Several conclusions can be drawn from these and previous findings. First, these data clearly indicate that the stress pathways are altered in addicted individuals compared with controls and that these alterations can last for at least 4 weeks of abstinence, if not longer, from chronic drug use. They also indicate that a hyperresponsive distress state that is susceptible to compulsive drug seeking ensues among addicted individuals who are in early recovery. This increased sensitivity to distress and drug craving, along with a decreased ability to recover and return to baseline after stress and cue exposure represents the dysfunctional state that could increase susceptibility to relapse among addicts faced with stress- and drug-related stimuli during recovery.

Stress-induced Relapse

A host of clinical and survey studies indicate that drug abusers and alcoholics often cite stress and negative affect as reasons for relapse to drug use (see [1,2•] for review). Furthermore, psychological research has long supported the need to address stress coping in empirically validated behavioral treatments of addiction [62,63]. However, despite the efficacy of several behavioral interventions in addiction treatment (see review in [64]), it is well known that relapse rates in addiction remain high and the chronic relapsing nature of addiction needs specific attention in addiction treatments [1,31,65].

There is now growing recognition from the preclinical and human neuroscience research that dysregulation in brain stress and reward pathways may play a key role in addiction relapse [1,66,67,68•]. Several animal models of relapse have shown that overactive brain CRF, noradrenergic, and glutamatergic systems, along with underactive dopamine and γ-aminobutyric acid systems contribute to the high craving states and the chronic relapsing nature of addiction [8,10,69–71]. Furthermore, using animal models of drug self-administration and relapse, preclinical studies have identified CRF antagonists, α-2–adrenergic agonists, and glucocorticoid agents as important in reducing stress- and cue-related drug seeking in addicted laboratory animals (see [67,70]). These findings suggest that human studies with addicts need to identify the viable treatment targets that could decrease the high-stress and drug-craving state that hampers recovery in addiction.

Human research also has begun to identify markers of the stress and craving states that are predictive of relapse outcomes. To better understand the relationship between relapse and increased distress with drug craving, we conducted a follow-up study of patients with cocaine or alcohol dependence. These were individuals described in previous sections of this paper, and they were followed for 90 days to assess relapse outcomes. For the cocaine group, we found that stress-induced cocaine craving in the laboratory significantly predicted time to cocaine relapse. 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 [72••]. Although in this study, drug cue-induced craving was not predictive of relapse, there was a high correlation between stress- and drug cue-induced drug craving and between 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.

There also is evidence 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 [40,67,73,74]. 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. These responses were predictive of nicotine relapse outcomes [47]. 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 glucocorticoid feedback or increased noradrenergic arousal) results in an enhanced susceptibility to addiction relapse. A schematic model of subjective distress, increased drug seeking, and relapse susceptibility is presented in Figure 1.

In considering the research on stress, drug craving, and relapse susceptibility highlighted in the previous sections, it is important to note several caveats. First, stress responses and stress-related coping are complex phenomena that are affected by multiple developmental, genetic,

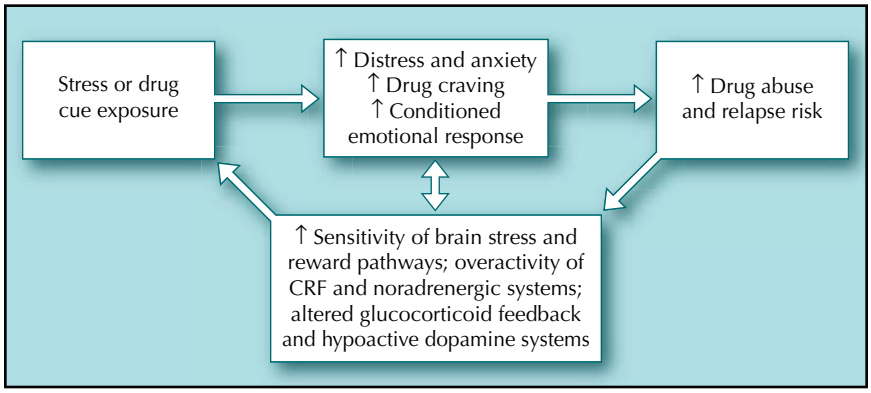

Figure 1. A schematic model of stress-related mechanisms that increase relapse susceptibility. CRF—corticotropin-releasing factor.

and individual factors. For example, early trauma and child maltreatment alter stress responses and affect addiction vulnerability [75,76]. Genetic factors are important in emotion processing and in response to stressful life events [77,78•] and may be important in stress-related relapse susceptibility in addictions. Psychiatric comorbidity and individual differences in coping ability, executive function, and impulse control can influence stress coping and addiction vulnerability as well [79•]. Clearly, future research needs to consider these factors in fully delineating the association between stress, drug craving, and relapse vulnerability, as these factors may significantly affect the clinical efforts to address stress and relapse susceptibility.

Clinical Implications of the Role of Stress in Addiction Relapse

The previous sections have identified recent trends in human neuroscience research that indicate an important role for stress pathways in the drug-craving state and in relapse vulnerability. This final section discusses the significant clinical implications of the role of stress in addressing addiction relapse. First, the patient vignettes described previously illustrate that clinicians can elicit relapse situations to identify stress- and drug cue-related cravings and compulsions in a clinical context. Clinicians also may have patients identify craving and distress levels as diagnostic markers to assess relapse propensity. Assessment of altered stress arousal and hormonal responses may further support the need to address stress-related dysfunction in addiction treatment. A caveat to the effective use of such assessments is consideration of the psychosocial context of drug abuse. Addicted individuals in recovery often are mandated by court and probation to treatment. Reporting of craving and relapse vulnerability could result in serious negative consequences such as incarceration, thereby preventing accurate reporting of cravings (more so for illicit drugs of abuse than drugs such as nicotine and alcohol). Nonetheless, if the confidentiality of the assessment and reporting can be ensured, such assessments could inform clinicians of the need to tailor their interventions toward stress regulation and reduction of stress-induced craving.

Second, although assessing stress-induced craving and hormonal responses can be informative in identifying those individuals who are highly susceptible to relapse, the findings presented earlier underscore the importance of developing treatments that target attenuation of stress-induced cocaine craving and regulation of stress-related HPA axis responses in cocaine relapse prevention. There currently are no empirically validated treatments that address stress-related drug craving and arousal. As described previously, animal studies have shown that both CRF antagonists and α-2–adrenergic agonists attenuate stress-induced drug and alcohol reinstatement in dependent laboratory animals [66,70]. Nonpeptide CRF antagonists currently are being investigated in the treatment of affective and anxiety disorders [80,81]. The findings presented in the present review are consistent with previously cited preclinical data and support examining the efficacy of CRF antagonists in attenuating stress-induced cocaine craving and HPA responses to improve addiction relapse outcomes. Furthermore, α-2–adrenergic agonists that inhibit norepinephrine centrally have shown promise in the treatment of attention-deficit/hyperactivity disorder [82], in reducing opiate withdrawal symptoms [83], and in reducing nicotine craving [84]. Most recently, our group has shown that lofexidine, an α-2–adrenergic agonist, significantly decreased stress-induced opiate craving and stress-induced anger ratings while also improving opiate relapse outcomes in a small study of naltrexone-treated, opiate-dependent individuals [85••]. The efficacy of these and other agents that target noradrenergic dysregulation and their role in stress-induced drug craving and relapse susceptibility need further testing in human studies. Behavioral treatments that target decreased stress regulation and attenuation of stress-related cocaine craving also could have potential relevance in addressing relapse susceptibility. Of note, mindfulness-based treatments that have been shown to decrease depression relapse [86] now are being tested in decreasing stress and relapse susceptibility in addiction [87•,88]. Finally, laboratory models of stress-induced drug craving such as those described in the previous sections could be effective in screening pharmacologic agents or testing behavioral strategies to attenuate stress-induced drug craving and related arousal.

Conclusions

Whereas clinical observations and behavioral interventions have focused on stress as a key aspect of addiction relapse, recent neurobiological evidence indicates an important role of brain stress pathways in addiction relapse. Human laboratory and clinical studies have shown that increasing levels of behavioral distress contributes to compulsive levels of drug seeking (craving) and relapse risk in abstinent, addicted individuals in early recovery. These changes are accompanied by high physiologic arousal, dysregulated HPA responses, and a persistent distress and craving state that is slow to return to baseline. Preclinical data have identified CRF antagonists and noradrenergic agents as potential therapeutic targets. Human laboratory studies to test such stress-related therapeutic targets as viable treatments for relapse prevention also have been initiated. This line of research has the potential for development of novel pharmacologic treatments to specifically reduce the high rates of addiction relapse.

Acknowledgments

Preparation of this review was supported by grants R01-AA13892, R01-DA18219, P50-DA16556 and K02-DA17232 from the National Institutes of Health (NIH) and the NIH Office of Research on Women's Health. Dr. Sinha serves on the scientific advisory board for Embera NeuroTherapeutics, Inc.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Sinha R: **How does stress increase risk of drug abuse and relapse?** *Psychopharmacology (Berl)* 2001, **158:**343–359.

2.• Sinha R: **Stress and drug abuse.** In *Handbook of Stress and the Brain, part 2. Stress: Integrative and Clinical Aspects,* vol 15. Edited by Steckler T, Kalin NH, Reul JM. Amsterdam: Elsevier; 2005:333–356.

This chapter provides an overview of the bidirectional association between stress and drug abuse.

3. Hughes JR: **Tobacco withdrawal in self-quitters.** *J Consult Clin Psychol* 1992, **60:**689–697.

4. Kouri EM, Pope HG, Jr, Lukas SE: **Changes in aggressive behavior during withdrawal from long-term marijuana use.** *Psychopharmacology (Berl)* 1999, **143:**302–308.

5. Mulvaney FD, Alterman AI, Boardman CR, Kampman K: **Cocaine abstinence symptomatology and treatment attrition.** *J Subst Abuse Treat* 1999, **16:**129–135.

6. Budney AJ, Hughes JR: **The cannabis withdrawal syndrome.** *Curr Opin Psychiatry* 2006, **19:**233–238.

7. Kreek MJ, Koob GF: **Drug dependence: stress and dysregulation of brain reward pathways.** *Drug Alcohol Depend* 1998, **51:**23–47.

8. Koob GF, Ahmed SH, Boutrel B, et al.: **Neurobiological mechanisms in the transition from drug use to drug dependence.** *Neurosci Biobehav Rev* 2004, **27:**739–749.

9. Volkow N, Fowler JS: **Addiction, a disease of compulsion and drive: involvement of the orbitofrontal cortex.** *Cereb Cortex* 2000, **10:**318–325.

10. Kalivas PW, Volkow ND: **The neural basis of addiction: a pathology of motivation and choice.** *Am J Psychiatry* 2005, **162:**1403–1413.

11. McLellan AT, Luborsky L, Woody GE, et al.: **Predicting response to drug and alcohol abuse treatments: role of psychiatric severity.** *Arch Gen Psychiatry* 1983, **40:**620–625.

12. Carroll KM, Power MD, Bryant KJ, Rounsaville BJ: **One year follow-up status of treatment-seeking cocaine abusers: psychopathology and dependence severity as predictors of outcome.** *J Nerv Ment Dis* 1993, **181:**71–79.

13. Tennant F, Shannon JA, Nork JG, et al.: **Abnormal adrenal gland metabolism in opioid addicts: implications for clinical treatment.** *J Psychoactive Drugs* 1991, **23:**135–149.

14. Doherty K, Kinnunen T, Militello FS, Garvey AJ: **Urges to smoke during the first month of abstinence: relationship to relapse and predictors.** *Psychopharmacology (Berl)* 1995, **119:**171–178.

15. Killen J, Fortmann SP: **Craving is associated with smoking relapse: findings from three prospective studies.** *Exp Clin Psychopharmacol* 1997, **5:**137–142.

16. Baker TB, Brandon TH, Chassin L: **Motivational influences on cigarette smoking.** *Annu Rev Psychol* 2004, **55:**463–491.

17. Contoreggi C, Herning RI, Na P, et al.: **Stress hormone responses to corticotropin-releasing hormone in substance abusers without severe comorbid psychiatric disease.** *Biol Psychiatry* 2003, **54:**873–878.

18. Adinoff B, Junghanns K, Kiefer F, Krishnan-Sarin S: **Suppression of the HPA axis stress-response: implications for relapse.** *Alcohol Clin Exp Res* 2005, **29:**1351–1355.

19. McDougle CJ, Black JE, Malison RT, et al.: **Noradrenergic dysregulation during discontinuation of cocaine use in addicts.** *Arch Gen Psychiatry* 1994, **51:**713–719.

20. Krystal JH, Webb E, Cooney NL, et al.: **Serotonergic and noradrenergic dysregulation in alcoholism: M-chrophenylpiperazine and yohimbine effects in recently detoxified alcoholics and healthy comparison subjects.** *Am J Psychiatry* 1996, **153:**83–92.

21. Bar KJ, Boettger MK, Neubauer R, et al.: **Heart rate variability and sympathetic skin response in male patients suffering from acute alcohol withdrawal syndrome.** *Alcohol Clin Exp Res* 2006, **30:**1592–1598.

22. Rechlin T, Orbes I, Weis M, Kaschka WP: **Autonomic cardiac abnormalities in alcohol-dependent patients admitted to a psychiatric department.** *Clin Auton Res* 1996, **6:**119–122.

23. Ingjaldsson JT, Laberg JC, Thayer JF: **Reduced heart rate variability in chronic alcohol abuse: relationship with negative mood, chronic thought suppression, and compulsive drinking.** *Biol Psychiatry* 2003, **54:**1427–1436.

24. Little KY, Zhang KL, Desmond T, et al.: **Striatal dopaminergic abnormalities in human cocaine users.** *Am J Psychiatry* 1999, **156:**238–245.

25. Staley JK, Hearn WL, Ruttenber AJ, et al.: **High affinity cocaine recognition sites on the dopamine transporter are elevated in fatal cocaine overdose victims.** *J Pharmacol Exp Ther* 1994, **271:**1678–1685.

26. Malison R, Best SE, van Dyck CH, et al.: **Elevated striatal dopamine transporters during acute cocaine abstinence as measured by [123I] beta-CIT SPECT.** *Am J Psychiatry* 1998, **155:**832–834.

27. Letchworth SR, Nader MA, Smith HR, et al.: **Progression of changes in dopamine transporter binding site density as a result of cocaine self-administration in rhesus monkeys.** *J Neurosci* 2001, **21:**2799–2807.

28. Beveridge T, Smith H, Nader M, Porrino L: **Effects of chronic cocaine self-administration on norepinephrine transporters in the nonhuman primate brain.** *Psychopharmacology (Berl)* 2005, **180:**781–788.

29. Dackis CA, Gold MS: **New concepts in cocaine addiction: the dopamine depletion hypothesis.** *Neurosci Biobehav Rev* 1985, **9:**469–477.
30. Tiffany S: **A cognitive model of drug urges and drug-use behavior: the role of automatic and non-automatic processes.** *Psychol Rev* 1990, **97:**147–168.
31. O'Brien CP, Childress AR, Ehrman RN, Robbins SJ: **Conditioning factors in drug abuse: can they explain compulsion?** *J Psychopharmacol* 1998, **12:**15–22.
32. Robinson TE, Berridge KC: **The neural basis of drug craving: an incentive-sensitization theory of addiction.** *Brain Res Brain Res Rev* 1993, **18:**247–291.
33. Robinson TE, Berridge KC: **The psychology and neurobiology of addiction: an incentive-sensitization view.** *Addiction* 2000, **95(Suppl 2):**S91–S117.
34. Stewart J, de Wit H, Eikelboom R: **Role of unconditioned and conditioned drug effects in the self-administration of opiates and stimulants.** *Psychol Rev* 1984, **91:**251–268.
35. Rohsenow DJ, Niaura RS, Childress AR, et al.: **Cue reactivity in addictive behaviors: theoretical and treatment implications.** *Int J Addict* 1991, **25:**957–993.
36. Childress A, Hole A, Ehrman R, et al.: **Cue reactivity and cue reactivity interventions in drug dependence.** *NIDA Res Monogr* 1993, **137:**73–95.
37. Foltin RW, Haney M: **Conditioned effects of environmental stimuli paired with smoked cocaine in humans.** *Psychopharmacology (Berl)* 2000, **149:**24–33.
38. Carter BL, Tiffany ST: **Meta-analysis of cue reactivity in addiction research.** *Addiction* 1999, **94:**327–340.
39. Childress AR, Ehrman RN, McLellan AT, et al.: **Can induced moods trigger drug-related responses in opiate abuse patients?** *J Subst Abuse Treat* 1994, **11:**17–23.
40. Cooney NL, Litt MD, Morse PA, et al.: **Alcohol cue reactivity, negative mood reactivity, and relapse in treated alcoholic men.** *J Abnorm Psychol* 1997, **106:**243–250.
41. Sinha R, Catapano D, O'Malley S: **Stress-induced craving and stress response in cocaine dependent individuals.** *Psychopharmacology (Berl)* 1999, **142:**343–351.
42. Sinha R, Fuse T, Aubin LR, O'Malley SS: **Psychological stress, drug-related cues and cocaine craving.** *Psychopharmacology (Berl)* 2000, **152:**140–148.
43. Sinha R, O'Malley SS: **Alcohol and craving: findings from the clinic and laboratory.** *Alcohol Alcohol* 1999, **34:**223–230.
44. Fox HC, Bergquist KL, Hong KI, Sinha R: **Stress-induced and alcohol cue-induced craving in recently abstinent alcohol dependent individuals.** *Alcohol Clin Exp Res* 2007, **31:**395–403.
45. Hyman SM, Fox HC, Hong K, et al.: **Stress and drug-cue-induced craving in opioid-dependent individuals in naltrexone treatment.** *Exp Clin Psychopharmacol* 2007, **15:**134–143.
46. Lovallo WR, Dickensheets SL, Myers DA, et al.: **Blunted stress cortisol response in abstinent alcoholic and polysubstance-abusing men.** *Alcohol Clin Exp Res* 2000, **24:**651–658.
47. Al'absi M, Hatsukami DK, Davis G: **Attenuated adrenocorticotropic responses to psychological stress are associated with early smoking relapse.** *Psychopharmacology (Berl)* 2005, **181:**107–117.
48. Sinha R, Talih M, Malison R, et al.: **Hypothalamic-pituitary-adrenal axis and sympatho-adreno-medullary responses during stress-induced and drug cue-induced cocaine craving states.** *Psychopharmacology (Berl)* 2003, **170:**62–72.
49. Grant S, London ED, Newlin DB, et al.: **Activation of memory circuits during cue-elicited cocaine craving.** *Proc Nat Acad Sci U S A* 1996, **93:**12040–12045.
50. Childress A, Mozely PD, McElgin W, et al.: **Limbic activation during cue-induced cocaine craving.** *Am J Psychiatry* 1999, **156:**11–18.
51. Kilts C, Schweitzer JB, Quinn CK, et al.: **Neural activity related to drug craving in cocaine addiction.** *Arch Gen Psychiatry* 2001, **58:**334–341.
52. Kilts C, Gross RE, Ely TD, Drexler KP: **The neural correlates of cue-induced craving in cocaine-dependent women.** *Am J Psychiatry* 2004, **161:**233–241.
53. Li CS, Kosten TR, Sinha R: **Sex differences in brain activation during stress imagery in abstinent cocaine users: a functional magnetic resonance imaging study.** *Biol Psychiatry* 2005, **57:**487–494.
54. LeDoux JE: **Emotional circuits in the brain.** *Annu Rev Neurosci* 2000, **23:**155–184.
55. Inglis FM, Moghaddam B: **Dopaminergic innervation of the amygdala is highly responsive to stress.** *J Neurochem* 1999, **72:**1088–1094.
56.•• Sinha R, Lacadie C, Skudlarski P, et al.: **Neural activity associated with stress-induced cocaine craving: a functional magnetic imaging study.** *Psychopharmacology (Berl)* 2005, **183:**171–180.

This study provides the first evidence in the literature of specific brain regions such as the dorsal striatum and insula and their correlation with stress-induced cocaine craving.

57.• Volkow ND, Wang GJ, Telang F, et al.: **Cocaine cues and dopamine in dorsal striatum: mechanism of craving in cocaine addiction.** *J Neurosci* 2006, **26:**6583–6588.

In this recently published study, the dorsal striatum, a region involved in generating and maintaining habits, was shown to be associated with cue-induced craving states.

58. Grusser S, Wrase J, Klein S, et al.: **Cue-induced activation of the striatum and medial prefrontal cortex is associated with subsequent relapse in abstinent alcoholics.** *Psychopharmacology (Berl)* 2004, **175:**296–302.
59. Heinz A, Siessmeier T, Wrase J, et al.: **Correlation between dopamine D(2) receptors in the ventral striatum and central processing of alcohol cues and craving.** *Am J Psychiatry* 2004, **161:**1783–1789.
60.•• Fox HC, Hong KA, Siedlarz K, Sinha R: **Enhanced sensitivity to stress and drug/alcohol craving in abstinent cocaine dependent individuals compared to social drinkers.** *Neuropsychopharmacology* 2007 [Epub ahead of print].

This recently published paper shows an altered and hyperresponsive response to stress and drug craving in abstinent cocaine patients compared with matched community controls, showing definite evidence that chronic cocaine abuse alters emotional stress responses and increases compulsive drug seeking.

61. Sinha R, Garcia M, Kemp K, et al.: **Alcohol craving and subjective emotional state during stress and alcohol cue exposure in alcoholics and social drinkers.** *Alcohol Clin Exp Res* 2005, **29:**150A.
62. Monti P, Abrams D, Kadden R, Cooney N: *Treating Alcohol Dependence: A Coping Skills Training Guide*. New York: Guilford Press; 1989.
63. Carroll KM: *A Cognitive-Behavioral Approach: Treating Cocaine Addiction*. Bethesda, MD: National Institute on Drug Abuse; 1998. [NIH publication no. 98-4308.]
64. Carroll K, Onken LS: **Behavioral therapies for drug abuse and dependence: a thirty-year progress report.** *Am J Psychiatry* 2005, **162:**1452–1460.
65. McKay JR, Alterman AI, Mulvaney FD, Koppenhaver JM: **Predicting proximal factors in cocaine relapse and near miss episodes: clinical and theoretical implications.** *Drug Alcohol Depend* 1999, **56:**67–78.
66. Weiss F: **Neurobiology of craving, conditioned reward and relapse.** *Curr Opin Pharmacol* 2005, **5:**9–19.
67. Breese GR, Chu K, Dayas CV, et al.: **Stress enhancement of craving during sobriety and the risk of relapse.** *Alcohol Clin Exp Res* 2005, **29:**185–195.
68.• Sinha R, Li CS: **Imaging stress- and cue-induced drug and alcohol craving: association with relapse and clinical implications.** *Drug Alcohol Rev* 2007, **26:**25–31.

This recent paper provides an overview of brain pathways involved in stress- and cue-induced craving states.

69. Goeders NE: **The HPA axis and cocaine reinforcement.** *Psychoneuroendocrinology* 2002, **27:**13–34.

70. Shaham Y, Shalev U, Lu L, et al.: **The reinstatement model of drug relapse: history, methodology and major findings.** *Psychopharmacology (Berl)* 2003, **168:**3–20.
71. O'Brien CP: **Anticraving medications for relapse prevention: a possible new class of psychoactive medications.** *Am J Psychiatry* 2005, **162:**1423–1431.
72.•• Sinha R, Garcia M, Paliwal P, et al.: **Stress-induced cocaine craving and hypothalamic-pituitary-adrenal responses are predictive of cocaine relapse outcomes.** *Arch Gen Psychiatry* 2006, **63:**324–331.
This recent paper shows for the first time that stress-induced cocaine craving and stress-related HPA arousal are predictive of cocaine relapse outcomes. This finding provides evidence to target stress-induced craving and stress responses in developing new treatments for relapse prevention in cocaine dependence.
73. Junghanns K, Backhaus J, Tietz U: **Impaired serum cortisol stress response is a predictor of early relapse.** *Alcohol Alcohol* 2003, **38:**189–193.
74. Brady KT, Back SE, Waldrop AE, et al.: **Cold pressor task reactivity: predictors of alcohol use among alcohol-dependent individuals with and without comorbid posttraumatic stress disorder.** *Alcohol Clin Exp Res* 2006, **30:**938–946.
75. Meaney MJ, Brake W, Gratton A: **Environment regulation of the development of mesolimbic dopamine systems: a neurobiological mechanism for vulnerability to drug abuse?** *Psychoneuroendocrinology* 2002, **27:**127–138.
76. Hyman SM, Paliwal P, Sinha R: **Childhood maltreatment, perceived stress, and stress-related coping in recently abstinent cocaine dependent adults.** *Psychol Addict Behav* 2007, **21:**233–238.
77. Caspi A, Sugden K, Moffitt TE, et al.: **Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene.** *Science* 2003, **301:**386–389.
78.• Hariri AR, Drabant E, Munoz K, et al.: **A susceptibility gene for affective disorders and the response of the human amygdala.** *Arch Gen Psychiatry* 2005, **62:**146–152.
This paper shows for the first time that altered amygdala response in affective disorders is influenced by specific genes.
79.• Brady KT, Sinha R: **Co-occurring mental and substance use disorders: the neurobiological effects of chronic stress.** *Am J Psychiatry* 2005, **162:**1483–1493.
This paper provides a recent review of the importance of stress mechanisms in the development of co-occurring psychiatric disorders.
80. Nemeroff CB: **The corticotropin-releasing factor (CRF) hypothesis of depression: new findings and new directions.** *Mol Psychiatry* 1996, **1:**336–342.
81. Holsboer F: **Corticotropin-releasing hormone modulators and depression.** *Curr Opin Investig Drugs* 2003, **41:**46–50.
82. Scahill L, Chappell PB, Kim YS, et al.: **A placebo-controlled study of guanfacine in the treatment of children with tic disorders and attention deficit hyperactivity disorder.** *Am J Psychiatry* 2001, **158:**1067–1074.
83. Kahn A, Mumford JP, Rogers GA, Beckford H: **Double-blind study of lofexidine and clonidine in the detoxification of opiate addicts in hospital.** *Drug Alcohol Depend* 1997, **44:**57–61.
84. Glassman AH, Jackson WK, Walsh BT, et al.: **Cigarette craving, smoking withdrawal, and clonidine.** *Science* 1984, **226:**864–866.
85.•• Sinha R, Kimmerling A, Doebrick C: **Effects of lofexidine on stress-induced and cue-induced opioid craving and opioid abstinence rates: preliminary findings.** *Psychopharmacology (Berl)* 2007, **190:**569–574.
This paper provides proof of concept support in humans that decreasing stress-induced drug craving with a specific medication could improve drug treatment outcomes.
86. Ma SH, Teasdale JD: **Mindfulness-based cognitive therapy for depression: replication and exploration of differential relapse prevention effects.** *J Consult Clin Psychol* 2004, **72:**31–40.
87.• Bowen S, Witkiewitz K, Dillworth TM, et al.: **Mindfulness meditation and substance use in an incarcerated population.** *Psychol Addict Behav* 2006, **20:**343–347.
This paper provides the first support for mindfulness-based interventions that target stress responses as being useful in substance use treatment outcomes.
88. Davis JM, Fleming MF, Bonus KA, Baker TB: **A pilot study on mindfulness based stress reduction for smokers.** *BMC Complement Altern Med* 2007, **7:**2.