Changes in inhibitory control and drug salience in response to stress: differences between opiate users, ex-users and non-users.

D.Clin.Psy. thesis (Volume 1), 2007
University College London

ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

Overview

This thesis aims to explore the relationships between stress, drug abuse and craving/relapse, and specifically the behavioural and cognitive processes that mediate the association between stress and craving.

Part 1 of this thesis comprises a literature review of the evidence linking stress, craving and relapse, highlighting both animal and human data. The conclusion drawn is that stress plays a significant role in inducing drug and alcohol craving and relapse in humans, but that much of the research is hampered by methodological limitations.

Part 2 comprises the empirical paper which reports a novel, experimental investigation of the effect of stress on inhibitory control and attentional bias of current opiate users in methadone maintenance treatment, ex-users in rehabilitation and non-users. The results were that stress resulted in attentional focus (rather than inhibitory dysregulation) across all three groups. Current opiate users showed a greater attentional bias towards drug-related stimuli than ex-users. Interestingly, ex-users showed a bias *away* from drug-related stimuli in the stress condition, which was found to be positively correlated with their length of abstinence. Clinical implications of these findings are discussed, focusing in particular on the use of attentional bias as a useful treatment outcome measure.

Part 3, a commentary of the research process, comprises a personal reflection on the experience and a critical appraisal of the design and methodology.

Contents

List of Tables

List of Figures

List of Figures Cont..

Acknowledgements

I would like to acknowledge the following individuals' contributions to this research: Val Curran for her enthusiasm and support throughout the project; Dominic O'Ryan for his advice and assistance in participant recruitment and Celia Morgan for her creativity in task development. Of course, the research would not have been possible without the contribution of all the participants and clinic staff. A special thanks to my colleague Stefania Battistella, whose support and encouragement proved invaluable throughout.

Part 1: Review Paper

What is the evidence for a relationship between stress, drug craving, salience and relapse?

Abstract

Rationale

Whilst relapse to drug taking, even after a substantial period of abstinence, is common, laboratory-based research documenting precursors to relapse in humans is limited.

Objectives

The purpose of this literature review is to evaluate evidence from both animal and human studies on the effect of acute stressors on drug craving and relapse.

Method

Attempts at conceptualizing the definition of stress have been unsuccessful (Chrousos & Gold, 1992). For the purposes of this review, stress was broadly defined in line with Piazza & Le Moal (1998) as coerced exposure to environmental conditions or events that would normally be considered aversive enough to motivate avoidance. This review considered both physical and psychological stressors and is limited to opiate (specifically heroin and morphine) and psychostimulant drugs (e.g. cocaine, amphetamine) in animals, and alcohol, opiates, nicotine, and cocaine in humans.

Conclusions

Results from animal studies of acute stress and relapse are inconsistent. Human studies, despite providing more consistent findings, have a range of methodological limitations. A greater understanding of *how* stress precipitates relapse is likely to have a significant impact on the way clinical interventions are offered to substance misusing individuals.

1. Introduction

Most major theories of addiction assert that both acute and chronic stress have an important part to play in both the etiology and maintenance of substance misuse. Wills and Shiffman's (1985) stress-coping model of addiction postulates that drug addiction develops as a maladaptive coping strategy for stress, whereby the function of substance use is to decrease negative affect and to increase positive affect. In this way, drug-using is a self-reinforcing behaviour, and thus the substance misuse continues. This is in line with Marlatt's relapse prevention model (Marlatt & Gordon, 1985) which states that individuals with poorly developed adaptive coping strategies are at increase risk of drug addiction.

Similarly, both the tension-reduction (Sher & Levenson, 1982) and self-medication models of addiction agree with the notion that substance misuse develops and is maintained by its reinforcing properties. That is to say that in an acute-stress state, individuals are motivated to abuse substances due to their mood enhancing and distress alleviating properties.

Koob and Le Moal (1997) have proposed a model designed to explain the transition from an initial lapse in self-regulation (initial, experimental drug use) to a large-scale breakdown in self-regulation (chronic, regular drug use). Their Spiraling Distress model describes how the first lapse in self regulation leads to initial drug use and can result in emotional distress. This sets up a cycle of repeated failures to self-regulate in an acute-stress state, with each failure triggering additional negative affect. These subsequent

failures precipitate drug use and result in spiraling distress and progressive dysregulation of the brain's reward system.

Therefore, models pertaining to the role of stress as a predisposing factor in the development of drug addiction as a coping mechanism have been around for a significant length of time. However, the evidence base in humans for these models is remarkably lacking (Sinha, 2001). Indeed, much of the research has focused on demonstrating a relationship between stress and relapse to drug seeking in rats. The next part of this review will focus on a brief presentation and evaluation of this evidence.

Databases used: UCL 'Metalib' database incorporating Web of Science, JSTOR, MEDLine and PsychInfo. **Key words:** Stress, drug relapse, drug craving, human studies

2. Animal Data Relating to Acute Stress and Relapse

Studies investigating the effect of environmental stressors on opiate and psychostimulant reinforcement and relapse use three procedures; (i) intravenous drug self-administration (SA) (ii) conditioned place preference (CPP) and (iii) drug reinstatement. The SA procedure is based on the theory that drugs function as positive reinforcers, and is used in the main to examine initiation and maintenance of drug administration in rats. In the CPP method, the rats are trained to associate a particular environment with drug provision (via injection) and another with non-drug provision. Following training, when given a choice between the two conditions, rats show preference for the drug-associated

environment. This procedure is typically used to demonstrate reinforcement via associative learning (secondary reinforcement).

Since this review is focused on drug relapse (rather than initiation or reinforcement), only studies using drug reinstatement procedures will be examined. De Wit and Stewart (1981) have proposed that this method is an adequate model of drug relapse in humans. This procedure involves initially training rats to self-administer a drug (i.e. by lever pressing to obtain intravenous SA) followed by the extinction of the conditioned response (CR, i.e. the lever pressing). Following extinction of the CR, the ability of a single re-introduction of the drug to induce the CR again is measured.

(i) Intermittent Footshock

The majority of the research into the demonstration of stress-induced reinstatement of drug seeking has used acute exposure to intermittent footshock as the stressor. This typically involves administering the footshock prior to the experimental testing, which occurs roughly six weeks following extinction training.

The majority of studies utilising the methodology described above have demonstrated a positive relationship between footshock and reinstatement of cocaine seeking (Erm, Shaham, & Stewert, 1996; Martin-Fardon, Ciccocioppo, Massi, & Weiss, 2000; Sutton, Karanian, & Self, 2000). Furthermore, several studies have demonstrated a superior effect of drug than natural reinforcers on reinstatement. For example, Ahmed and Koob (1997) along with Mantsch and Goeders (1999) have shown reinstatement of cocaine but not food seeking behaviour.

Several studies have followed this line of research to examine the relevance of context-specific reinstatement, the duration of the withdrawal period and the amount of the drug administered during the initial training period.

Shalev, Highfield, Yap and Shaham (2000) showed a context-dependent ability of a stressor to reinstate drug seeking behaviour. That is to say that footshock only resulted in reinstatement of heroin-seeking behaviour when it was administered in the original training environment i.e. the context associated with drug use. These results are in accordance with data from earlier studies that observed an interaction between stressor and environment (Bouton & King 1983) and are in line with observations regarding the environmentally dependent effect of the behavioural and neurochemical responses to drugs (Crombag & Shaham, 2002; Robinson et al., 1998)

One of the most interesting studies relating to relapse used a slightly modified reinstatement model to examine the effect of variable withdrawal periods on relapse (Shalev, Morales, Hope, Yap & Shaham, 2001). In effect, their question was whether the effect of a footshock stressor on reinstatement of drug seeking is dependent on the length of the withdrawal period. The researchers used a training period of 10 days, where rats were trained to self-administer heroin. Following this, extinction and reinstatement procedures were carried out in different groups, with duration of withdrawal (1, 6, 12, 25 or 66 days) as the independent variable. Their results showed that footshock resulted in maximum reinstatement of heroin-seeking (as measured by lever pressing) after 6 and 12 days of withdrawal, instead of the predicted 1 days'

withdrawal, when conspicuous heroin withdrawal symptoms are at their most heightened.

In their study investigating short versus extended access to heroin, Ahmed, Walker and Koob (2000) found that rats provided with a longer drug acquisition period (11 hours per day) had higher lever pressing responses following footshock than rats with shorter training periods (one hour per day). The researchers concluded that reinstatement of heroin as a result of footshock stress is greater when the amount of drug intake during the initial training period is larger.

(ii) Conditioned Fear

The few studies that have examined this concept have produced inconclusive results. In this classical conditioning procedure, the conditioned stimulus (e.g. a neutral tone) is paired with an unconditioned (fear-inducing) stimulus. Using this model Sanchez & Sorg (2001) showed that a CPP procedure, where a stimulus was paired with shock, reinstated cocaine place preference after extinction. However, Shaham, Erb and Stewert (2000) reported that a similar classical conditioning procedure did not reinstate drug-seeking in rats where cocaine or heroin SA methodology was used. The authors argued that a possible reason for this was that the predominant behavioural effect of shock is freezing, a behaviour that is incompatible with lever-pressing.

(iii) Food Deprivation/Restriction

Several recent studies have shown an effect of food restriction on both heroin and cocaine reinstatement. For example, Shalev, Highfield, Yap and Shaham (2000)

demonstrated reinstatement of heroin seeking by 21 hours, but not 1 hour of food deprivation. Furthermore, Shalev et al. (2003) found reinstatement of cocaine and heroin seeking after 24 hours of food deprivation. The researchers conclude that the increased level of stress that results from a longer period of food deprivation is responsible for the drug reinstatement. Interestingly however, and in contrast to the results of the aforementioned studies, one hour of food deprivation is enough to cause cocaine reinstatement in a specific breed of mice, a finding which has been attributed to differences in metabolic rates between rats and mice used in the studies (Couture & Hulbert, 1995).

(iv) Restraint

Two studies investigating this form of stress-induced reinstatement have generated mixed results. In physical restraint procedures, rats are held in a restraining device for variable amounts of time. Shalev, Highfield, Yap and Shaham (2000) found no effect of restraint (5, 15 or 30 minutes) on heroin reinstatement using the SA procedure, where the restraint was given outside the original drug administration environment. However, Sanchez et al. (2003) reported that the same periods of restraint resulted in reinstatement of cocaine seeking behaviour, using the CPP procedure. These results are somewhat inconclusive, and the discrepancy between the data is not yet fully understood. For example, it is possible the discrepancy may be due to either the type of drug used (cocaine versus heroin), the type of procedure employed (SA versus CPP) or some other extraneous variable yet to be accounted for.

3. Summary of Animal Data

It appears as though the data pertaining to relapse in rats is mixed in terms of the reproducibility of results. For example, the studies that use restraint and conditioned fear as their stressor provide mixed results. Robust, replicable findings are absent, largely due to methodological inconsistencies. On the other hand however, the evidence for an effect of footshock on drug reinstatement is plentiful. Here, researchers have provided further evidence to suggest that the effect of a stressor, at least in animal subjects, is both context and time-dependent.

In their review of stress-induced relapse in rats, Lu, Shepard, Scott-Hall & Shaham (2003) state that the degree to which gender differences affect the relationship between stress and relapse has been almost completely unresearched. Furthermore, the authors go on to make some comments pertaining to the generalisablity of the animal data to the human population. They highlight that humans are invariably exposed to both chronic and acute stressors across the lifespan, and can be experiencing multiple stressors at any one time. They state however that,

'...the interaction between chronic and acute stressor in the context of drug reinforcement and relapse has yet to be systematically determined. This issue appears to be especially pertinent for reinstatement studies, in which investigators only employed acute stressors.' (p.484).

4. Human Data Relating to Acute Stress, Craving and Relapse

In addition to the animal data, clinical observations in human participants also go some way in providing evidence to suggest an important role of stress in drug relapse. Sinha, Catapano & O'Malley (1999) refer to the hypothesis pertaining to the association between stress and relapse, in that stressful experiences serve as cues to drug taking which initially originated as a maladaptive response to psychological distress. Early research, mainly consisting of clinical surveys investigating the precipitating factors for relapse in alcohol and drug users, have consistently shown a positive association between both negative affect and stressful situations and relapse to substance using (Littman, Eiser & Rawson, 1977; Bradley, Phillips, Green & Gossop, 1989; Wallace, 1989).

(i) Negative Affect and Relapse

One example of such research is the study conducted by McKay, Rutherford, Alterman, Cacciola and Caplan (1995), whose retrospective approach using a structured interview aimed to investigate factors involved in the onset, duration and termination of relapses that participants had experienced in the previous 18 months. The researchers recruited 65 men and 30 women who were undergoing treatment for their cocaine use. Results indicated that affect states involving feeling 'lonely', 'down', 'tense', 'disappointed', 'worried', 'bad about self', and 'angry' were experienced by between 40 and 60% of the sample on the day of their relapse. The authors also suggested that, in consideration of cocaine alone, it is possible that it is the *absence* of positive affect, rather than the *presence* of negative affect, which is linked to subsequent relapse. The most important limitation of this study involves the reliance on retrospective self-report data as the only

means of gathering information pertaining to the relapse processes. The validity of such measures has received much attention in the research literature, due to factors such as forgetting, time distortions and social desirability. The design of the study would have been much improved if a multi-method approach to data gathering had been adopted, although the feasibility of achieving this within the constraints of a retrospective approach is limited.

Childress et al. (1994) investigated the relative ability of four hypnotically generated affect states to induce drug craving in abstinent opiate users. The mood states that were examined were depression, euphoria, anxiety and anger. The results showed that inducing negative affect (i.e. depression, anxiety and anger) resulted in increased self-rated craving for opiates. In contrast, exposure to external drug cues resulted in no additional increases in subjective craving. The authors postulated that, in the context of repeated attempts at self-medicating distress, negative affect states have become conditioned stimuli, and in this capacity have the ability to trigger drug craving, which has become the conditioned response.

Similar results have been found with alcohol dependent participants. Studies by Litt, Cooney, Kadden, & Gaupp (1990) and Cooney, Litt, Morse & Bauer (1997) showed not only that negative affect induction increases craving for alcohol, but that these craving ratings were equal to the cravings produced by alcohol cue exposure. There is also a wealth of evidence pointing towards a link between negative affect states and both the urge to smoke and increased smoking behaviour (Pomerleau & Pomerleau, 1987; Payne, Schare, Levis & Colleti, 1991; Drobes & Tiffany, 1997).

(ii) Stress and Craving

Sinha's extensive series of studies (1999; 2000; 2003; 2006) used personalised stress imagery tasks to explore the impact of psychological stress on affect and craving in cocaine dependent individuals. These studies signified the first real attempt at studying the relationship between stress and relapse in a laboratory context with cocaine users. In 1999, Sinha and her colleagues conducted two laboratory-based studies. In the first, they compared the effect of two psychological stressors on cocaine craving and affect state in cocaine users. One of the stressors was a speech stressor task, which involved the participant preparing a speech on a brief article provided to them and presenting it to the researchers in front of a video camera. The second stressor involved a personalised emotional imagery procedure, which involved participants describing in detail and subsequently imagining a recent stressful experience. All participants completed the Speech task first and the Imagery task second. Sinha's reasoning for utilising emotional imagery paradigms as stress inducers derives from their wide use in anxiety disorders research, which has in turn resulted in the provision of highly effective evidence-based behavioural therapies for such disorders, including panic, OCD and PTSD (c.f. Foa & Kozak, 1986).

The results indicated that both stressors resulted in statistically significant reductions in positive and neutral affect states, as well as significant increases in fear ratings. Furthermore, the Imagery task resulted in significant increases in cocaine craving, although the Speech stressor task did not. The researchers concluded that the Imagery Task was superior over the Speech task in inducing cocaine craving in the laboratory. However, it is important to note methodological limitations in that the order of the stress

tasks was not counterbalanced. Although the authors provide some evidence to suggest there was no carry-over effect, it is not entirely possible to rule out an accumulative effect of stress (rather than the results being a unique effect of the Imagery stressor). Furthermore, the 'control' element of the study was conspicuously lacking. That is to say that the researchers employed neither a control participant group nor a control stress condition.

The second study compared the effects of stress imagery versus neutral imagery, as measured by cocaine craving, self-reported anxiety and various physiological responses, in cocaine abusers. The purpose of this study was to replicate the results of the first study, and extend them in terms of controlling for any non-specific effects of engaging in mental imagery by including a neutral imagery condition in the design. The results of this second study indicated significant main effects of imagery type in that there were significant increases in cocaine craving, subjective anxiety, heart rate and salivary cortisol levels following the stress imagery procedure. Furthermore, examination of stress indicators indicated that subjective anxiety, cocaine craving and salivary cortisol levels were all significantly elevated in the recovery period following the stress imagery task as compared to the neutral imagery task. There was no significant effect on heart rate.

The authors concluded that:

"The major finding from the two laboratory studies presented here is that exposure to personal stress situations leads to consistent and significant increases in cocaine

craving along with activation of emotional stress and a physiological stress response." (p.348)

The researchers proposed that their Stress Imagery Task, which involved the recall and re-experiencing of a stressful situation, provided a historical context for psychological distress, which then triggered drug craving. It is likely that the speech stress task utilized in the first study did not provide a historical context for drug use in these specific participants (although it is possible that in some groups of participants this stress task might prove salient). The researchers also noted that the type of and/or the severity of the stressor is an important factor to take into consideration when attempting to recreate acute stress in the laboratory. It is of worth also to note that this piece of research used three reliable indicators of physiological stress reactivity, and thus did not rely solely on participants' self-report data. Despite the aforementioned methodological limitations associated with these two studies, they provided the first formal laboratory-based documentation of the association between acute stress and relapse in cocaine abusers.

Sinha, Fuse, Aubin and O'Malley's (2000) study aimed to compare the ability of psychological stress and drug cues to produce similar and consistent patterns of cue reactivity in 20 cocaine dependent individuals. All participants, (21-55 years old; 2 females), were exposed to drug cues, psychological stress and a control neutral imagery condition. The neutral imagery was always presented as the middle condition, with the order of the stress and drug cues conditions counterbalanced. Prior to the testing period, researchers met with the participants to develop their personalized imagery scripts. The stress imagery scripts consisted of imagining non-drug related stressful situations (i.e.

arguments with family/partners, being fired from employment) whilst the neutral imagery scene script was based around a relaxing beach scene, which none of the participants endorsed as a trigger situation for drug use. The drug cues script involved imagining a positive-affect drug-related trigger situation. Reactivity was assessed using cocaine and alcohol craving ratings, emotional state ratings, subjective anxiety ratings (using an anxiety dial rather that subjective paper and pencil ratings), heart rate and salivary cortisol measures.

The results of this study revealed main effects of the imagery condition for cocaine and alcohol craving, subjective anxiety, heart rate and salivary cortisol. That is to say that the two experimental conditions produced cocaine and alcohol cravings, anxiety ratings, heart rates and cortisol levels that were significantly greater than those produced by the neutral imagery condition. There was also a similar effect of imagery condition on the positive emotion state of joy and on neutral ratings, in that ratings on both were observed to be significantly lower in the stress and drug cues conditions than in the neutral imagery condition. A main effect of imagery condition was also found for the negative emotions of fear, anger and sadness in that the ratings for these emotions were significantly elevated during the stress and drug cues conditions. Furthermore, for cocaine and alcohol craving, subjective anxiety and the positive and negative emotion ratings discussed above, the results found *during* exposure to the various conditions were also maintained after the 5-minute recovery period.

The authors concluded that psychological stress-induced craving and exposure to drug cues-induced craving produced similar patterns of reactivity in cocaine-dependent

individuals. Furthermore, Sinha and her colleagues propose that because elevations in negative affect state ratings were consistent across both stress and drug cue conditions, that this affect state is a pertinent part of the relationship between stress and relapse, and so support the negative reinforcement models of drug craving and relapse. That is to say that relapse is more likely to occur in situations that create affect states opposite to the effects of the drug. Thus using the drug removes negative affect states and replaces them with more positive ones, thus strengthening the negative reinforcement properties of the drug and maintaining its use.

The ecological validity of this study warrants consideration. It would also be difficult to generalize the findings to cocaine users who were not also alcoholics, since nearly 80% of the sample were alcohol (as well as cocaine) dependent. In terms of research design, the three conditions were only partially counterbalanced, and although the drug cue and stress imagery scripts were personalized, the neutral scripts were not.

Sinha's recent research has focused largely on the psychobiological changes that occur during exposure to drug cues known to elicit craving and relapse responses. Sinha et al. (2003) examined whether the brain's stress systems are implicated in cocaine and alcohol craving. Based on earlier preclinical research that implicated an elevated response of brain stress systems in the association between stress and craving and relapse in humans, Sinha and her colleagues assessed levels of adrenocorticotrophic hormone (ACTH), cortisol, prolactin, norepinephrine (NE) and epinephrine (EPI). The researchers also measured subjective levels of anxiety and drug/alcohol craving. The study involved the same imagery conditions as the (2000) study with assessments of the

above variables taken before, during and after each imagery session. Half of the participants were dependent on both cocaine and alcohol.

The results indicated that exposure to imagined drug/alcohol cues and stress imagery produced a significant activation of stress systems (i.e. increases in ACTH, cortisol prolactin, NE and EPI levels) when compared to the neutral imagery condition. Furthermore, these results were supported by significantly elevated ratings of cocaine and alcohol craving and subjective anxiety. Additionally, the researchers observed a slower return to baseline in the stress and drug-cue exposed conditions than in the neutral conditions in terms of anxiety, craving and physiological measurements. The authors concluded that:

"*These results indicate that brief 5-min exposure to stress and to drug cues produced an altered psychobiological state, with significant changes in subjective and physiological measures along with peripheral neurochemical changes that are traditionally associated with activation of brain stress systems.*" (p.69).

This study was characterized by specific methodological improvements which render the results more robust and increase the ecological validity of the findings. Notable changes include full counterbalancing of the three conditions and better representation of females (33%). However, all of the participants were treatment seeking, thus the results are non-generalisable to cocaine users in the various different stages of use. Furthermore, consistent with the earlier failings of this series of research, the researchers omitted using a control group of non-drug users.

(iii) Stress and Relapse

Most recently, Sinha and her colleagues have extended their results with a prospective study looking at specific relapse outcomes. Sinha et al. (2006) looked at whether stress-induced and drug cue- induced cocaine craving and psychobiological stress system responses in the laboratory are predictive of subsequent cocaine relapse in "the real world". The researchers used *time to relapse* (period of time between inpatient discharge and first day of any cocaine use), *frequency* (number of days of cocaine use), and *quantity* (amount of cocaine used per occasion in the 90-day follow-up phase) as their outcome measures. Sinha et al. had a sample of 49 participants (32 males, 17 females), who met criteria for cocaine dependence but who were currently undergoing inpatient treatment for their drug use. Personalised imagery scripts for the stress, drug-cue and neutral experimental conditions were developed with each participant. The study consisted of three days of testing, with just one imagery condition presented each day, and the order of imagery conditions was randomised across participants. Subjective ratings of cocaine craving and anxiety were measured using a 10-point numerical scale. Physiological measurements included heart rate, corticotrophin and cortisol.

The results of this study showed that stress-induced cocaine craving was associated with a shorter time to relapse during the 90-day follow-up period, even after allowing for differences in baseline cocaine use prior to inpatient admission. Using regression analyses, researchers calculated that each additional unit increase in stress-induced cocaine ratings was associated with a 31% increase in the likelihood of relapse during the follow-up period. Stress-induced physiological responses were not found to be predictive of either time to relapse or frequency of relapse. Stress-induced corticotrophin

response was, however, significantly associated with *quantity* of cocaine used during the follow-up period. The researchers used a median-split to provide high and low corticotrophin and cortisol responders across the three conditions. Results demonstrated that the high stress-induced corticotrophin and cortisol groups used more cocaine on average over time than the low responder groups in the stress condition. Interestingly, drug-cue induced craving, anxiety or physiological responses were not found to be predictive of quantity, frequency or time to relapse.

The authors conclude that stress-induced, but not drug cue-induced cocaine craving is predictive of a shorter time to relapse, while stress-related physiological responses were significantly associated with amount of cocaine used per occasion during the follow-up phase. The researchers commented that:

"Consistent with the clinical literature that recognises relapse and recurrence as a multidetermined process, the current findings suggest that specific components of the stress response are associated with different aspects of he relapse process." (p.329)

The main methodological limitation associated with this study is again a distinct under-representation of females, which makes it impossible to draw conclusions pertaining to gender-specific differences in relapse. Despite this, the current study provided the first documentation of evidence that stress-related cravings and physiological responses produced in a laboratory setting are predictive of subsequent cocaine relapse.

These findings were found to be consistent with the tension-reduction and self-medication models of drug use, where substance use is a means to escape or avoid distress, stress and negative affect. The authors postulate that stress-related increases in cravings for drug could reflect relapse sensitivity. That is to say that individuals who display higher levels of stress-reactivity in the laboratory may be more likely to relapse in response to distress in the "real world". Furthermore, the researchers make some allusion to the link between stress and inhibitory control processes, whereby increases in levels of distress mean that the self-regulatory or inhibitory control processes that function adequately under mild/moderate levels of distress are overridden by the urge to combat the negative affect. Indeed, Tice, Bratslavsky and Baumeister's (2001) research using non-substance misusing populations demonstrated that impulse control processes fail in the context of distress because greater priority is given to the more urgent goal of affect regulation. Volkow and Fowler (2000) propose that repeated exposure to drugs results in dysfunction in the frontal brain regions involved in inhibitory decision-making processes. Lubman, Yucel & Pantelis (2004) suggest that, under provocation, this inhibitory control system is overridden by intense motivational drives, which results in the disinhibited or impulsive behaviour that is often seen to characterise a relapse episode. The authors state that relapses in addicted individuals would be better conceptualised as compulsions (similar to the behaviours seen in OCD), because they are unable to inhibit their behavioural responses due to brain circuitry impairments.

(iv) Exceptions to the Rule

The research evaluated thus far appears to point heavily to an association between negative affect, craving and relapse. However, there are several exceptions to these

findings. For example, Hall, Havassy & Wasserman's (1991) prospective study failed to provide evidence in support of a direct relationship between acute stress and relapse to cocaine use. In this study, the absence of positive affect, rather than the explicit presence of negative affect, was predictive of relapse. Similarly, the researchers' earlier prospective research (Hall, Havassy & Wasserman, 1990) failed to demonstrate a relationship between negative affect and subsequent relapse to alcohol, opiates or nicotine. However, it is important to stress that these studies used different measures to assess affect, and thus the feasability of distinguishing between the lack of positive affect and the presence of negative affect is potentially limited. Another important limitation of these prospective studies, and one which can also be applied to Sinha et al. (2006), has been discussed in McKay et al. (1995). That is, although prospective studies do not rely on the arguably distorted memories that retrospective studies rely on, they are methodologically limited in their own way. The authors state that:

"...unless subjects are interviewed immediately prior to relapse, it is not clear whether the factors assessed at one point in time that are found to predict future relapses are actually occurring at the time of the relapses." p. 41.

5. Summary of Human Data

The data reviewed so far provides evidence to suggest that stress plays a significant role in inducing drug and alcohol craving and relapse. Indeed, there appear to be few exceptions to these findings, which are consistent across prospective, retrospective and laboratory based studies. The research has focused largely on induction of negative affect states and exposure to personalized stress imagery tasks as a means of measuring

stress. These stressors have reliably been shown to result in elevated drug cravings and an increased physiological stress response. Furthermore, stress-induced cravings were maintained for a longer period of time than drug-induced cravings. Lastly, whilst physiological stress indicators were predictive of shorter time to relapse, drug-induced cravings were not.

Some of the global limitations that were evident included the conspicuous lack of control groups in the studies. For example, most studies utilised just one group of participants, usually current users, with one notable study using abstinent individuals. Meaningful and even more convincing research would have been provided if researchers had compared the effects of the same stressor on different groups of individuals. Furthermore, cocaine dependent males remain heavily over-represented in human research, with females and other drug-using populations (e.g. opiate users) almost completely overlooked.

6. Clinical Implications and Directions for Future Research

The human studies that examine the effect of stress on craving and relapse have important clinical implications for the development of effective addiction treatments. The research so far points heavily to emphasizing the role of stress as a precursor to relapse. The relapse prevention component of any substance misuse intervention is undoubtedly essential, but this research seems to suggest that identification of stress needs to be at its core. The research seems to, albeit indirectly, imply that if individuals are more aware of their stress-related 'relapse signature', they would be less vulnerable to the effects of that stressor. This would mean increasing the individual's awareness of

the events, people and specific situations or contexts that elicit a stress response. Simply being aware of a stressor is unlikely to prevent a relapse, but coupling this awareness with response prevention, coping and problem solving strategies may better equip drug users with the skills to prevent or at least to minimise their return to drug taking. However, these techniques are already salient aspects of most psychological addiction interventions. So the question remains: why do these treatments remain relatively ineffective?

The research literature has alluded to a link between stress, inhibitory control and relapse in so far as impulsivity is implicated in distress regulation. However, direct experimental examination of this specific behavioural process is lacking and this would appear to be the next logical step in terms of future research. Should evidence be found in support of a mediating effect of impaired inhibitory control in the relationship between acute stress, drug salience and relapse, significant clinical implications would emerge. For example, not only would stress management be an important goal of intervention, but treating the underlying inhibitory dysregulation, as well as enhancing the salience of alternative rewards, would also be of paramount importance.

7. References

Ahmed, S.H., & Koob, G.F. (1997). Cocaine, but not food-seeking behaviour is reinstated by stress after extinction. *Psychopharmacology, 132,* 289-295.

Ahmed, S.H., Walker, J.R., & Koob, G.F. (2000). Persistent increase in the motivation to take heroin in rats with history of drug escalation. *Neuropsychopharmacology, 22,* 413-421.

Bouton, M.E., & King, D.A. (1983). Contextual control of the extinction of conditioned fear: tests for the associative value of the context. *Journal of Experimental Psychology: Animals and Behavioural Processes, 9,* 248-265.

Bradley, B.P., Phillips, G., Green, L., & Gossop, M. (1989). Circumstances surrounding the initial lapse to opiate use following detoxification. *British Journal of Psychiatry, 154,* 354-359.

Childress, A.R., Ehrman, R., McLellan, A.T., MacRae, J., Natalie, M., & O'Brien, C.P. (1994). Can induced moods trigger drug-related responses in opiate abuse patients. *Journal of Substance Abuse Treatment, 11,* 17-23.

Chrousos, G.P., & Gold, P.W. The concepts of stress and stress system disorders. Overview of physical and behavioural homeostasis. *Journal of the American Medical Association, 267,* 1244-1252.

Cooney, N.L., Litt, M.D., Morse, P.A., & Bauer, L.O. (1997). Alcohol cue reactivity, negative mood reactivity and relapse in treated alcoholics. *Journal of Abnormal Psychology, 106,* 243-250.

Couture, P., & Hulbert, A.J. (1995). Relationship between body mass, tissue metabolic rate and sodium pump activity in mammalian liver and kidney. *American Journal of Physiology, 268,* 641-650.

Crombag, H.S., & Shaham, Y. (2002). Renewal of drug-seeking by contextual cues after prolonged extinction in rats. *Behaviour and Neuroscience, 116,* 169-173.

de Wit, H., & Stewart, J. (1981). Reinstatement of cocaine-reinforced responding in the rat. *Psychopharmacology, 75,* 134-143.

Drobes, D.J., Tiffany, S.T. (1997). Induction of smoking urge through imaginal and in vivo procedures: physiological and self-report manifestations. *Journal of Abnormal Psychology, 106,* 15-25.

Erb, S., Shaham, Y., & Stewart, J. (1996). Stress reinstates cocaine-seeking behaviour after prolonged extinction and drug-free periods. *Psychopharmacology, 128,* 408-412.

Foa, E.B., & Kozak, M.J. (1986). Emotional processing of fear: exposure to corrective information. *Psychological Bulletin, 99,* 20-35.

Hall, S.H., Havassy, B.E., & Wasserman, D.A. (1990). Commitment to abstinence and acute stress in relapse to alcohol, opiates and nicotine. *Journal of Consulting and Clinical Psychology, 58,* 175-181.

Hall, S.M., Havassy, B.E., & Wasserman, D.A. (1991). Effects of commitment to abstinence, positive moods, stress and coping on relapse to cocaine use. *Journal of Consulting and Clinical Psychology, 59,* 526-532.

Koob, G.F., & Le Moal, M. (1997). Drug abuse: Hedonic homeostatic Dysregulation. *Science, 278,* 52 – 58.

Litt, M.D., Cooney, N.L., Kadden, R.M., & Gaupp, L. (1990). Reactivity to alcohol cues and induced moods in alcoholics. *Addictive Behaviours, 15,* 137-146.

Littman, G.K., Eiser, J.R., & Rawson, N.S. (1977). Towards a typology of relapse: a preliminary report. *Drug and Alcohol Dependence, 2,* 157-162.

Lu, L., Shepard, J.D., Scott Hall, F., & Shaham, Y. (2003). Effect of environmental stressors on opiate and psychostimulant reinforcement, reinstatement and discrimination in rats: a review. *Neuroscience and Biobehavioural reviews, 27,* 457-491.

Lubman, D.I., Yucel, M., & Pantelis, C. (2004). Addiction, a condition of compulsive behaviour ? Neuroimaging and neuropsychological evidence of inhibitory dysregulation. *Addiction, 99,* 1491-1502.

Mantsch, J.R., & Goeders, N.E. (1999). Ketoconazole blocks the stress-induced reinstatement of cocaine-seeking behaviour in rats: relationship to the discriminative stimulus effects of cocaine. *Psychopharmacology, 142,* 399-407.

Marlatt, G.A., Gordon, J.R. (1985). *Relapse Prevention: Maintenance Strategies in the Treatment of Addictive Behaviours.* Guilford Press, New York.

Martin-Fardon, R., Ciccocioppo, R., Massi, M., & Weiss, F. (2000). Nociceptin prevents stress induced ethanol but not cocaine-seeking behaviour in rats. *Neuroreport, 11,* 1939-1943.

McKay, J.R., Rutherford, M.J., Alterman, A.I., Cacciola, J.S., & Kaplan, M.R. (1995). An examination of the cocaine relapse process. *Drug and Alcohol Dependence, 38,* 35-43.

Payne, T.J., Schare, M.L., Levis, D.J., & Colleti, G. (1991). Exposure to smoking-relevant cues: effects on desire to smoke and topographical components of smoking behaviour. *Addictive Behaviours, 16,* 467-479.

Piazza, P.V, & Le Moal, M. (1998). The role of stress in drug self-administration. *Trends in Pharmacological Science, 19,* 67-74.

Pomerleau, C.F., & Pomerleau, O.F. (1987). The effects of a psychological stressor on cigarette smoking and subsequent behavioural and physiological responses. *Psychophysiology, 24,* 278-285.

Robinson, T.E., Browman, K.E., Crombag, H.S., & Badiani, A. (1998). Modulation of the induction or expression of psychostimulant sensitization by the circumstances surrounding drug administration. *Neuroscience of Behaviour Review, 22,* 347-354.

Sanchez, C.J., Bailie, T.M., Wu, w., Li, N., & Sorg, B.A. (2003). Manipulation of dopamine d1-like receptor activation in the rat medial prefrontal cortex alters stress and cocaine induced reinstatement of conditioned place preference behaviour. *Neuroscience, 119,* 497-505.

Sanchez, C.J., & Sorg, B.A. (2001). Conditioned fear stimuli reinstate cocaine-induced conditioned place preference. *Brain Research, 908,* 86-92.

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

Sinha, R., Catapano, D., & O'Malley, S. (1999). Stress-induced craving and stress response in cocaine dependent individuals. *Psychopharmacology, 142,* 343-351.

Shaham, Y., Erb, S., & Stewert, J. (2000). Stress-induced relapse to heroin and cocaine seeking in rats: a review. *Brain Research review, 33,* 13-33.

Sinha, R., Fuse, T., Aubin, l.R., & O'Malley, S.S. (2000). Psychological stress, drug-related cues and cocaine craving. *Psychopharmacology, 152,* 140-148.

Sinha, R., Garcia, M., Paliwal, P., Kreek, M.J., & Rounsaville, B.J. (2006). Stress-induced cocaine craving and hypothalamic-pituitary-adrenal responses are predictive of cocaine relapse outcomes. *Archives of General Psychiatry, 63,* 324-331.

Sinha, R., Talih, M., Malison, R., Cooney, N., Anderson, G.M., & Kreek, M. (2003). Hypothalamic-pituitary-adrenal axis and sympatho-adreno-medullary responses during stress-induced and drug cue-induced cocaine craving states. *Psychopharmacology, 170,* 62-72.

Shalev, U., Highfield, D., Yap, J., & Shaham, Y. (2000). Stress and relapse to drug taking in rats: studies on the generality of the effect. *Psychopharmacology, 150,* 337-346.

Shalev, U., Marinelli, M., Baumann, M., Piazza, P.V., & Shaham, Y. (2003). The role of corticoserone in food deprivation-induced reinstatement of cocaine seeking in the rat. *Psychopharmacology, 156,* 98-107.

Shalev, U., Morales, M., Hope, B.T., Yap, J., & Shaham, Y. (2001). Time-dependent changes in extinction behaviour and stress-induced reinstatement of drug seeking following withdrawal from heroin in rats. *Psychopharmacology, 156,* 98-107.

Sher, K.J., & Levenson, R.W. (1982). Risk for alcoholism and individual differences in the stress-response dampening effect of alcohol. *Journal of Abnormal Psychology, 91,* 350-368.

Sutton, M.A., Karanian, D.A., & Self, D.W. (2000). Factors that determine a propensity to relapse to cocaine-seeking behaviour in rats. *Neuropsychopharmacology, 22,* 626-641.

Tice, D. M., Bratslavsky, E., & Baumeister, R.F. (2001). Emotional distress regulation takes precedence over impulse control: If you feel bad, do it! *Journal of Personality and Social Psychology, 80, 53-67.*

Volkow, N.D., & Fowler, J.S. (2000). Addiction: a disease of compulsion and drive: involvement of the orbitofrontal cortex. *Cerebral Cortex, 10,* 318-325.

Wallace, B.C. (1989). Psychological and environmental determinants of relapse in crack cocaine smokers. *Journal of Substance Abuse Treatment, 6,* 95-106.

Wills, T.A., Shiffman, S. (1985). Coping and substance abuse: a conceptual framework. In: Shiffman, S, Wills T.A (eds): *Coping and Substance Use.* Academic Press, Orlando.

Part 2: Empirical Paper

Changes in inhibitory control and drug salience in response to stress: differences between opiate users, ex-users and non-users

Abstract

Objectives

To examine the effect of a mild stressor on inhibitory control and drug-related attentional bias of current users (methadone maintained), ex-users (currently abstinent) and non-users (controls).

Method

Forty-eight participants (16 in each group) were exposed to both stress and non-stress conditions, after which inhibitory control and attentional bias was assessed using a Go-no-go and Dot probe task respectively. Subjective rating- measures of both stress levels and drug craving were employed.

Results

Current users had significantly higher cravings ratings than both other groups at all times. They also showed a greater attentional bias towards drug-related stimuli than the ex-users. Interestingly, ex-users were biased *away* from drug-related stimuli in the stress condition, and this bias away was correlated with their length of abstinence from opiates. In terms of inhibitory control, all groups had faster reaction times and fewer false alarms in the stress condition.

Conclusions

These results indicate that successful treatment is associated with an attentional bias away from drugs, and suggest that attentional bias could be a useful treatment outcome measure.

Key words: Stress, drug craving, inhibitory control, attentional bias, chronic opiates, salience

1. Introduction

Why, in the face of adverse psychological and physical effects, is drug abuse both persistent and subject to high rates of relapse? This is a question that researchers in the field of addiction are still making attempts to answer. Furthermore, despite welcomed advances in the provision of both pharmacological and psychotherapeutic interventions, many addictions appear to be treatment resistant (Gossop, Marsden, Stewert & Kidd, 2003). Researchers are attempting to provide integrative models of addiction in order to understand the mechanisms underlying chronic substance abuse.

One such model is proposed by Volkow et al. (2003), who suggest that four brain circuits are implicated in drug abuse and addiction. These neural networks are those responsible for (i) reward, (ii) motivation/drive, (iii) memory/learning and (iv) inhibitory control. Volkow et al (2003) suggest that patterns of activity within this network of brain circuits may be responsible for behavioural choice, and may help to explain why substance abusers continue to use despite the adverse consequences of the drug. This model describes several mechanisms underpinning the decision to use or not use drugs. In a drug dependent individual, the inhibitory control circuit (responsible for regulating behaviour) is seen to be overridden by the reward, memory and motivational circuits. It is this process that plays a major role in compulsive drug taking. The authors propose that, in addicted individuals, drug saliency becomes enhanced in the reward and motivation/drive circuits and that the saliency of other reinforcers is conspicuously decreased. Through a process of conditioned learning, and a lack of competition by other natural reinforcers (e.g. food, sex), the individual becomes motivated to acquire the drug, and thus drug-seeking behaviour is facilitated. This overractivation of the memory

and motivation/drive circuits results in the deactivation of the behaviour regulation provided by the control circuit. Volkow and her colleagues state that,

"Without the inhibitory control, a positive-feedback loop is set forth that results in compulsive drug-intake" (pg 1447)

In summary, using this model as a framework, a decision to take a drug will be dependent on the expected reward for taking it (i.e. the associated positive feelings). This reward expectancy is moderated by the individual's previous knowledge and memory pertaining to their drug use. Volkow et al. (2003) suggest that addiction is the result of disruptions to this network that cause a greater and more durable activation of the reward circuit than the control circuit. In this way, the mechanism responsible for the regulation of behaviour in substance abusers is said to be inhibited.

Addicted people have been found to show performance deficits on cognitive tasks that tap into the functioning of prefrontal regions associated with inhibitory dysregulation. Inhibitory control, as measured by response inhibition, has been tested using Go/No-go tasks (also known as the Stop-Signal Task) (Kiehl, Liddle & Hopfinger, 2000). In this computer-based task, participants are required to inhibit their response to a non-target stimulus. According to Logan and Cowan (1994), the ability to inhibit a response in this task is determined by a competition between the primary-task processes within cognition that generate impulsive behaviour, and the stop-signal processes, which have an inhibitory effect on impulsive behaviour. Research has shown that substance abusers have a higher error rate in these tasks than non-users (Franken, 2003).

(i)Stress, Craving and Relapse

Addiction however, is more than a result of malfunctioning neurobiological systems. Undoubtedly, substance misuse occurs via an interaction between organic and environmental factors, a concept that is crucial when looking at relapse. One of the most important factors that has been studied in the field of addiction is stress. The concept of stress is one that has been notoriously difficult to define. For the purposes of this study, stress has broadly been defined in line with Piazza & Le Moal (1998) as coerced exposure to environmental conditions or events that would normally be considered aversive enough to motivate avoidance. Research has documented a positive relationship between stress and substance use, with qualitative investigations demonstrating a link between stressful life experiences and relapse (Karlsgodt et al. 2003). Sinha's comprehensive series of studies (1999; 2000; 2003; 2006) proved to be the first real attempt at documenting the effect of psychological stress on craving and relapse in the laboratory. Sinha and her colleagues used personalised stress imagery tasks to explore the impact of psychological stress on affect and craving in cocaine dependent individuals. Taken together, the findings of these studies revealed that acute stress resulted in an increase in negative affect, cocaine craving and elevated physiological stress response. Indeed, there appear to be few exceptions to these findings, which are consistent across prospective, retrospective and laboratory based studies (Littman, Eiser & Rawson, 1977; Bradley, Phillips, Green & Gossop, 1989; Wallace, 1989; McKay, Rutherford, Alterman, Cacciola and Caplan, 1995)

(ii) Stress, Impulse Control and Relapse

Tice, Bratslavsky and Baumeister's (2001) research using non-substance misusing populations demonstrated that impulse control processes fail in the context of distress because greater priority is given to the more urgent goal of affect regulation. However, in substance using populations, there has been scant research of the link between stress, inhibitory control and craving/relapse.

Sinha et al. (2006) looked at whether stress-induced and drug cue-induced cocaine craving and psychobiological stress system responses in the laboratory are predictive of subsequent cocaine relapse in "the real world". Their findings were found to be consistent with the tension-reduction and self-medication models of drug use, whereby substance use is a means to escape or avoid distress, stress and negative affect. The authors postulated that stress-related increases in drug cravings could reflect relapse sensitivity. That is to say that individuals who displayed higher levels of stress-reactivity in the laboratory were retrospectively more likely to relapse in response to distress in the "real world". Furthermore, the researchers make some allusion to the link between stress and inhibitory control processes, whereby increases in levels of distress mean that the self-regulatory or inhibitory control processes, which function adequately under mild/moderate levels of distress, are overridden by the urge to combat the negative affect.

(iii) Stress and Attentional Bias

A number of addiction theories propose that conditioned responses to stimuli associated with drug use play an important role in the maintenance of addiction and precipitation of

relapse. Robinson and Berridge's (1993) incentive-sensitisation theory of addiction suggests that drug cues that consistently and reliably produce a drug reward are likely to become salient to, and therefore gain the attention of, an addicted individual. Lubman et al. (2000) argue that the implications of this attentional bias on the likelihood of renewed drug taking or relapse are significant. The researchers used a pictorial dot probe task to investigate attentional bias in opiate users. Their results showed that opiate users had faster reaction times to probes that replaced drug pictures as opposed to neutral pictures, hence providing evidence in support of a drug attentional bias in opiate users. Indeed, despite support for the role of drug- cue salience in addiction (Franken, 2000; Hester, Dixon & Garvan, 2006; Weinstein, 2006) and its ability to predict relapse (Marissen et al. 2006) the relationship between stress and salience remains unknown.

(iv) Aims and Objectives

Previous research has demonstrated the importance of a dysregulated control system in addiction, in that it leads to the impulsive behaviour underlying relapse. The presence of attentional biases towards drug cues has been well documented in drug using populations. Furthermore, stress has been strongly implicated as an important precursor to relapse. Despite this, the role of specific cognitive mechanisms, including inhibitory control and attentional bias, involved in the relationship between stress and substance use remains unknown. To our knowledge, no research to date has examined the interaction between stress and either inhibitory control or drug salience. Moreover, nearly all of the existing research on bias and salience has been with cocaine-dependent individuals, and mostly males, making it difficult to apply the findings to other

substance-using groups. In addition, the use of control groups in previous research is rare.

The aim of the present study was to directly examine the effect of a mild psychological stressor on inhibitory control and attentional bias to drugs in opiate-dependent individuals. In light of previous research, it is hypothesised that the stressor will impair inhibitory control and attentional bias in current opiate users as seen by:

(i) a higher error rate in Go/No go tasks (based on the inhibitory control literature)

(ii) longer reaction times to a dot probe when it appears in the position of a neutral compared to a drug salient picture (based on the attentional bias literature)

(iii) an increase in self ratings of drug craving (based on Sinha's 1999; 2000; 2003; 2006 studies)

Furthermore, on the basis of limited research (Cox, Hogan, Kristian & Race, 2002), it is tentatively hypothesised that abstinent ex-users will show less attentional bias to drugs as compared to current users. If attentional bias toward drugs is a pre-existing factor that facilitates drug use, current users will show similar patterns to ex-users, but differ from non-users. If, however, it is an influence of current drug use, current users will show a different pattern of attentional bias than both ex-users and non-users. There is no evidence in the literature relating to response inhibition in abstinent individuals, so this component of the study is exploratory.

2. Method

(i) Design

A mixed between and within subjects design was used. There were three independent groups: current opiate users, ex-users (now abstinent) and non-users (controls). Half of each participant group (current users, abstinent and non-users) received the stress test first, followed by the inhibitory control/dot probe tasks. They then performed the non-stress test and then repeated the inhibitory control/dot probe tasks. For the other half of each group, the order was counterbalanced so that they started with the non-stress test.

(ii) Participants

In total, 48 participants were recruited, 16 in each of the three groups. The current user group consisted of opiate users who were undergoing methadone maintenance treatment at the Margarete Centre, a large substance misuse treatment clinic in Camden, London. An informal research presentation was used as a means to inform managers and key-workers about the study in the first instance. Posters detailing basic information about the research were designed and displayed around the waiting room and reception area of the clinic. Furthermore, flyers were placed in staff pigeon holes reminding them of the research, the inclusion criteria and of the researchers' contact details. Once referrals had been passed onto the researchers, prospective participants were contacted either by telephone or by written correspondence to arrange a suitable date for testing. Participants were tested in a room at the Margarete Centre.

The ex-users group were opiate abstinent participants who were attending rehabilitative programmes at drug rehabilitation clinics across London. All clinics were sent a letter

informing them of the study (Appendix A). Written correspondence was then followed up with a phone call and potential interest in helping to facilitate the study was established. Meetings were arranged with clinic managers and staff where they were informed of the background of the study and provided with more information to share with their residents. Researchers were then contacted by the managers if any residents had expressed an interest in taking part. These ex-users were tested at the clinics.

The non-user group consisted of individuals who had never used opiates. This group of participants was recruited using snowball sampling methodology (Rossi, Freeman & Lipsey, 1999) and, as far as possible, were similar to the experimental groups in terms of their demographic characteristics i.e. (age, gender, educational history and employment status). These participants were all tested in the psychopharmacology laboratories at UCL, except two who were tested in their own homes.

All participants were given a choice between a £7 supermarket/ music store voucher or £7 cash as compensation for their time. Informed consent (Appendix B) was provided by all participants (see Appendix C for participant information sheets) prior to giving their consent. The study was approved by the Camden and Islington Research Ethics Committee (Appendix D).

(iii) Inclusion/Exclusion Criteria

Non-users were assessed for suitability using the Cut-down, Annoyed, Guilty, Eye-opener Scale (CAGE: Ewing, 1984) to detect problematic alcohol use, and the CAGE-aid (Midanik, Zahnd & Klein, 1998) to detect problematic drug use. Control participants

were excluded if they scored two or more affirmative responses on either measure. Participants from all groups were excluded from taking part in the study if they were under the acute effect of drugs commonly co-used in opiate-using populations (alcohol, benzodiazepine and crack) or if they breathalysed positive for alcohol on the day of testing (clinic populations only). They were also excluded if they reported use of benzodiazepines or crack within the period of the drug's reactive half-life (e.g. one month for benzodiazepines; three days for crack). Participants were also ineligible for participation if they met criteria for a psychotic disorder, or were registered as blind or deaf. Participants were required to have English as their first language, and were asked whether they had adequate reading ability.

(iv) Measures

1. CAGE (Ewing, 1984) and CAGE-aid (Midanik, Zahnd & Klein, 1998)

These measures are used to screen for alcohol and drug dependency. They consist of four 'Yes/No' items relating to substance use. The CAGE has been found to have good sensitivity, ranging from 61 to 100% in various populations, and good specificity, ranging from 77 to 96% (Cherpitel, 1997). Similarly, the CAGE-aid has been found to have sensitivity of 70% and a specificity score of 85% (Brown & Rounds, 1995).

2. Subjective Numerical Scales (SNS)

Two 10- point numerical scales were used to assess self-reported stress and drug cravings, with one anchored at '0 = Not at all stressed'/ '10 = Extremely Stressed' and the other anchored at '0 = No cravings for drugs'/ '10 = Extremely high cravings for drugs'.

3. Spot the Word Test (STW; Baddeley, 1993)

Premorbid IQ was estimated using Baddeley's (1993) 'Spot the Word' Test. This test involves presenting the participant with pairs of items comprising one word and one non-word, designed so as to look like a real word. The participant is required to identify the real word in the pair and is instructed to guess if they are unsure. Performance on this test correlates highly with performance on the National Adult Reading Test (NART). The STW has been found to have a good reliability and reasonable validity with Alpha coefficient scores of 0.78 and 0.69 respectively.

4. Beck's Depression Inventory (BDI, 1961) and Beck's Anxiety Inventory (BAI, Beck & Steer, 1993)

The BDI is a commonly used 21-item self report questionnaire measuring the occurrence and severity of symptoms of depression over the past week. Statements are rated on a 4-point rating scale; each question has a set of at least four possible answer choices, ranging in intensity. Similarly, the BAI consists of 21 items, each describing a common symptom of anxiety. The respondent is asked to rate how much he or she has been bothered by each symptom over the past week on a 4-point scale ranging from 0 to 3 where 0= not at all, 1= mildly, 2 = moderately, and 3 = severely. The items are summed to obtain a total score that can range from 0 to 63. The BDI has been found to have a good internal consistency (as measured using the Alpha coefficient) of 0.86 (Beck & Steer, 1987). Similarly, the BAI has also been shown to have good internal consistency, with the Alpha coefficient ranging from 0.85 to 0.94 (Beck and Steer, 1990).

5. Mental Arithmetic Task (Stress Condition: MAT1; Back et al. 2005).

In condition 1 of this task, participants were asked to serially subtract sevens from 3,022 as quickly and as accurately as they could for 3 minutes. When participants made an incorrect response they were informed of their mistake and asked to provide a correct response and continue from there. When participants made a mistake, researchers said "Stop. That is an incorrect response. The correct answer is...". The participants' verbal responses were recorded using an external microphone linked to a tape player placed in front of them.

6. Mental Arithmetic Task (Non-Stress Condition: MAT2)

In condition 2, participants were given a handout consisting of a series of arithmetic sums (additions and subtractions). They were asked to examine them and simply circle the number 7 every time it appeared on its own or as part of another number for 3 minutes. Participants were told that they could take their time, and that accuracy was not an issue.

7. The Go-No Go task

Inhibitory control was measured using a simple form of the Go/No go task presented on a laptop. During the practice or 'priming' phase of this task participants were initially asked to press a key on the laptop whenever a symbol appeared on the computer screen. Following this they were instructed to press a key when they saw specific targets (e.g. !; %; &; ^) but not respond when presented with a specific non-target symbol (e.g. *) . Inhibitory dysregulation is measured by the error rate i.e. the number of times the

participant responds to the non-target symbol. Participants are required to complete this task as accurately as possible for five minutes.

8. Picture Dot probe

The Picture Dot Probe is designed to measure attentional bias towards drug-related cues and was presented on a laptop computer. As shown in Figure 1, participants were presented with two pictures (cues), one opiate and one non-opiate related (neutral). Each pair of pictures was presented for a long (2000ms) or short duration (200ms). This is so that comparisons could be made between automatic (unconscious) and strategic (effortful) cognitive processes (Mogg, Philippot & Bradley, 2004). On the disappearance of the cues, an asterisk appears where one of the pictures was previously. Participants were asked to press a computer key to indicate on which side of the screen (i.e. left or right) the asterix appeared. Attentional bias is primarily measured by response time and secondly by error rate. Once again participants were asked to respond as accurately and quickly as possible.

Figure 1. Example of dot probe trial: Drug Vs Non-drug related cues

9. Dot-probe ratings

The opiate and non-opiate related pictures presented in the dot probe tasks were presented again to participants who were asked to rate each one on a 7- point scale to

indicate how pleasant they found the picture. The rating scale ranged from -3 (very unpleasant) to + 3 (very pleasant).

(v) Procedure

Key workers gave the information sheet to any of their clients who expressed an interest in participating in the study. This ensured that they had sufficient time (at least one day) to read the information before deciding to take part. Participants took part in a single laboratory session lasting approximately an hour and 15 minutes. After obtaining informal verbal confirmation of alcohol and drug-free state, and if necessary by using a breathalyser test, participants were seated in the testing chair. They were given a brief verbal outline of the form and content of the testing session, followed by an opportunity to ask any questions. They were then provided with the informed consent form, which each participant signed and returned to the researcher. Table 1 shows the order of testing for all participants in each group. Once urine samples had been obtained, participants were given payment and offered a verbal debriefing, where they were told that the experiment was designed to test their response to stress in terms of their ability to withhold fine-motor reactions, and the amount of attention they paid to drug-related pictorial cues.

Table 1.
Order of Testing[1]

	ORDER OF TESTING	
1	CAGE and CAGE-AID	
2	VAS 1	
3	Spot the Word	
4	Verbal Learning Task	
5	Semantic Priming Task	
6	Verbal Learning Task – Delayed Recall	
7	BDI	
	Counterbalanced order	
8	Condition 1 MAT	Condition 2 MAT
9	SNS 2	SNS 2
10	Go-no-go	Go-no-go
11	Dot Probe	Dot Probe
12	BAI	BAI
13	Condition 2 MAT	Condition 1 MAT
14	SNS 3	SNS 3
15	Go-no-go	Go-no-go
16	Dot probe	Dot probe
17	SNS 4	SNS 4
18	Dot probe picture ratings	Dot probe picture ratings
19	Obtain urine sample	Obtain urine sample

3. Results

(i) Data Preparation

The normality of the data was tested by examining the distribution of each variable within each group. Where appropriate, and in accordance with Tabachnik and Fidell's (1996) recommendations, two measures were transformed to reduce their skewness, (BAI, Spot the Word) and used in analyses, although untransformed means and standard deviations (SD's) of these variables are reported to ease comprehension.

[1] Tests 4,5 and 6 (in grey) were incorporated in the design of this study because they make up part of another individual's Doctoral thesis (Appendix E). For this reason these measures are not discussed here.

During the analysis of the Dot Probe data, 9 outliers were identified as being more than 3 SD's away from the mean and were excluded from the analysis. These outliers were spread across the three groups with 3, 4 and 2 outliers in the current user, ex-user and non-user groups respectively. However these results were compared to results gleaned when outliers were left in the data and their inclusion did not affect the outcome of the analysis. Therefore, the analysis was then run on the whole dataset. Attentional bias scores were calculated by subtracting the mean RT when the drug-related picture and probe were in a congruent position (i.e. picture and probe in the same location on the screen) from the mean RT when the drug-related picture and probe were in an incongruent position. This generated attentional bias scores at the short (200ms) and the long stimulus presentation (2000ms) times.

(ii) Statistical Analyses

One-way ANOVAs were used to test for group differences (users, ex-users, controls) on demographics and questionnaires. Chi-squared analyses were performed on categorical demographic data. A Fisher's exact test was used on recoded academic achievement data. This data was collapsed into two groups (qualifications at GCSE level or below and qualifications at 'A' Level or above) due to cell numbers not meeting criteria for Chi Squared tests. A repeated measures ANOVA was conducted on stress and craving ratings, with group as a between participants factor and time as a within subjects factor. Repeated measures ANOVAs were also used to analyse the Dot-probe and Go-no-go data, with group as a between subjects factor and condition (stress/no stress) as a within subjects factor. Post-Hoc comparisons, to which Bonferroni corrections were applied,

were used to further investigate main effects and interactions. Bonferroni adjusted corrections were made using SPSS syntax procedures. Within-group Pearsons correlations were performed to explore the relationship between relevant variables.

(iii) Group Characteristics

Drug urine results were returned for 22 samples. Table 2 shows the methadone status along with some polysubstance use of the current user group and no positive screens for the ex-users.

Table 2.
Number of positive urine results for the current user group

	Group	
Drug	**Current Users (N=12)**	**Ex-Users (N=10)**
Opiates	9	0
Cocaine	6	0
Methadone	11	0
Benzodiazepine	2	0
Amphetamines	0	0
Cannabis	0	0

There were no significant group differences in age, gender or employment status. There was a trend towards a group difference on Spot the Word scores ($F_{2,45}$, = 2.56 p = .089) with controls tending to score higher than both current users and ex-users.

Table 3.
(i) Group means (sd) for demographic data (ii) percentage of sample male, unemployed, qualifications above GCSE level.

	Users	Ex-Users	Non-Users
Age	37.56 (6.98)	35.38 (6.45)	32.69 (8.37)
Male	8	12	7
Unemployed	13	14	11
No. above GCSE	7	2	10
Spot the Word Score	45.81 (7.55)	44.32 (5.02)	49.06 (5.60)
BDI Total Score	32.19 (10.52)	13.25 (7.94)	8.75 (8.57)
BAI Total Score	27.44 (17.80)	8.44 (6.87)	6.13 (6.22)

There was a significant group difference in BDI scores ($F_{2,45} = 30.07, p < .001$) with current users scoring higher than both ex-users and control participants (both $p < .001$) (Table 3).There was also a significant group difference on BAI scores ($F_{2,45} = 15.86, p < .001$), again with current users having higher scores than both ex-users and control participants (both $p < .001$).

There was a significant effect of group on academic qualifications above or below GCSE level ($\chi^2 = 7.22, p < .05$), with ex-users having significantly fewer qualifications above GCSE standard than both other groups.

(iv) Stress Tasks

There was no significant group difference in the number of errors made on the stress task (MAT 1; $F_{2,45} = .136, p = .173$). Errors were at floor for the non-stress task (MAT 2).

(v) Stress Ratings

As seen in Figure 2, current users had higher baseline mean stress ratings, and higher ratings at all subsequent time points. All groups rated higher stress following the stress task.

Table 4.
Mean (sd) stress and craving ratings at baseline, following the stress (MAT1) and non-stress tasks (MAT2) and at end of testing

	Current Users	**Ex-Users**	**Non-Users**
Baseline Stress	3.88 (2.73)	1.31 (1.58)	1.13 (1.26)
MAT 1 Stress	5.75 (2.54)	2.75 (2.41)	4.06 (3.07)
MAT 2 Stress	4.00 (3.12)	1.69 (1.85)	1.38 (1.26)
End Stress	4.38 (2.74)	2.19 (2.17)	1.62 (1.46)
Baseline Craving	3.44 (2.71)	0.75 (1.44)	0.37 (1.03)
MAT 1 Craving	3.75 (2.32)	0.50 (0.97)	0.44 (0.81)
MAT 2 Caving	3.31 (2.30)	0.50 (0.89)	0.44 (1.09)
End Craving	4.06 (2.44)	0.94 (1.61)	0.56 (1.32)

The statistical tests revealed main effects of group ($F_{2,45} = 8.75, p = .001$) and time ($F_{2,45} = 21.89, p < .001$) but no interaction. Post-hoc analyses of the groups' stress ratings confirmed that the current user group had significantly higher stress ratings than both ex users and control participants at all times except following the stress task, where current users differed significantly only from the ex-users ($p = .009$)

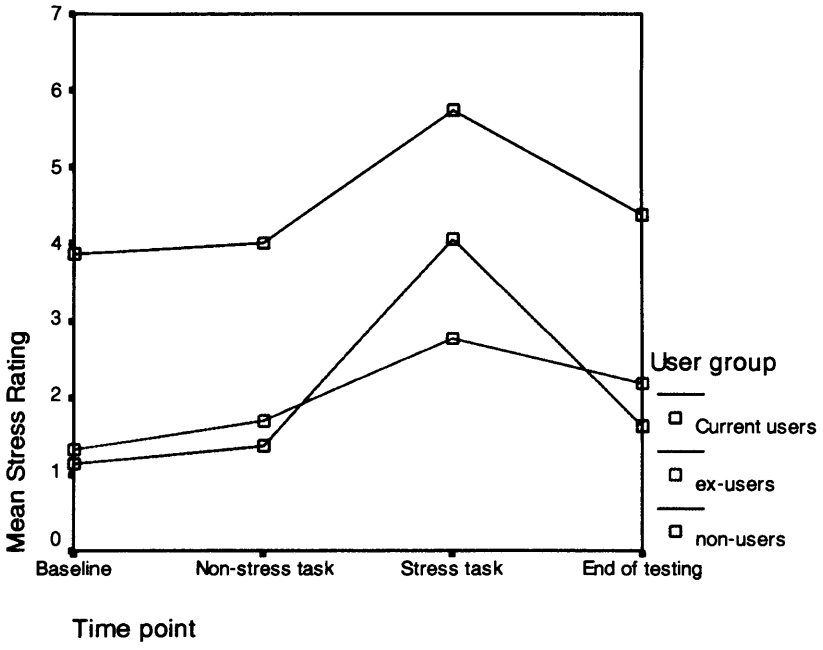


Figure 2. Group mean stress ratings over time

(vi) Craving Ratings

Current users also had higher craving ratings at each time point. There was a significant main effect of group ($F_{2,45} = 21.39, p < .001$) and a tendency towards an effect of time point ($F_{2,45} = 2.33, p = .078$) but no interaction.

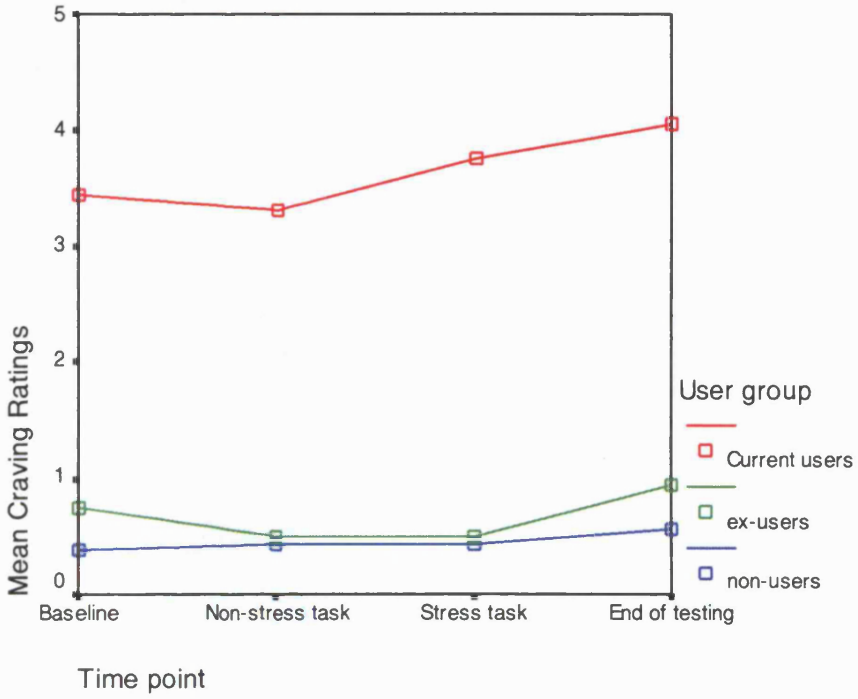


Figure 3. Group mean craving ratings over time

(vii) Go-No-Go Data

As seen in Figure 4, current users appeared to have fewer correct responses across both conditions, with non-users having the most correct hits. A tendency emerged towards a significant effect of group ($F_{2,45} = 2.88, p = .067$) but there was no significant effect of condition (Non-stress/Stress) on the mean number of correct responses.

In terms of the number of 'false alarms' (where participants fail to inhibit their responding), there was a tendency towards a significant effect of stress condition ($F_{2,45} = 3.84, p = .056$), but a non-significant effect of group ($p = .166$). As seen in Table 5 there were greater false alarms in the non-stress condition, which is contrary to the initial

hypothesis relating to the effect of stress on the amount of errors made on the inhibitory control task.

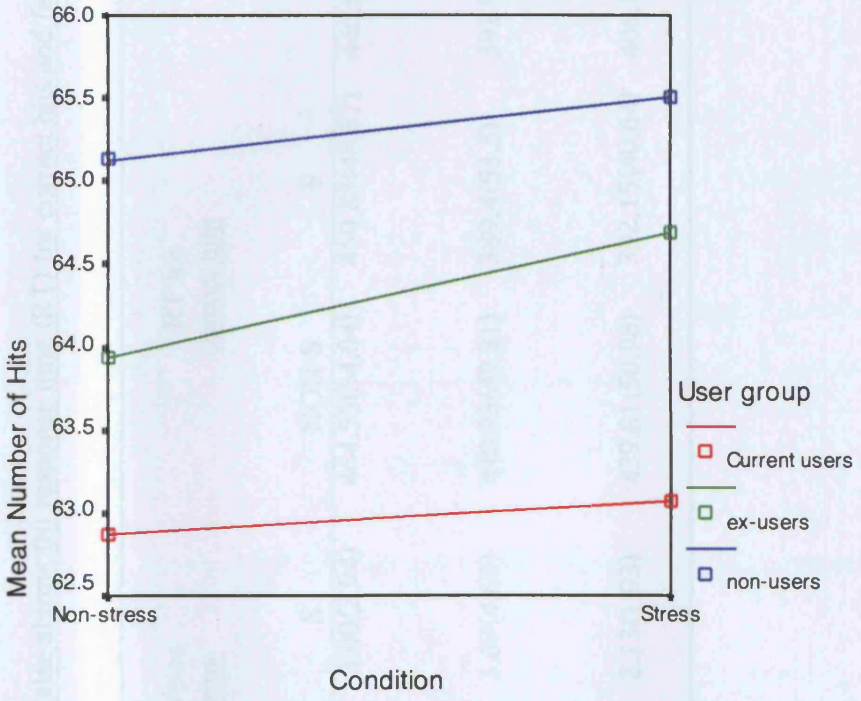


Figure 4. Group mean number of correct hits after non-stress and stress conditions

Response time for correct hits (Figure 5), showed a tendency towards an interaction of group and time ($F_{2,45} = 2.77, p = .073$) as well as main effects of both group ($F_{2,45} = 7.73$, $p = .001$) and condition (Non-stress/Stress; $F_{2,45} = 2.77, p < .001$). Post-hocs revealed that, following the non-stress condition, current users had significantly slower reaction times than non-users ($p = .013$). Following the stress condition, current users were significantly different from both ex-users ($p = .002$) and non-users ($p = .004$).

Table 5.
Group means (sd) for (i) number of correct responses and false alarms (ii) response time (RT) for correct hits and false alarms

Group	No. Correct Responses		No.'false Alarms		RT for correct hits		RT for false Alarms	
	NON-S	S	NON-S	S	NON-S	S	NON-S	S
Current Users	62.87(4.00)	63.06(5.70)	3.38(2.60)	3.00(2.94)	464.55(54.04)	450.88(48.87)	446.58(115.28)	422.72(108.26)
Ex-Users	63.94(2.05)	64.69(1.89)	5.06(3.28)	3.69(4.60)	440.93(49.81)	389.4(53.5)	391.93(78.13)	344.94(75.35)
Non-Users	65.13(1.86)	65.50(0.82)	2.94(2.72)	2.13(1.93)	439.81(50.98)	392.15(40.64)	406.1(94.01)	327.26(62.76)

Note [2]

[2] NON-S = Non-Stress Condition (MAT 2); S = Stress Condition (MAT 1)

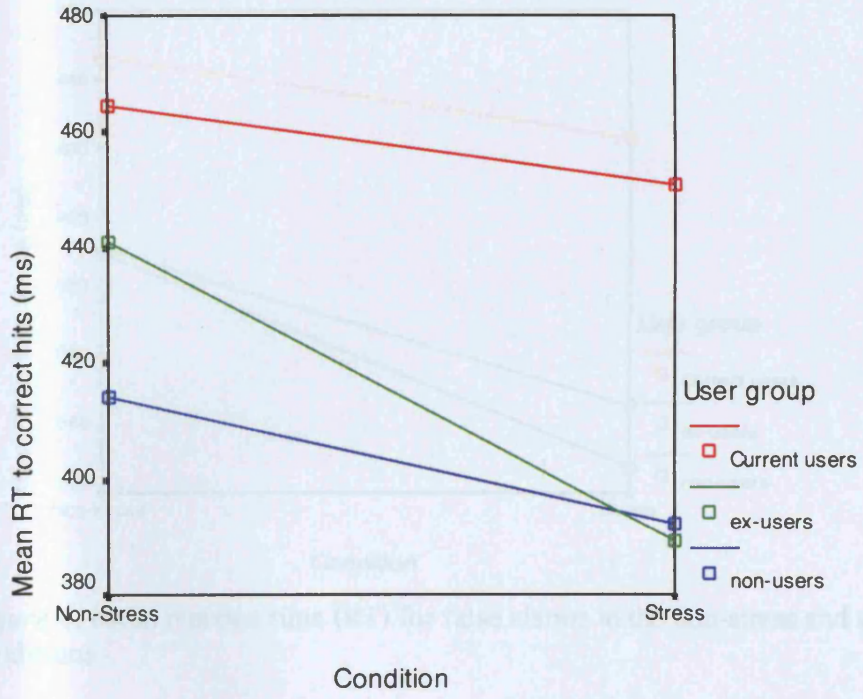


Figure 5. Group mean reaction times (RT) to correct hits after both non-stress and stress conditions

In terms of the mean reaction time for 'false alarms', Figure 6 shows that current users had slower mean reaction times for false alarms than both other groups and in both conditions. All groups had faster reaction times for false alarms in the stress condition. Statistical analysis revealed no interaction but a main effect of both condition (non-stress/stress) ($F_{2,33} = 4.96, p = .033$) and group ($F_{2,33} = 4.25, p = .023$) on reaction times to false alarms. Post hoc tests showed that current users had significantly slower reaction times to false alarms than non-users ($p = .036$).

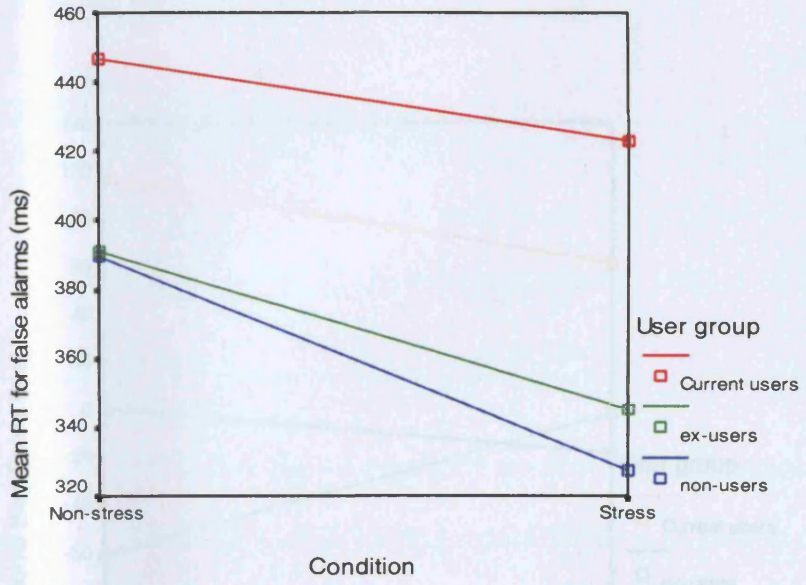


Figure 6. Mean reaction time (RT) for false alarms in the non-stress and stress conditions

(viii) Dot-probe analyses

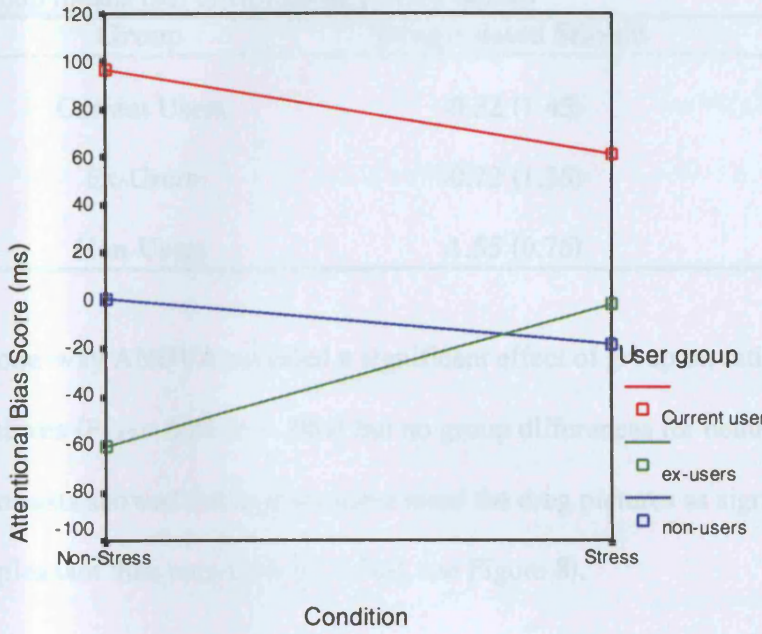
Statistics revealed a main effect of group ($F_{2,44} = 4.21, p = .021$) on attentional bias (Figure 8). Post hocs showed a greater attentional bias towards drug cues for current users as compared to ex-users. ($p = .045$) and a trend towards a greater bias than non-users ($p = .051$). Stress condition (stress/non-stress; $p = .262$) and picture presentation duration (200ms/2000ms; $p = .842$) had no effect on attentional bias.

Table 6.

Group means (sd) for attentional bias scores at short and long cue exposure durations

Group	Short Exposure Duration (Non-S)	Short Exposure Duration (S)	Long Exposure Duration (Non-S)	Long Exposure Duration (S)
	M (SD)	M (SD)	M (SD)	M (SD)
Current Users	96.93 (240.55)	60.77 (130.23)	33.59 (97.73)	15.51 (115.02)
Ex-Users	-60.34 (202.16)	-1.86 (32.80)	-12.58 (91.18)	61.89 (115.27)
Non-Users	0.45 (118.86)	-18.18 (88.19)	-33.21 (162.53)	38.77 (46.91)

(a)



(b)

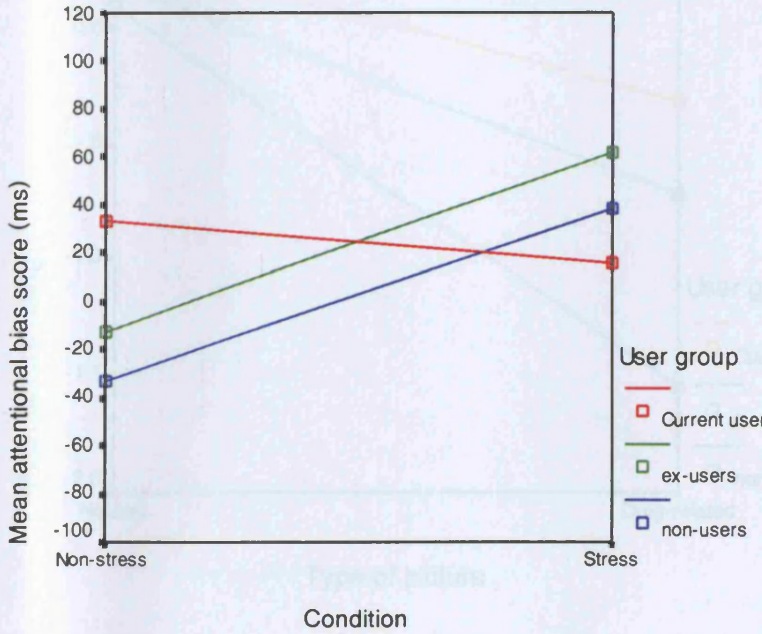


Figure 7. Group mean attentional bias scores across stress conditions for a) the short (200ms) and b) the long (2000ms) duration presentation

(ix) Dot-probe picture ratings

Table 7.
Group means (sd) of Dot-probe picture ratings

Group	Drug-related Stimuli	Neutral Stimuli
Current Users	-0.32 (1.45)	0.35 (0.35)
Ex-Users	-0.72 (1.35)	0.19 (0.36)
Non-Users	-1.55 (0.76)	0.10 (0.23)

A one-way ANOVA revealed a significant effect of group on ratings for the drug-related pictures ($F_{2,47} = 6.41, p = .004$) but no group differences for neutral pictures. Post hoc contrasts showed that current users rated the drug pictures as significantly less unpleasant than non-users ($p = .020$, see Figure 8).

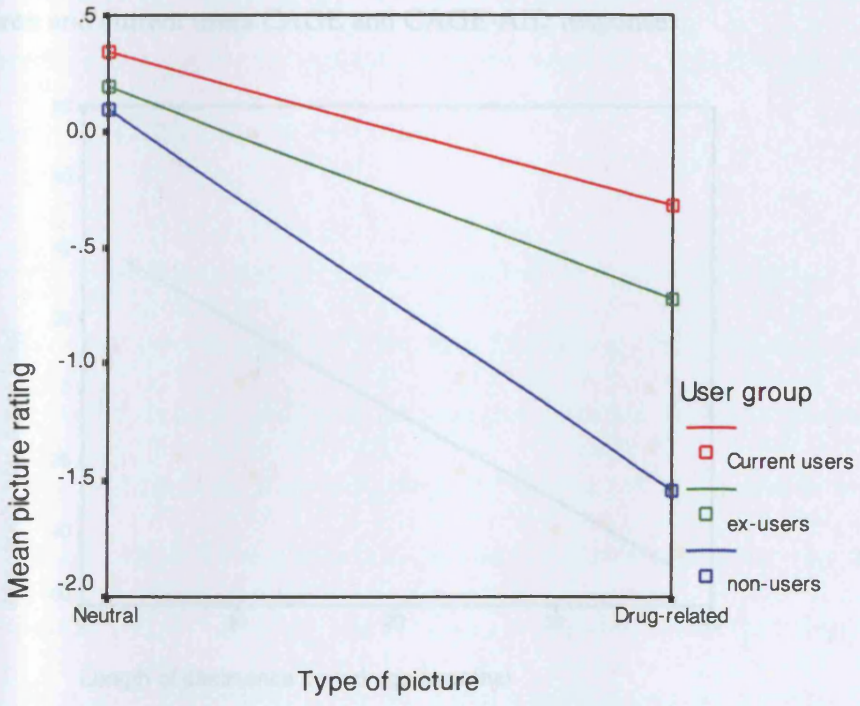


Figure 8. Group mean picture ratings for neutral and drug-related stimuli.

(x) Correlations

There was a negative correlation between attentional bias scores (short presentation) away from drug-related stimuli in the stress condition and length of abstinence from drugs ($r = .538, p = .031$) in the ex-user group. This is illustrated in Figure 9 as a scatterplot and suggests that the greater the length of abstinence, the less the attentional bias.

There was no significant relationship between length of abstinence from alcohol and performance on the Go-no-go task or attentional bias scores in either condition. There was no significant correlation between (i) stress ratings (at any time point) and BAI or BDI scores in the current users group and (ii) attentional bias scores and go-no-go data scores and current users CAGE and CAGE-AID responses.

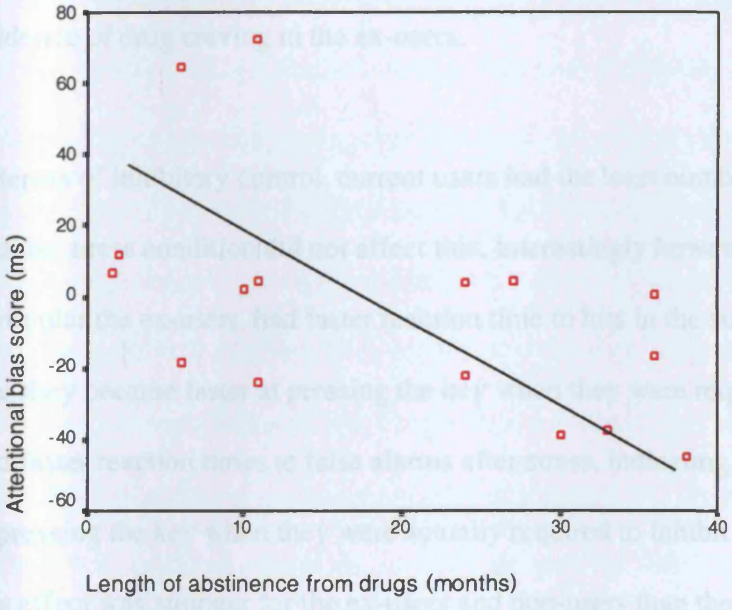


Figure 9. Scatterplot of attentional bias scores *away* from drug-related stimuli (short version, stress condition) and length of abstinence from drugs in ex-users.

4. Discussion

(i) Summary of findings

This study aimed to examine the effect of a mild psychological stressor on inhibitory control and attentional bias in opiate dependent and opiate abstinent individuals. It was initially hypothesized that current users would report greater levels of craving following the stress task, and that they would show an attentional bias towards drug-related stimuli as well as a higher error rate in Go-no go task.

All groups reported significantly higher levels of stress following the stress task, indicating that the stressor worked and that the task has construct validity. Current users had higher levels of self-reported stress at baseline. In terms of cravings, current users had significantly higher ratings than both other groups at all times, as well as a trend towards an increase in cravings following the stress task. Interestingly, there was no evidence of drug craving in the ex-users.

In terms of inhibitory control, current users had the least number of correct responses and the stress condition did not affect this. Interestingly however, all groups, and in particular the ex-users, had faster reaction time to hits in the stress condition, indicating that they became faster at pressing the key when they were required to do so. All groups had faster reaction times to false alarms after stress, indicating that they were all quicker at pressing the key when they were actually required to inhibit their response, although this effect was stronger for the ex-users and non-users than the current users. There was no significant increase in the number of false alarms following the stress task. Indeed, all groups seemed to make fewer false alarms in the stress condition as compared to the non- stress condition. These results seem to suggest that, in contrast with our

preliminary hypotheses, rather than stress having a disinhibitory effect it actually facilitated attentional focus. This facilitation resulted in faster reaction times and fewer errors on the Go-no-go task. Interestingly, informal qualitative feedback from several participants reflected this. Some participants remarked that following the stress task they felt a 'rush' of adrenaline and felt 'ready to go'. It is possible that the mild stressor provided an optimal level of stress and associated increase in physiological arousal to improve task performance (Yerkes and Dodson, 1908)

In terms of attentional bias, current users had a greater attentional bias towards drug-related stimuli than the ex-users. Thus, as hypothesized, these findings show that current users are attentionally biased towards drug stimuli. The lack of attentional bias in ex-users is fascinating. Indeed, the most intriguing aspect of the attentional bias results, although non-statistically significant, was that the ex-users had a tendency to become biased *away* from drug-related stimuli in the stress condition (short 200ms version). This perhaps suggests that on a non conscious level (i.e. without the time to make a controlled response), the drug-related stimuli had become less attention-grabbing or salient. Interestingly, there was a negative correlation between the ex-users' attentional bias *away* from the drug cues and their length of abstinence. Therefore, the longer that the ex-users had been abstinent from drugs, the more likely they were to unconsciously focus their attention on the neutral stimuli and away from drug stimuli. This may indicate that successful treatment (and all ex-users screened negative for *every* drug) is associated with a bias away from drugs and provides a buffer against the effects of stress. Indeed, in a recent study, Cox, Pothos & Hosier (2007) examined the cognitive and motivational predictors of change in excessive drinkers (not in treatment). Their

findings indicated that low levels of attentional bias towards alcohol-related stimuli, as well as a family history of alcohol problems, were predictive of long term reductions in alcohol consumption. Certainly in the present study, ex-users tended to rate the drug pictures as more unpleasant than the current users, and it might be this difference in perspective that contributes to the discrepancy in attentional bias between the current users and the ex-users.

It is possible that the current users' rather flat stress reactivity is reflective of a lack of motivation to perform well. However, it is more likely that this was a ceiling effect due to their high baseline levels of stress, which would have limited their potential to show change. That is to say that their high baseline stress levels would have left little effective 'room' to increase on the scale used.

In terms of the demographic information, current users reported significantly more symptoms of anxiety and depression than both other groups and ex-users had significantly fewer academic qualifications than participants in the other groups. However, there were no significant correlations between anxiety or depression scores and attentional bias or Go-no-go performance. Groups were suitably matched on all other demographic factors.

(ii) Strengths and Limitations

To our knowledge, this is the first study to measure the acute effects of stress on inhibitory control and attentional bias in opiate users. It had certain design strengths including the use of an abstinent as well as a non-user control group and the use of a

control stress condition in a counterbalanced design. Incorporating a non-stress condition increases the internal validity of the results as it reduces the possibility that the results were affected by extraneous variables. The counterbalanced design helps to eliminate any practice or carry-over stress effects. A further strength was that objective verification of the drug-free status of the ex-user group and the methadone-maintained status of the current users was obtained.

However, certain limitations that influence the interpretation of the findings must be noted. Firstly, no information about current users' methadone dose or length of time in methadone maintenance treatment (MMT) was obtained. This oversight meant that this factor could not be used in the statistical analysis. It is possible that current users with longer MMT durations may have shown a different pattern of results than those in methadone treatment for a shorter duration. Similarly, it might have been useful to have some indication of duration of substance misuse to see whether the pattern of results varies in relation to how long an individual has been using drugs. However, this may be subject to idiosyncratic conceptualizations regarding initial drug use and might therefore be difficult to ascertain.

Furthermore, although the stressor was effective, its ecological validity is questionable in that it is unlikely to be reflective of 'real world' stress. It is arguable that future research would benefit from a more personally salient stressor, such as the stress imagery task for example. This would not only provide a greater personal context for drug-use, but may also induce greater levels of stress. However, any researchers attempting to undertake this would need to carefully consider the ethical implications of inducing higher levels of stress in an already vulnerable population.

Previous research (Sinha, Catapano & O'Malley, 1999) has highlighted that the effects of stress are both severity and context specific, especially when trying to induce stress in a laboratory setting. Future research might therefore aim to test both the independent and interactional effects of severity of stressor and historical context specificity, to examine which one is the most critical in creating stress reactions. Furthermore, stemming from our ex-user attentional bias findings, longitudinal research would be essential in following users through the different stages of rehabilitation to examine the variable effects of stress on attentional bias and inhibitory control. However, the chaotic nature of this client group and the associated recruitment difficulties would make such longitudinal research difficult.

One of the criticisms of the stress literature is the relative neglect in examining the interaction between chronic and acute stress in the context of relapse to drug taking. Lu, Shepard, Scott-Hall & Shaham (2003) highlight that humans are invariably exposed to both chronic and acute stressors across the lifespan, and can be experiencing multiple stressors at any one time. With this in mind, future research would benefit from taking into consideration the effect of chronic stress (or exposure to multiple stressors) on acute stress reactivity in the laboratory.

It is arguable that our results are not opiate-specific results and that this might make it difficult to apply the findings to a group of opiate-only users. However, this, coupled with the fact that our current user group were highly symptomatic of both depression and anxiety, is viewed more as a strength of the study rather than a limitation, because it

represents the comorbidity and polysubstance using nature of the client group, which in itself increases the ecological validity of the findings.

(iii) Clinical implications

Some of the findings from this study have important clinical implications, in particular for the way that rehabilitative interventions are offered. Undoubtedly, stress management is, and should be, one of the most fundamental elements of any intervention package.

One of the more novel and interesting clinical implications suggested by the results is the utility of using attentional bias assessments to monitor outcome in opiate rehabilitation. Substance users' biases towards drug-related stimuli could be assessed during the initial stages of rehabilitation, monitored throughout the intervention phase and assessed again at termination of treatment to determine change. Cox, Hogan, Kristian & Race (2002) successfully used attentional bias processes to differentiate between alcohol dependent individuals whose addiction treatment was successful from those whose treatment was not successful. Their results showed that those who were successful showed a pattern of attentional bias away from alcohol-related stimuli that was akin to that of the control group participants. Similarly, dependent individuals whose treatment was unsuccessful showed a significant increase in attentional bias towards alcohol-related stimuli from the first testing point (upon admission to an inpatient unit) to the second (3-months post-discharge). The findings from the present study are in line with Cox et al.'s research and suggest that the effect of treatment on attentional bias could be one effective means of measuring treatment outcome.

5. References

Back, S.E., Brady, K.T., Jackson, J.L., Salstrom, S., & Zinzow, H. (2005). Gender differences in stress reactivity among cocaine-dependent individuals. *Psychopharmacology, 180,* 169-176.

Baddeley, A.D., Emslie, H., & Nimmo-Smith, I. (1993). The Spot-the-Word test: Arobust estimate of verbal intelligence based on lexical decision. *British Journal of Clinical Psychology, 32,* 55-65.

Beck, A.T., & Steer, R. A. (1987). *Manual for the Beck Depression Inventory.* The Psychological Corporation, San Antonio.

Beck, A. T., & Steer, R. A. (1990). Manual for the Beck Anxiety Inventory. The Psychological Corporation, San Antonio

Beck A.T., Ward C., Mendelson M. (1961). Beck Depression Inventory (BDI). *Archives of General Psychiatry 4,* 561-571.

Bradley, B.P., Phillips, G., Green, L., & Gossop, M. (1989). Circumstances surrounding the initial lapse to opiate use following detoxification. *British Journal of Psychiatry, 154,* 354-359.

Brown, R.L., & Rounds, L.A. (1995). Conjoint screening questionnaires for alcohol and other drug use: Criterion validity in a primary care practice. *Wisconsin Medical Journal, 94,* 135-140.

Cohen, J. (1992). A power primer. *Psychological Bulletin, 112,* 155-159.

Cox, W.M., Hogan, L.M., Kristian, M.R., & Race, J.H. (2002). Alcohol attentional bias as a predictor of alcohol abusers' treatment outcome. *Drug and Alcohol Dependence, 68,* 237-243.

Cox, W.M., Pothos, E.M., & Hosier, S.G. (2007). Cognitive-motivational predictors of excessive drinkers' success in changing. *Psychopharmacology, 192,* 499-510

Ewing, J.A. (1984). Detecting alcoholism: the CAGE questionnaire, *Journal of the American Medical Association, 252,* 1905-1907.

Franken, I.H.A. (2000). Selective cognitive processing of drug cues in heroin dependence. *Journal of Psychopharmacology, 14,* 395-400.

Franken, I.H.A. (2003). Drug craving and addiction: Integrating psychological and neuropsychopharmacological approaches. *Progress in Neuropsychopharmacology: Biological Psychiatry, 27,* 563-579.

Gossop, M., Marsden, J., Stewert, D., & Kidd, T. (2003). The National Treatment Outcome Research Study (NTORS): 4-5 year follow-up results. *Addiction, 98,* 291-303.

Hester, R., Dixon, V., & Garavan, H. (2006). A consistent attentional bias for drug-related material in active cocaine users across word and picture versions of the emotional stroop task. *Drug and Alcohol Dependence, 81,* 251-257.

Kiehl, K.A., Liddle, P.F., & Hopfinger, J.B. (2000). Error processing and the rostral anterior cingulate: An event-related fMRI study. *Psychophysiology, 37,* 216-223.

Littman, G.K., Eiser, J.R., & Rawson, N.S. (1977). Towards a typology of relapse: a preliminary report. *Drug and Alcohol Dependence, 2,* 157-162.

Logan, G.D., & Cowen, W.B. (1994). On the ability to inhibit thought and action: A theory of an act control. *Psychological Review, 91,* 295-327.

Marissen, M.A.E., Franken, I.H.A., Waters, A.J., Blanken, P., van den Brink, W., & Hendriks, V.M. (2006). Attentional bias predicts heroin relapse following treatment. *Addiction, 101,* 1306-1312.

McKay, J.R., Rutherford, M.J., Alterman, A.I., Cacciola, J.S., & Kaplan, M.R. (1995). An examination of the cocaine relapse process. *Drug and Alcohol Dependence, 38,* 35-43.

Midanik, L.T, Zahnd, E.G, Klein, D (1998). Alcohol and drug CAGE screeners for pregnant, low-income women: the California Perinatal Needs Assessment. *Alcoholism, Clinical and Experimental Research,* 22, 121-125.

Mogg, K., Philippot, P., & Bradley, BP. (2004). Selective attention to angry faces in clinical social phobia. *Journal of Abnormal Psychology, 113,* 160-165.

Piazza, P.V, & Le Moal, M. (1998). The role of stress in drug self-administration. *Trends in Pharmacological Science, 19,* 67-74.

Robinson, T.E., & Berridge, K.E. (1993). The neutral basis of drug craving: an incentive-sensitisation theory of addiction. *Brain Research Review, 18,* 247-291.

Rossi, P.H., Freeman, H.E., & Lipsey, M.W. (1999). *Evaluation: A Systematic Approach.* (6th Edition) California: Sage.

Sinha, R., Catapano, D., & O'Malley, S. (1999). Stress-induced craving and stress response in cocaine dependent individuals. *Psychopharmacology, 142,* 343-351.

Sinha, R., Fuse, T., Aubin, L.R., O'Malley, S.S. (2000). Psychological stress, drug-related cues and cocaine craving. *Psychopharmacology, 152,* 140-148.

Sinha, R., Garcia, M., Paliwal, P., Kreek, M.J., & Rounsaville, B.J. (2006). Stress-induced cocaine craving and hypothalamic-pituitary-adrenal responses are predictive of cocaine relapse outcomes. *Archives of General Psychiatry, 63,* 324-331.

Sinha, R., Talih, M., Malison, R., Cooney, N., Anderson, G.M., & Kreek, M.J. (2003). Hypothalamic-pituitary-adrenal axis and sympatho-adrenal-medullary responses during stress-induced and drug cue-induced cocaine craving states. *Psychopharmacology, 170,* 62-72.

Volkow, D. N., Fowler, J.S., & Wang, G.J. (2003). The addicted human brain:insights from imaging studies. *The Journal of Clinical Investigation, 111,* 1444 – 1451.

Wallace, B.C. (1989). Psychological and environmental determinants of relapse in crack cocaine smokers. *Journal of Substance Abuse Treatment, 6,* 95-106.

Weinstein, A. (2006). Cognitive processing of drug related stimuli: the role of memory and attention. *Journal of Psychopharmacology, 20,* 850-859.

Yerkes, R. M., & Dodson, J. D. (1908). The relation of strength of stimulus to rapidity of habit-formation. *Journal of Comparative Neurology and Psychology, 18,* 459-482.

Part 3: Critical Appraisal

1. Reflections on the process

(i) Overarching considerations

The aims of the research were initially clear. These involved comparing aspects of stress-reactivity of three groups of participants using fairly standard computer-based tasks. Initial optimism, and also realism relating to the recruitment process, was facilitated by the fact that I was familiar with the client group, with whom I had worked as an Assistant Psychologist prior to Clinical Psychology training. Furthermore, I was to conduct this research alongside a colleague, who was collecting data from the same participants for her own thesis. We developed the research protocol early on in the research process and applied for ethical approval ahead of the majority of our peers. Furthermore, we received this approval with no conditional amendments. However, the practical reality of what turned out to be 7 months of active recruitment was somewhat different.

Certain overarching considerations relating to recruitment were relevant across all participant groups. The first of these was the importance of engaging staff in the research process. Essentially, building sound relationships with regular clinic staff was the lynchpin to the recruitment procedure. For example, my colleague and I were encouraged to give a presentation to a key sample of clinic staff from which current users were to be recruited. This served several purposes. It enabled us to make ourselves known to the staff; describe the study and its objectives; highlight its clinical utility; outline our inclusion criteria and provide staff with written information about the study to disseminate to their colleagues. Furthermore, we took the time to visit each clinic before beginning recruitment in order to familiarise ourselves with the day to day

running of the clinic and establish the feasibility and practicalities of carrying out the research.

(ii) Current Users

In addition to the research presentation outlined above, we observed the pharmaceutical dispensary within the clinic to initially familiarise ourselves with the client group and their routine. This helped to establish when might be the best time to approach them but also served to gain insight into their existing commitments and pressures on their time. What soon became apparent was that these pressures were plentiful, and quite often took priority over participation in a research study.

As anticipated, the current user group was the most difficult to engage and recruit. Their transient and chaotic lifestyles meant that they often missed scheduled appointments or were non-contactable by phone or letter. This meant that we spent a great deal of time 'chasing' the participants who had agreed to take part, and ensuring that the appointment date/time was as suitable for them as possible. Towards the end of the recruitment phase, appointments were arranged less frequently as it proved more effective to liaise with key workers and determine their clients' pre-existing clinic appointments and join in with them. However, what surprised me was that clients often failed to attend clinic appointments even to pick up their methadone or their scripts. A further recruitment complication was that on some occasions, participants had to be turned away because they attended their research appointment under the acute influence of drugs or alcohol. Key workers were instrumental in this respect in term of advising us about the best time of day to test a particular client. For example, it was useful to know the days, or time of

day, that clients were less likely to have consumed any alcohol. Indeed, communication with the key workers was paramount, not only in terms of helping to arrange appointments with their clients, but also to avoid any appointment clashes. This was important as it occasionally became apparent that some participants were choosing not to attend pre-existing key worker appointments in favour of their research appointment because of the monetary incentive involved in the latter.

Sadly, one of our participants died from an overdose over the Christmas period. This proved to be not only a tragic reminder of the stark social contrast between ourselves and the participants, but also proved to be somewhat anxiety provoking as our assessments were requested for use in the Coroner's report. This certainly highlighted to me the importance of supervision especially since the research was taking place very much within a clinical context. Furthermore, it accentuated the need for careful analysis, and if necessary the follow up, of scores on the depression inventory before the participant left the room and liaising with key worker and supervisors if any concerns became apparent.

(iii) Ex-users

My colleague and I had calculated that, if we used pre-existing links with established rehabilitation clinics, recruitment of this group should not take longer than three weeks at the most. However, this calculation was an underestimate, mainly due to our recruitment being hampered by many rehab clinics declining to meet with us, but also because we needed participants whose primary dependence had been opiates. Many clinics could offer us only one or two participants each, and some met with us to discuss

our research but did not return our follow-up phone calls. For these reasons it was necessary for us to build relationships with rehabilitation clinics that had never been a part of research before. On the whole however, the process of recruiting from rehabilitation centres was in stark contrast to the experience of recruiting current users. All of the clinics were residential, which made recruitment and appointment-keeping considerably easier. For most clinics, recruitment was completed in one day, which was helpful for both ourselves and also for staff, as we were not disturbing them all day. Although most rehabilitation centres ran a tight schedule of rehabilitation programmes, all staff were extremely helpful in accommodating us and some even helped to put us in touch with other centres who they thought we might find useful.

(iv) Non-users

Although we had anticipated that this group would require less time to recruit, the reality was again slightly less straightforward than predicted. We had originally planned on recruiting from Job Centres who had been involved in this type of research before. However, all of the Job Centres that we contacted were undergoing managerial or structural changes, and for this reason, were unable to facilitate our research. After several weeks without success we were forced to rethink our recruitment strategy. We revisited our inclusion criteria and decided that we should start recruiting as many people as we could who matched our current user group in terms of employment and educational status. We began by recruiting an opportunist sample of people who we already knew, and from then on, a snowballing effect ensured we gained our sample.

(v) Advantages V's disadvantages of joint research

The testing process involved working very closely with my colleague to ensure recruitment goals were achieved. This proved invaluable for a number of reasons. With such a difficult client group to engage, the division of labour and the sharing of both resources and responsibilities were invaluable. Having two people as a presence at the clinic undoubtedly helped the staff to familiarise themselves with us quickly. We also established quite rapidly, especially for the current user group, that it was more effective to recruit on separate days, as room space was often a problem. This meant that we were able to be present at the clinics for two days per week, leaving us both with a day per week to continue researching the literature and writing up the thesis. Furthermore, we were able to motivate each other through the inevitable frustrating periods of the process and both share and allay each others anxieties.

However, this research has also highlighted to me that joint research can often take a greater amount of coordination, project management and communication than research undertaken alone.

(vi) 'The journey'

Inevitably, as with any research process, there were welcomed peaks and unexpected troughs. Reflecting on this has made me realise how I have come 'full circle'. That is to say that I embarked on this research with a sense of almost naïve optimism. Having worked with the client group before, and being acutely aware of recruitment difficulties, I was sure that I was well equipped to manage most obstacles that would arise. Following the difficulty recruiting the current user group and the decision to stop testing

at 16 per group (as opposed to the original 20 planned), there followed a period of uncertainty and frustration. There had to be a balance between a desire to do justice to the research and therefore continue recruitment, and analysing the data we had managed to collect so that the thesis could be written up in time for submission. My 'journey' culminated in the easier recruitment of the rehab and control groups, with enough time to devote to writing the empirical paper. Recruiting the rehab participants provided me with an almost reparative experience. Whereas recruiting the current users had seemed overwhelming and disheartening, not least because we were understandably being exposed to the harsh reality of their position as one of the most marginalised sectors of society, recruiting the rehab participants was an entirely different experience. Speaking with them and learning of their journeys to abstinence, and their achievements since then, gave me a more hopeful and optimistic stance. The fact that this group were often extremely interested in the research and the results gave me the welcomed motivation to complete it and provide them with some feedback. I am grateful for this return to optimism, which perhaps was born out of immersing myself in the client group and their experiences, because it has taught me about the natural path of research, and will hopefully help me to be confident in future research attempts.

2. Critical Appraisal of the Research

(i) Ethical considerations

One of the most important features of this study was the nature of the two clinical groups of participants: current users and ex-users. Their emotional, psychological and social vulnerability had important implications for the design of the study. One of the initial considerations was related to the length of the study. From my previous contact

with this particular group of participants, as well as conversations with substance misuse workers, it was clear that the study should not be too lengthy. Key workers stressed that their clients found it difficult to sustain attention and concentration for prolonged periods of time. Furthermore, since part of the study involved inducing mild levels of stress, it was even more important to design a study of a reasonable length. The literature highlighted several stress tasks that could be used in the study (Sinha et al., 1999; 2000; 2003; 2006). However, most of these were not considered appropriate since they involved inducing high stress levels and required participants to engage in multiple testing sessions. The mental arithmetic task (Back, 2005) was chosen above both guided imagery procedures and public speaking tasks due to its significantly shorter duration, and its milder level of elicited stress. Since the stress task worked (i.e. it elicited significantly higher self-reported levels of stress than the non-stress task), it can be assumed that it is an effective stress inductor.

(ii) Feedback from research presentation

Some of the feedback gleaned from the presentation we undertook at the clinic prior to recruitment highlighted some important areas for thought, some of which remain relevant now. Key workers thought that the testing session was too long and queried whether participants would be able to maintain their concentration and attention. Some participants were able sustain their motivation to complete the study, whereas there were certainly some who complained about the duration and said that towards the end they 'gave up' doing their best at the tasks due to boredom. The key workers also commented that the clinical utility of the research was not immediately apparent, so we spent some time with them and their clients explaining in layman's terms the motivation for carrying out the research and the objectives for the study.

(iii) Validity of the pictoral dot-probe

A considerable amount of time was spent trying to ensure that the dot-probe task would be valid for the client group. To facilitate this, my colleague met with a service user at the Margarete Centre who commented that on the whole the pictoral cues were fine. However, he did suggest that two neutral pictures should be altered as they might be unexpected heroin cues. The picture of a plastic jug reminded him of the one used to pour the methadone at the Margarete Centre, and the wine glass would have been salient for users who were also dependent on alcohol. Choosing the right pictures and taking realistic photos was a long but necessary process. It meant that we could be confident that the heroin cues were realistic and that the neutral cues were actually neutral.

(iv) Qualitative feedback from participants

During the testing, and during the verbal debriefing at the end, participants were asked for some informal feedback about the testing process. Some general themes arose relating to the length of the study and insufficient payment considering how many studies they participate in as a group. This stirred feelings of guilt within me, that I tried to allay by reminding participants that they could withdraw at any time and still receive their compensation.

What was highlighted to me throughout this research process is the importance of listening to the participants' comments as they complete the study. For example, several participants mentioned that they felt 'wired' and experienced an 'adrenaline rush' after the stress task. Many of them likened it to the feeling experienced during an exam, whereby an optimal level of stress or nerves enables them to perform well. Some of

these remarks provided the impetus for the 'attentional focus' interpretation of the inhibitory control results.

One current user remarked that the way you respond to the pictures depends on whether you are a heroin smoker or injector. Although there was a mixture of both heroin injecting and smoking pictures, it would have been useful to ask participants more about the form of their drug use. It is possible that for those whose preference is to smoke, rather than to inject, the drug, the injecting picture cues may not have been so salient

3. Future Directions

This experience of research has facilitated a steep learning curve in terms of the demands of conducting research whilst also practicing clinically. This is an especially difficult client group to research, which has undoubtedly contributed to the 'slow but steady' nature of the research to date. Clinicians engaged in this type of research will be helped by being well-supported and networking with relevant substance misuse services and staff. Personally, I will endeavour to remain research active in my work as a qualified clinical psychologist and I hope that the learning experience gained from conducting this piece of research will help me do so. Indeed, one area of interest that has arisen for me is how to use measures of cognitive processes as robust measures of clinical outcome. It will be interesting to see whether this is a direction in which future research is taken.

I have, without doubt, experienced a welcomed sense of achievement in finding some clinically relevant results. I wonder whether my experience of this research process as a

whole would have been different had this not been the case. Nevertheless, I hope that the findings will be applied in clinical settings in the near future. Of course, this will not be an immediate consequence of this study, and replications of the results will be necessary before adaptations to treatment approaches can be made.

4. References

Back, S.E., Brady, K.T., Jackson, J.L., Salstrom, S., & Zinzow, H. (2005). Gender differences in stress reactivity among cocaine-dependent individuals. *Psychopharmacology, 180*, 169-176.

Sinha, R., Catapano, D., & O'Malley, S. (1999). Stress-induced craving and stress response in cocaine dependent individuals. *Psychopharmacology, 142,* 343-351.

Sinha, R., Fuse, T., Aubin, L.R., O'Malley, S.S. (2000). Psychological stress, drug-related cues and cocaine craving. *Psychopharmacology, 152,* 140-148.

Sinha, R., Garcia, M., Paliwal, P., Kreek, M.J., & Rounsaville, B.J. (2006). Stress-induced cocaine craving and hypothalamic-pituitary-adrenal responses are predictive of cocaine relapse outcomes. *Archives of General Psychiatry, 63,* 324-331.

Sinha, R., Talih, M., Malison, R., Cooney, N., Anderson, G.M., & Kreek, M.J. (2003). Hypothalamic-pituitary-adrenal axis and sympatho-adrenal-medullary responses

during stress-induced and drug cue-induced cocaine craving states. *Psychopharmacology, 170,* 62-72.

Appendices

A: Letter sent to Rehabilitation Clinics

Camden and Islington NHS
Mental Health and Social Care Trust
Islington & Camden Drug Services
The Margaretee Centre

19th March 2007

Dear Sir/Madam

We are two third year Trainee Clinical Psychologists working on a research project at University College London and the Margarete Centre (South Islington and Camden Drug Services). Our research is supervised by Professor Valerie Curran (UCL) and Dr Dominic O'Ryan (Margarete Centre).

We are following up a piece of research that was conducted last year at UCL, and we are looking at the effects that drugs (opiates) have on memory and response inhibition.

We would be very grateful if we could come in and speak to you regarding the possibility of recruiting participants for our study in your service. We are looking to recruit 20 participants (male and female) who no longer use heroin or methadone. The participants would take part in a one-off research session which would last approximately one hour and fifteen minutes, and which consists of a variety of pen-and-paper and computer tasks. They would receive a £7 supermarket voucher for taking part.

We appreciate that you are a busy service and we would be careful not to encroach on your time and would be as discreet as possible. We also promise to feedback our findings when the research is completed. Due to the limited funds available for this study we are not able to offer large incentives to participants. However, as already mentioned, each participant would receive a £7 supermarket voucher, and chocolates and immense gratitude would be offered to your service.

We very much hope that you will be able to help us with our participants' recruitment and we will be telephoning you to discuss this with you in more detail. In the meantime we attach a Participant Information Sheet for your perusal, and please do not hesitate to contact us on the above number should you wish to ask any questions before then.

Yours sincerely

Stefania Battistella
Trainee Clinical Psychologist

Natasha Constantinou
Trainee Clinical Psychologist

Supervised by,
Dr Dominic O'Ryan
Chartered Clinical Psychologist

B: Informed Consent Sheet

Camden and Islington NHS
Mental Health and Social Care Trust

Participant identification code:

Consent form

Confidential

Research study: Inhibition and memory in opiate users, ex-users and non-users.

Name of researchers: Natasha Constantinou and Stefania Battistella

1. I confirm that I have read and that I understand the information sheet dated - _____ for the above study.
   Yes/No

2. I have had an opportunity to ask questions and discuss this study
   Yes/No

3. I understand that I am free to withdraw from this study:
   - At any time
   - Without reason
   - Without affecting my management at the clinic/hostel

   Yes/No

4. I agree to take part in the above study.
   Yes/No

_____	_____	_____
Name of participant	Date	Signature of participant

_____	_____	_____
Name of researcher	Date	Signature of researcher

C: Participant Information Sheets

Camden and Islington NHS
Mental Health and Social Care Trust

Participant Information Sheet (Current Users)

Research Study: Inhibition and memory in opiate users, ex-users and non-users

Researchers: Natasha Constantinou and Steffania Batistella (Trainee Clinical Psychologists)

You are invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please read the following information. Please ask us if there is anything that is unclear or if you would like more information. Take time to decide whether you wish to take part.

What is the purpose of the research study?
To understand what effect methadone has on people's memory and the way they control their responses. Research has shown that different drugs affect these two functions. In this study we are looking at 1) people who are using methadone at the moment, 2) people who no longer use methadone or heroin, and 3) people who have never used.

Why have I been chosen?
We have asked you to take part because you are using methadone at the moment. We will also be approaching around 30 other people who also currently use methadone.

Do I have to take part?
You do not have to take part in the study if you not wish to. Your decision to take part will not affect your care management in any way. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you do decide to take part you can withdraw at any time without having to give a reason.

What will happen if I take part?
We will arrange to meet you once for about an hour at the Margarete Centre, after you have taken your methadone. First we will ask you a little about your drug use. You will then be asked to complete some computer tasks. We will also ask you to complete some questionnaires. When this is completed, we will give you a voucher worth £7. All information collected about you during the study is strictly confidential and will be coded by number. Your name will not appear on any forms.

What are the advantages and disadvantages of taking part?
We do not foresee that taking part will cause you distress. We hope that the information we collect from this study will improve our understanding of the effects of methadone, and so help to improve services to methadone clients.

What will happen to the results of the study?
The results will be written up as part of a thesis, which we hope will be published in a scientific journal. A summary of the findings will be available to all who took part.

Who is organising and funding the study?
The study is organised and funded by Camden and Islington NHS Trust and University College London.

Contact for further information:
If you would like further information or have any questions, then please leave a message for us at the Margarete Centre.

Thank you for taking time to read this.

All proposals for research using human participants are reviewed by an ethics committee before they can proceed. This proposal was reviewed by Camden and Islington Health Services NHS Trust Ethics Committee.

Camden and Islington NHS
Mental Health and Social Care Trust

Participant Information Sheet (Non-Users)

Research Study: Inhibition and memory in opiate users, ex-users and non-users

Researchers: Natasha Constantinou and Stefania Battistella (Trainee Clinical Psychologists)

You are invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please read the following information. Please ask us if there is anything that is unclear or if you would like more information. Take time to decide whether you wish to take part.

What is the purpose of the research study?
To understand what effect methadone has on people's memory and the way they control their responses. Research has shown that different drugs affect these two functions. In this study we are looking at 1) people who are using methadone at the moment, 2) people who no longer use methadone or heroin, and 3) people who have never used.

Why have I been chosen?
We have asked you to take part because you do not and have never used methadone. We will also be approaching around 30 other people from the Jobcentre.

Do I have to take part?
You do not have to take part in the study if you not wish to. Your decision to take part will not affect your care management in any way. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you do decide to take part you can withdraw at any time without having to give a reason.

What will happen if I take part?
We will arrange to meet you once for about an hour and a quarter. As we are looking to hear from people who do not use opiates, you will first be asked some questions about your drug use. You will then be asked to complete some computer tasks. We will also ask you to complete some questionnaires. When this is completed, we will give you a voucher worth £7. All information collected about you during the study is strictly confidential and will be coded by number. Your name will not appear on any forms.

What are the advantages and disadvantages of taking part?
We do not foresee that taking part will cause you distress. We hope that the information we collect from this study will improve our understanding of the effects of drugs, and so help to improve drug treatment services.

What will happen to the results of the study?
The results will be written up as part of a thesis, which we hope will be published in a scientific journal. A summary of the findings will be available to all who took part.

Who is organising and funding the study?
The study is organised and funded by Camden and Islington NHS Trust and University College London.

Contact for further information:
If you would like further information or have any questions, then please leave a message for us at the Jobcentre.

Thank you for taking time to read this.

All proposals for research using human participants are reviewed by an ethics committee before they can proceed. This proposal was reviewed by Camden and Islington Health Services NHS Trust Ethics Committee.

Camden and Islington NHS
Mental Health and Social Care Trust

Participant Information Sheet (Ex-Users)

Research Study: Inhibition and memory in opiate users, ex-users and non-users

Researchers: Natasha Constantinou and Stefania Battistella (Trainee Clinical Psychologists)

You are invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please read the following information. Please ask us if there is anything that is unclear or if you would like more information. Take time to decide whether you wish to take part.

What is the purpose of the research study?
To understand what effect opiates (heroin/methadone) have on people's memory and the way they control their responses. Research has shown that different drugs affect these two functions. For this study we are inviting three groups of participants: 1) people who are using methadone at the moment, 2) people who no longer use methadone or heroin, and 3) people who have never used these types of drugs.

Why have I been chosen?
We have asked you to take part because you no longer use opiates. We will also be approaching around 40 other people from the Jobcentre and other clinics.

Do I have to take part?
You do not have to take part in the study if you do not wish to. Your decision to take part will not affect your care management in any way. If you decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you can withdraw at any time without having to give a reason.

What will happen if I take part?
We will arrange to meet you once for about an hour at the centre. As we are looking to hear from people who do not use opiates, you will first be asked some questions about your drug use. You will then be asked to complete some computer tasks and questionnaires. When this is completed, we will give you a voucher worth £7. All information collected about you during the study is strictly confidential and will be coded by number. Your name will not appear on any forms.

What are the advantages and disadvantages of taking part?
We do not foresee that taking part will cause you distress. We hope that the information we collect from this study will improve our understanding of the effects of drugs, and so help to improve drug treatment services.

What will happen to the results of the study?
The results will be written up as part of a thesis, which we hope will be published in a scientific journal. A summary of the findings will be available to all who take part.

Who is organising and funding the study?
The study is organised and funded by Camden and Islington NHS Trust and University College London.

Contact for further information:
If you would like further information or have any questions, then please leave a message for us at the centre.

Thank you for taking time to read this. All proposals for research using human participants are reviewed by an ethics committee before they can proceed. This proposal was reviewed by Camden and Islington Health Services NHS Trust Ethics Committee.

D: Letter of Ethical Approval

E: Statement of Joint Working

This thesis arose from a joint research project. Participant recruitment was shared between Stefania Battistella and myself, with each of us running each others' tests during the laboratory sessions. All other aspects, including the analysis and write-up of the results, were conducted separately.