Effects of alcohol preload on attentional bias towards cocaine related cues

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Running Head: Attentional bias in cocaine users

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Abstract

Background: Drug and alcohol users have an 'attentional bias' for substance-related cues, which is likely to reflect the incentive-motivational properties of those cues. Furthermore, administration of an alcohol preload increases attentional bias for alcohol and tobacco-related cues in heavy drinkers and tobacco smokers, respectively. The present study investigated attentional bias for cocaine cues in cocaine users and non-users following administration of either alcohol or placebo. *Method:* Thirty-two regular cocaine users and 40 nonusers took part. Participants were administered alcohol or placebo and administration was double-blind. After drink administration, a Visual Probe task and Modified Stroop task were used to assess attentional bias. Subjective craving and alcohol outcome expectancies were also measured. *Results:* There was a significant interaction between group and drink type on the visual probe task indicating that cocaine users who had received alcohol had increased attentional bias for cocaine pictures compared to non-users and cocaine users who received placebo. The cocaine Stroop revealed no differences between cocaine users and non-users, and no effects of alcohol in either group. *Conclusions:* Alcohol preload in regular cocaine users increases attentional bias for cocaine cues. However, cocaine users who received placebo did not show attentional bias for cocaine stimuli. Future research should investigate the effects of alcohol preload on attentional bias in cocaine dependent individuals.

Introduction

A number of theoretical models suggest that drug-related cues should have powerful incentive-motivational properties in chronic drug users (see Field & Cox, 2008). Although different theoretical models emphasise either neurobiological (e.g. Franken, 2003; Robinson & Berridge, 1993) or cognitive (e.g. Ryan, 2002) mechanisms to explain this effect, there is broad agreement that environmental 'cues' (e.g. the sight of cocaine powder or a marijuana cigarette) should be able to attract the attention of experienced substance abusers. Once this 'attentional bias' has been established, it may theoretically contribute to increased motivation to consume the drug in the future (see Field & Cox, 2008). The evidence for attentional bias in substance abusers is compelling. For example, previous research has shown that smokers (Mogg et al. 2003; Waters et al. 2003), heroin dependent individuals (Franken et al. 2000a), cocaine misusers (Hester et al. 2006) and heavy social alcohol drinkers (Cox et al. 1999; Townshend & Duka, 2001) all show an attentional bias for substance-related stimuli. Franken (2003) suggested that presentation of drug-related stimuli in attentional bias tasks may result in dopamine release in the mesolimbic reward pathway, causing those cues to grab attention which subsequently leads to increased craving and drug seeking. A recent meta-analysis investigated the link between craving and attentional bias in substance users (Field et al. 2009) and found that while the correlation between craving and attentional bias was significant, it was weak and was moderated by a number of factors, including the type of drug (with a larger correlation when assessing attentional bias for cues related to illicit drugs such as cocaine, rather than cues related to alcohol or tobacco), and the current strength of subjective craving (with a larger correlation between attentional bias and craving when craving was high, compared to when it was low).

Given that dopamine activity in the mesolimbic pathway is hypothesised to be responsible for incentive salience attribution and attentional bias (e.g. Robinson & Berridge,

1993; see Franken et al., 2004, for supportive evidence), acute administration of drugs that increase dopaminergic activity should lead to increases in attentional bias for drug-related cues. As with other drugs of abuse, alcohol has been shown to increase dopamine levels in the mesolimbic reward pathway, specifically the nucleus accumbens (Boileau et al. 2003). Studies of attentional bias have shown that administration of alcohol increases attention to alcohol cues compared to neutral cues in social drinkers, although these effects are dose dependent. Both Duka & Townshend (2004) and Schoenmakers et al. (2008) demonstrated that administration of a low dose alcohol preload (0.3g/kg) led to increased attentional bias for alcohol-related pictures (relative to placebo), although attentional bias after a high dose preload (0.6g/kg) was not significantly different from that seen after administration of placebo (Duka and Townshend 2004). There is also an emerging literature demonstrating that alcohol administration leads to dose-dependent increases in subjective alcohol craving (see Field, Schoenmakers, & Wiers, 2008, for a review). Alcohol priming doses can also increase attentional biases for cues associated with other drugs in individuals who abuse those drugs. For example, in regular smokers alcohol administration (0.4g/kg) increased attentional bias for tobacco cues and craving for cigarettes (Field et al. 2005). Therefore, in summary, alcohol may increase the incentive-motivational properties of a variety of abused substances, as inferred from both self-reported craving and measures of the ability of those cues to attract attention.

While previous research has investigated attention to cocaine cues in cocaine users (e.g. Franken et al. 2000b; Hester et al. 2006; Rosse et al.1997), less attention has been paid to how alcohol administration may affect this. In the UK, and internationally, prevalence of powdered cocaine use has increased over recent years, particularly in young people (EMCDDA 2008; Hoare, 2009). Alcohol and cocaine are used in higher quantities during concomitant use than when either is used alone (Gossop et al., 2006) and a range of clinical

studies have shown that the cocaine-alcohol combination produces additive psychological and physiological effects (Pennings et al., 2002). Increased toxicity is hypothesised to be a result of the production of the coca-ethylene metabolite which produces similar, but reportedly longer lasting behavioural and pharmacological effects to cocaine (Harris et al., 2003; Hearn et al., 1991). In 2007, a quarter of cocaine related deaths in England and Wales were associated with use of the drug alongside alcohol (ONS, 2008).

Accordingly, administration of alcohol to cocaine users may affect their attentional bias for cocaine cues through a number of different mechanisms. Firstly, if an individual co-administers the two drugs, this should result in excessive incentive salience attribution to both alcohol- and cocaine-related cues because the combination leads to much greater levels of dopamine release compared to when either drug is used by itself (e.g. Sobel & Riley 1997). This increased incentive salience attribution should lead to long-lasting increases in attentional bias for both cocaine- and alcohol-related cues. Secondly, alcohol intoxication may increase attentional bias for cocaine cues among individuals who regularly use the drugs together, because the interoceptive effects of alcohol have been repeatedly paired with the effects of cocaine in the past. Therefore the experience of these interoceptive effects may increase attentional bias for cocaine cues through a classical conditioning process (see Field et al., 2005, for an elaboration of this argument with regard to the co-administration of alcohol and nicotine). Thirdly, administration of alcohol may increase subjective craving for both alcohol and cocaine. Franken (2003) proposes that attentional bias and craving have a reciprocal relationship, such that increases in craving may elicit increases in attention to drug cues, which may further increase craving. Thus administration of alcohol could increase craving for cocaine and alcohol which would further increase attentional bias for both cues. Finally, the phenomenon of cross-sensitization suggests that dopaminergic sensitization produced by repeated use of one drug (e.g. cocaine) could render the mesolimbic dopamine

system hypersensitive to other drugs and cues associated with those drugs (see Biala & Budzynska, 2008; Smith, Greene-Naples, Felder, Iordanou et al. 2009). Therefore, regular use of cocaine may produce dopaminergic sensitization that renders the individual hypersensitive to alcohol's dopaminergic effects.

There are a number of experimental paradigms used to assess attentional bias (see Field & Cox, 2008). The present study used a cocaine-related modification of the Stroop task and a visual probe task. The modified Stroop is a widely used measure of attentional bias in drugs users and has consistently shown that drug and alcohol users exhibit attentional bias for drug-related stimuli, in comparison with individuals who use those drugs infrequently or not at all (e.g. Cox et al. 2003; Duka & Townshend, 2004; Franken et al. 2000a; Franken et al. 2000b; Waters et al. 2003). In a typical modified Stroop task two categories of words are presented: substance-related words and emotionally neutral words. Each word is printed in a different coloured ink, and the participant is required to name the colour of the ink and ignore the written word. If participants' colour naming is impaired for substance related words (i.e. they take longer to name all colours) then this indicates involuntary processing of the semantic content of the words. The attentional bias score is the difference between times taken in the two conditions. While the modified Stroop has not previously been used in cocaine users following preload with alcohol, prior research suggests that the addiction Stroop is a valid tool for assessing attentional bias in substance using samples (Cox et al. 2006). The version of the task used here also has a high level of test-retest reliability (e.g. Field, Rush, Cole & Goudie, 2007). In a visual probe task, participants are presented with a pair of stimuli (in the present study, pictures), one depicting something related to substance use, the other a perceptually similar neutral picture. Participants are required to respond to a probe replacing one of the pictures as quickly and accurately as they can (in the present study this was an arrow); reaction times should be faster if the probe is presented in the location at

which they were attending (Posner et al. 1980). Consequently, in substance-use studies, participants who are attending to the drug pictures are faster to respond to probes and an attentional bias score is calculated by subtracting reaction times to probes that replace substance-related pictures from reaction times to probes that replace neutral pictures. Visual probe tasks have consistently demonstrated attentional bias that is present in substance users, but is not seen in non-users or light users of a given drug (e.g. Bradley et al. 2003; Field et al. 2004a; Lubman et al. 2000; Townshend & Duka, 2001). Again, the reliability of the visual probe task is demonstrated by studies that administer the task on different testing sessions, and these studies suggest that the task has a high level of test-retest reliability (e.g. Field et al. 2004b).

Both of these tasks have also been used to assess attention to emotionally valenced stimuli. Previous research has shown that individuals with emotional disorders exhibit attentional bias for cues that they perceive as threatening (MacLeod et al. 1986; Mogg et al. 1995; Mogg et al. 2004), with some studies finding that individuals who do not meet the diagnostic criteria for anxiety disorders may exhibit an attentional bias for cues that they perceive to be threatening (e.g. Fox et al. 2001). As cocaine use has been associated with sub-clinical anxiety and depression in young non-treatment-seeking users (Herrrero et al. 2008), users of cocaine in the present study may demonstrate differences in attentional bias that are not primarily due to the increased incentive salience of the stimuli. Consequently in the present study state anxiety, arousal and depression were measured so that their influence on attentional bias could be statistically controlled.

The present study sought to assess attention to cocaine related cues following ingestion of a moderate dose of alcohol (0.4g/kg). It was hypothesised that there would be a significant difference in attentional bias for cocaine related cues in regular cocaine users compared to nonusers, but that within cocaine users, the magnitude of attentional bias would

be significantly greater following administration of alcohol compared to placebo Furthermore, it was also hypothesised that alcohol would increase subjective craving for cocaine in the cocaine user group.

Method

Design

A 2x2 factorial between groups design was implemented with group (2 levels, cocaine user vs. nonuser) as the grouping variable and preload type (2 levels, alcohol vs. placebo) as the independent variable. Dependent measures for the main analyses were the attentional bias scores on the visual probe and modified Stroop tasks.

Participants

32 cocaine users (mean age 19.70, 15 male) and 40 nonusers (mean age 19.78, 19 male) were recruited from the student population at Liverpool John Moores University and the general population in the surrounding area (see Table 2 for participant characteristics). For both groups the inclusion criteria were fluency in written and spoken English; normal or corrected to normal colour vision; consumption of at least 10 units of alcohol in a typical week in the previous month; consumption of 4 units of alcohol in one session in the last month; weight of at least 50kg (females) or 60kg (males); absence of alcohol use disorder; abstention from alcohol use on the day of testing (verified by use of an alcometer (AL6000 Prestige)).

In addition, the cocaine user group was required to have used at least 1g of cocaine in the previous month (1g is a typical UK 'deal'). Non-cocaine users had not used an illegal stimulant drug in their lifetime (e.g. cocaine, amphetamine, ecstasy), but may have used other illicit drugs. The study was approved by the Liverpool John Moores University Research Ethics Committee.

<u>Materials</u>

Desire for Alcohol Questionnaire (DAQ)- Love et al. (1998)

Desires for alcohol were measured using the DAQ- brief version, a 14 item questionnaire assessing intentions/urges to drink at that time. Each item is scored on a 7-point Likert scale from 1 (strongly disagree) to 7 (strongly agree). The DAQ contains 4 scales: Positive and Negative Reinforcement, Strong Desires and Intentions, Mild Desires and Intentions and Control Over Drinking (items on this scale were reverse scored). A total composite score was used in the analyses. In the current sample, the DAQ showed good test-retest reliability with strong correlations between Time 1 and 2 (Pearson's r = 0.78), Time 2 and 3 (r = 0.86) and Time1 and 3 (r = 0.80). Internal consistency was also good, Cronbach's alpha = 0.88.

Cocaine Craving Questionnaire (CCQ) Tiffany et al. (1993)

The CCQ is a multidimensional questionnaire consisting of 45 items relating to an individual's desire to use cocaine. Items are scored on a 7-point Likert scale ranging from Strongly Disagree to Strongly Agree. The CCQ contains 5 subscales (each containing 9 items) measuring Desire to use Cocaine, Intention and Planning to use Cocaine, Anticipation of Positive Outcome, Anticipation of Relief from Withdrawal or Dysphoria & Lack of Control Over Use. A total composite score was used in the analyses. In the current sample, the CCQ showed good test-retest reliability with strong correlations between Time 1 and 2 (Pearson's r = 0.84), Time 2 and 3 (r = 0.91) and Time1 and 3 (r = 0.84). Internal consistency was also good, Cronbach's alpha = 0.88.

Alcohol Expectancy Questionnaire (AEQ- Fromme et al. 1993)

The AEQ is a 40-item questionnaire based on the Comprehensive Effects of Alcohol Questionnaire (Fromme et al. 1993). It assesses expected positive and negative effects of

drinking ("Drinking makes me feel flushed", "I'm more clumsy after I drink") and is comprised of 8 scales: Global Positive Effects, Social and Physical Pleasure, Social Expressiveness, Sexual Enhancement, Power and Aggression, Tension Reduction and Relaxation, Cognitive and Physical Impairment and Careless Unconcern. Participants respond Agree or Disagree to the items, and a score for each scale is calculated by summing the number of "agree" responses in that scale. In the present study, the AEQ showed high internal consistency with a Cronbach's alpha of 0.92.

Stimulant Effect Expectancy Questionnaire- Short Form (SEEQ, Aarons et al. 2001)

The SEEQ-Short contains 46 items relating to one's beliefs about the effects of stimulants e.g. "stimulants make me less hungry", "stimulants make me shaky". Items are on a 5-point Likert scale ranging from Strongly Disagree to Strongly Agree and 5 subscales are calculated: Global Positive Effects, Global Negative Effects, General Arousal, Anxiety and Relaxation and Tension Reduction. In the present study, the SEEQ showed good internal consistency with a Cronbach's alpha of 0.83.

The UWIST Mood Adjective Checklist (UMACL- Matthews et al. 1994)

This is an 18 item checklist, and participants have to indicate how they are feeling at the time of testing on a 5–point Likert scale ranging from "not at all" to "extremely". The test yields scores for State Anxiety (items include: tense, calm), Arousal (items include: fatigued, alert) and Depressed Mood (items include: sad, cheerful). A total score for each scale is calculated by summing the component responses, taking account of reverse scored items, thus a high score (above the midpoint of 18) is indicative of higher levels of anxiety, arousal and depression. Internal consistency for Depressed mood (Cronbach's $\alpha = 0.74$), arousal (Cronbach's $\alpha = 0.79$) and anxiety (Cronbach's $\alpha = 0.80$) were all adequate.

Subjective Intoxication- Addiction Research Centre Inventory (ARCI-Haertzen 1974)

The ARCI is a questionnaire based on experienced substance users' descriptions of intoxication. There are 15-items related to alcohol intoxication (e.g. "My Speech is Slurred") that are answered in a True/False format. A total score for subjective alcohol intoxication is calculated by summing the responses to all 15 items, with a higher score indicating higher subjective alcohol intoxication. In the present study, the ARCI showed adequate internal consistency with a Cronbach's alpha of 0.76.

Substance use

Substance use history was assessed with an inventory previously used in published research from our group (e.g. Sumnall et al 2004). Questions assess prevalence and frequency of use of a range of legal and illegal substance.

Alcohol Use Disorders Identification Test (AUDIT: Saunders et al. 1993)

The AUDIT consists of 10 Likert scaled items and is used to identify the signs of hazardous drinking, asking questions on the frequency and intensity of recent alcohol use. A score of greater than 8 indicates a strong likelihood of hazardous or harmful alcohol consumption. In the present study, the AUDIT showed good internal consistency with a Cronbach's alpha of 0.81.

Modified Stroop

A modified Stroop task with three conditions was used in this research: congruent colour words (with all colour words written in their congruent colour e.g. Green written in green ink; this condition served as a baseline measure of stimulus processing), colour animal words (semantically-related control words e.g. dog, monkey) and colour cocaine-related words (culturally relevant cocaine related words e.g. line, snort). The culturally relevant cocaine

words were provided by recreational cocaine users who did not take part in the present study. Each word was rated by a panel of experts and the most relevant words were chosen. Each condition consisted of 25 words in 5 rows of 5 words, presented on a laminated card on a grey background. The colours used for each word list were the same (although colours did not appear in the same location on each card): RED (4), GREEN (4), YELLOW (4), BLUE (4), WHITE (4), PINK (3) and ORANGE (2). The dependent measure for each trial was the time taken to read aloud the colour in which all 25 words were printed[1]. See Table 1 for full list of cocaine and animal words used. Colour naming times for each of the 3 lists were recorded using a stopwatch, and the experimenter was unaware of the user status of participants. The presentation order of the three Stroop cards was counterbalanced across participants and a bias score was calculated by subtracting the colour naming time for the Cocaine Stroop from the colour naming for the Animal Stroop, thus a positive score is indicative of attentional bias for cocaine stimuli.

Insert Table 1 About Here

Visual Probe Task

Stimuli

The stimuli for the visual probe task were ten pairs of images: one cocaine related image, and a corresponding neutral image. Each cocaine related image depicted cocaine (e.g. lines of cocaine), cocaine paraphernalia (e.g. a rolled bank note with mirror and razor), or a close up of an individual apparently using cocaine. Each cocaine related image was matched with a neutral image which was as perceptually similar to the cocaine image as possible, but did not have any cocaine content (for example 3 parallel pencils vs. 3 parallel lines of cocaine).

Visual Probe Procedure

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[1] Only 2 participants made any errors on this task so errors were not analysed separately.

This task was used to assess attentional bias for cocaine related pictures. At the beginning of each trial, participants were presented with a central fixation cross (500 ms) followed by a pair of pictures (500ms). After this, a visual probe (an arrow pointing up or down) was presented in the location previously occupied by one of the pictures. Participants were required to rapidly identify the orientation of the arrow probe (up or down) by pressing the appropriate arrow on the keyboard as quickly as possible. The inter-trial interval was set at 500 ms. Participants received 10 practice trials in which neutral picture pairs were presented, before completing the main block of trials. After two buffer trials (in which neutral picture pairs were again presented), the main block of the task consisted of 80 experimental trials. Each of the 10 cocaine – control picture pairs were presented 8 times (4 times on right and four times on left of screen). Visual probes replaced cocaine-related and control pictures with equal frequency, and there were an equal number of up and down arrow probes. Presentation of trials was randomised for each participant. A score for attentional bias was calculated for each participant by subtracting reaction times (RTs) to probes that replaced cocaine pictures from RTs to probes that replaced neutral pictures. Thus a positive score indicates attentional bias for cocaine pictures and a negative score indicates avoidance of cocaine pictures. To assess the reliability of the visual probe task in the present study, we calculated split-half reliability for the congruent (probe replaces a cocaine-related picture) and incongruent (probe replaces a neutral picture) trials. Both trial types had high reliability with Spearman-Brown coefficients of 0.97 and 0.95 respectively.

Procedure

Testing took place in the Psychology laboratories at Liverpool John Moores University. Participants were tested between midday and 6pm. They were instructed not to drink alcohol on the day of testing and to eat a light meal about one hour before participation. On entering the lab, participants gave informed consent, were weighed and were breathalysed (all

participants had a breath alcohol level of zero at the beginning of the study). Participants then completed the drug use questionnaire, the AUDIT, the AEQ, SEEQ, DAQ (Time 1), CCQ (Time 1), UWIST Mood Adjective Checklist and the Attitude to Drugs Questionnaire. Participants then ingested either the alcohol or placebo drink. Drink administrations were double-blind. Participants who received the alcohol drink ingested 0.4g/kg alcohol as a vodka and tonic water mixture (with a maximum of 100ml vodka). The drink was made up of one part vodka, 3 parts tonic water and several drops of Tabasco sauce (see Schoenmakers et al. 2008). Participants who received placebo ingested the same volume of tonic and Tabasco, with vodka wiped around the rim of the glass. Participants were asked to consume their beverage over 5 minutes in the lab and then waited in the lab for 10 minutes while the alcohol was absorbed. Participants tolerated the mixture well.

Following this, participants completed the ARCI, the DAQ (Time 2), the CCQ (Time 2) and an experimenter again performed a breathalyser reading (Time 2). Participants then completed the Visual Probe task and Modified Stroop tasks. The order of these two assessments was counterbalanced.

Following completion of these tasks, participants again completed the DAQ and CCQ (Time 3), and an experimenter again breathalysed them. After administration of the alcohol beverage, BAL rose to 0.12 mg% (Time 2- Ten minutes after beverage) and remained elevated at 0.12 mg% at Time 3 (Thirty minutes after beverage administration). Participants were advised to remain in the lab until they were below the legal limit to drive (35µg/ml in the UK), and were also advised not to drive or ride a bike for the rest of the day. Participants received a £10 shopping voucher as compensation for their time.

Analyses

Mixed ANOVAs were used to analyse group differences in craving with time point of CCQ and DAQ administration (3 levels in each case) as the within groups independent

variable and group and drink type as the between groups variables. A 2x2 ANOVA was used to analyse the Visual Probe Scores with Drink Type and Group as the between groups variables and attentional bias score as the dependent variable. For the Modified Stroop a 2x2 ANOVA was used with Group and Drink Type as the between groups variables and Stroop bias score as the dependent variable. All analyses were conducted using SPSS (v17), significance was set at $p < 0.05$.

Participant characteristics

The means and standard deviations for the background variables are set out in Table 2. Two cocaine user participants were excluded from all analyses due to extreme outlying scores on the visual probe task. For AUDIT scores and age, 2x2 ANOVAs were used with Drink Type and Group as the between groups variables. Three separate MANOVAs were used for the measures of state Anxiety, Arousal and Depression, SEEQ scales and AEQ scales (again with Group and Drink Type as the between group variables). For age and state mood scores the effects of Group, Drink Type and the Group x Drink Type interactions were all non-significant (F<1 in all cases) so they are not discussed further. For AUDIT scores there was a main effect of Group $F(1,66) = 15.73$, $p<.001$ indicating that the cocaine user group had significantly higher scores than the nonusers. Therefore, we included AUDIT score as a covariate in all subsequent analyses. The effects of Drink Type and the Group x Drink Type interaction were non-significant. On the SEEQ there was a multivariate main effect of group $F(5,60) = 6.46$, $p<.001$, although effects of Drink Type and the Group x Drink Type interactions were non-significant. On the AEQ, the multivariate main effects were non-significant.

Insert Table 2 about here

Indices of substance use for all conditions are shown in Table 3. The cocaine users reported regular use of a range of other illicit drugs: cannabis, ecstasy, ketamine and amyl nitrate poppers. In the nonuser group this was restricted to the use of cannabis and amyl nitrate poppers.

Insert Table 3 About Here

Subjective craving, intoxication and Breath Alcohol Levels

Measures for cocaine and alcohol craving at the 3 timepoints are displayed in Table 4. A repeated measures factorial ANOVA was used to analyse the data with Time as the within groups variable and Group (Cocaine vs. Nonuser) and Drink Type (Alcohol vs. Placebo) as the between groups variables. For the DAQ, there was a significant main effect of time $(F(2,64) = 3.08, P<.05)$, indicating that regardless of group and Drink Type, DAQ scores tended to be higher at Time 2 compared to the other timepoints. The Time x group, Time x Drink Type and Time x Group x Drink Type interactions were non significant. The effect of Group was significant, $F(1,65) = 4.28, p<.05$ indicating higher craving in cocaine users. Group differences due to Drink Type, and the Group x Drink Type interaction were non-significant (F<1 in both cases).

Insert Table 4 About Here

Scores for the CCQ were analysed in the same manner as the DAQ. Similarly, there was a significant main effect of Time indicating that cocaine craving changed over Time regardless of group or Drink Type, $F(2,62) = 5.38, p<.01$. The Time x Group interaction was also significant, $F(2,62) = 3.71, p<.05$ indicating that Cocaine Users exhibit a significant increase in subjective craving over time compared to nonusers. The Time x Drink Type and Time x Group x Drink Type interactions were non significant. There was a significant effect of Group, $F(1,63) = 20.66, p<.001$ indicating that the cocaine users exhibited higher craving than nonusers at all timepoints. However, the effect of Drink Type and the Group x Drink Type interaction were non-significant (F<1 in both cases).

BALs are reported in Table 2. BAL at times 2 & 3 were analysed using a mixed ANOVA with BAL time within groups and Group and Drink Type between groups. The effects of Group were significant $F(1,66) = 5.82, p<.05$, as were the effects of Drink Type

F(1,66) = 273.50, p<.0001. The Group x Drink Type interaction was also significant F(1,66) = 5.82, p<.05 indicating that cocaine users who received alcohol had higher BALs than nonusers who received alcohol. For subjective intoxication (ARCI), there was a main effect of Drink Type F(1,66) = 6.77, p<.01 indicating that those who ingested alcohol reported greater subjective drunkenness. The effect of Group and the Group x Drink Type interactions were non-significant.

Insert Figures 1 & 2 About Here

Attentional bias

Bias scores for the visual probe task are shown in Figure 1. Main effects of Group and Drink Type were non-significant. However the Group x Drink Type interaction was significant F(1,65) = 4.31, p<.05 (homogeneity of regression was achieved p>.05 for the covariate interactions). Post-Hoc t-tests showed that there was a significant difference between cocaine users who received alcohol and placebo t(28) = -2.27, p<.05. All other post-hoc t-test comparisons were non-significant.

Bias scores for the modified Stroop are shown in Figure 2. For the colour word Stroop, all groups performed similarly and there was no effect of Group or Drink Type and the Group x Drink Type interaction was non-significant (F<1 in all cases). Again, homogeneity of regression was achieved with respect to the covariate interactions p>.05). Subsequent analyses on the visual probe and Stroop including Gender as a covariate did not have an effect so gender is not discussed further.

Discussion

The results of the present study show that regular non treatment seeking cocaine users exhibited significant attentional bias for cocaine cues following pre-treatment with alcohol in a visual probe task, but not a modified Stroop. Craving for cocaine also increased as a function of Group and Time, showing that individuals in the cocaine group had higher craving than those in the nonuser group, and that cocaine users had significant increases in craving over the course of the experiment, although contrary to expectations, administration of alcohol did not increase alcohol craving.

The increase in attentional bias on the visual probe task, in the cocaine users pretreated with alcohol is in line with our predictions. This is also supportive of previous research that alcohol increases attention to alcohol and tobacco cues in regular users of alcohol and tobacco, respectively (Field et al. 2005; Duka & Townshend, 2004; Schoenmakers et al. 2008). However, there is little support for attentional bias for cocaine cues in cocaine users in the whole sample, indeed inspection of Figure 1 shows that cocaine users who received placebo showed less attentional bias for the cocaine cues than all other 3 groups (as indexed by the large negative score). It is unclear why there was no main effect of group on visual probe performance, especially in light of previous research suggesting that cocaine users will show attentional bias for cocaine-related cues when tested sober (Franken et al. 2000; Hester et al. 2006; Rosse et al.1997). As there was a significant difference between the cocaine users who received alcohol and placebo, with alcohol priming increasing bias for cocaine stimuli, it may be that in recreational non-dependent cocaine users the presentation of cocaine stimuli alone does not elicit the attentional bias that is seen in treatment-seeking users. However following priming with alcohol attentional bias emerges due to alcohol activating the mesolimbic dopamine system.

Responding on the modified Stroop task was not affected by alcohol administration and there were no differences between cocaine users and non-users. Therefore, the results from the visual probe and modified Stroop tasks were difficult to reconcile. While both tasks were employed to measure attentional bias, there is evidence to suggest that while the visual probe task measures a bias in visuo-spatial attention (Field, 2006), the Stroop may measure a variety of cognitive processes including inhibition, generic cognitive slowing, and distraction (see Field & Cox, 2008 for review). Therefore, one plausible explanation for our results is that alcohol administration may only potentiate biases in visuo-spatial attention for drug-related cues (as measured by the visual probe task), but it may not affect the various cognitive processes that are measured by the Stroop task.

We postulated that increased attentional bias would be greatest in the cocaine users pretreated with alcohol, and the hypothesis was supported. As discussed in the introduction, there are a number of plausible explanations for this effect. For example, if alcohol and cocaine have been used together in the past, the interoceptive effects of alcohol may function as a conditioned stimulus that leads to exaggerated responses to cocaine-related cues. Alternatively, alcohol's effects on the mesolimbic dopamine system might increase the salience of cocaine-related cues in the environment, but only among individuals in whom cocaine-related cues already have incentive properties (i.e. experienced cocaine users). Unfortunately, the nature of our experimental design means that we cannot distinguish between these different explanations, although future work could make use of alternative methodologies (e.g. recording of levels of activation in the mesolimbic system) in order to explicitly test some of these explanations. It also remains a possibility that the increase in BAL in the cocaine users compared to the nonusers could have further potentiated this effect, and we will need to investigate this further.

Craving for alcohol was elevated at Time 2 (10 minutes after beverage administration, and immediately prior to the attentional bias measures) in all groups. In addition, Cocaine users also exhibited elevated cocaine craving at Time 2 compared to nonusers. Surprisingly there was no effect of alcohol administration on craving for alcohol. Increases in subjective craving in social drinkers following priming with alcohol are a robust finding (Field et al. 2008), however not all studies have found this. Duka & Townshend (2004) found no effect of low or high dose alcohol administration on any subscale of the DAQ. Similarly, Schulze & Jones (1999) found a low dose prime did not increase scores on the DAQ.

There were a number of limitations of the present study. We had to rely on participants' self-reports of previous cocaine and other drug use. All cocaine users reported using at least 1g of cocaine in the month prior to testing, and regular use over the last year. Nonetheless it remains a possibility that individuals were unable to accurately recall this information. In addition, the mean AUDIT scores were high, and all groups scored above the cut off for hazardous drinking. However, this is not an uncommon finding in a University sample where excessive drinking can be the norm (e.g. Kypri et al. 2009), or indeed in adolescents (Shields et al. 2004; Thomas & McCambridge, 2008), and no participant in the present sample reported currently seeking support for an alcohol use disorder. The cocaine users did have significantly higher scores on the AUDIT than the nonusers indicating hazardous drinking, although we maintain that these scores are not atypical in students. Furthermore, we statistically controlled for these group differences in AUDIT scores before conducting our primary analyses, and this did not affect any of the results reported here. It is also a possibility that administration of craving and expectancy questionnaires could have influenced the results in the present study. As we wished to ascertain craving before beverage administration, the questionnaires were administered before the attentional bias measures, and it remains a possibility that the cocaine related questions contributed to the increased

attentional bias that was seen after alcohol administration in the visual probe task. However, this is unlikely as the increase in attentional bias was not seen in the cocaine users who received placebo, and there were no increases in attentional bias on the modified Stroop, even though all participants completed the measures prior to these tasks. Finally, as noted above previous research in users of nicotine, cannabis and heroin has used heavy users or dependent users. It is likely that individuals who are dependent on a substance would exhibit increased attentional bias for the cues as they have increased incentive salience. Therefore future research could focus on the effects of alcohol preload in dependent cocaine users.

In summary, the present study found increased attentional bias for cocaine cues following preload with alcohol in regular cocaine users using a visual probe task, although this was not found using a modified Stroop. These biases are consistent with the incentive salience model of drug use and addiction, and future research should investigate whether such cues may predispose individuals to heavy use and dependence.

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Table 1

Stimuli for Animal and Cocaine Stroop

Animal Words	Cocaine Words
CAT	SNORT
MONKEY	COKE
GIRAFFE	LINE
OWL	CHARLIE
TIGER	FREEBASE
MEERCAT	POWDER
SEAL	GRAM
PENGUIN	CRACK
LION	CUT
DOG	MIRROR
GORILLA	RAZOR
FOX	SNOW
HEDGEHOG	COCA
HORSE	NOSE
EAGLE	CARD
WHALE	SNIFF
DEER	BLOW
CHEETAH	ROCK
WOLF	COCAINE
MOUSE	BANK NOTE
RABBIT	COLUMBIAN
DUCK	BIG C
ELEPHANT	NOSE CANDY
DONKEY	HIGH
PARROT	EUPHORIA

Table 2 Background variables

	Cocaine Users				Nonusers			
	Placebo		Alcohol		Placebo		Alcohol	
	N=17; 6 male		N=13; 7 male		N=20; 7 male		N=20; 12 male	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age	19.29	4.78	20.23	2.08	19.59	1.37	20.00	1.88
AEQ								
Global Positive	1.69	1.14	1.92	1.55	1.45	1.05	0.94	1.26
Social & Physical Pleasure	4.38	0.89	3.92	1.61	4.15	1.14	4.06	0.80
Social Expressiveness	4.44	0.96	4.46	0.88	4.65	0.49	4.28	0.75
Sexual Enhancement	2.63	1.67	3.15	1.72	3.05	1.50	2.00	1.33
Power & Aggression	3.63	1.71	4.15	1.41	3.35	1.66	2.83	1.34
Tension reduction & relaxation	3.94	1.53	3.54	1.27	3.75	1.45	3.17	1.10
Cognitive & Physical Impairment	4.00	1.37	4.46	1.20	3.85	1.31	4.28	.89
Careless Unconcern	3.38	0.62	3.69	0.63	4.00	2.66	2.78	1.06
SEEQ								
Global Positive	28.06	5.63	28.75	4.11	28.90	4.92	28.94	5.04
Global Negative	48.47	9.90	51.00	9.38	54.05	7.21	54.17	5.37
General Arousal**	34.41	3.66	33.50	4.46	30.00	5.63	31.39	4.88
Anxiety	26.59	5.33	24.92	3.12	25.29	3.51	26.28	4.34
Relaxation & Tension Reduction	7.82	2.65	8.50	1.98	8.86	1.74	8.39	2.15
State Arousal	18.88	4.21	19.38	3.86	20.35	4.15	20.00	3.96
State Anxiety	12.41	3.24	11.38	3.85	11.68	2.92	12.06	3.08
State Depression	12.35	2.73	12.00	3.00	11.68	2.68	12.28	2.79
BAL2 (mg%)	0	0	0.14	0.05	0	0	0.11	0.05
BAL3 (mg%)	0	0	0.14	0.04	0	0	0.10	0.05
ARCI*	3.17	2.18	5.08	2.21	3.82	2.04	4.61	2.12
AUDIT**	19.52	5.67	17.62	5.80	13.36	7.01	11.94	5.60

* Difference significant at p<.01

** Difference significant at p<.001

Table 3: Drug Use Indices for participants reporting previous drug use

| Days Used in Last Month | Cocaine Users | | | | | | Nonusers | | | | | |
| | Placebo | | | Alcohol | | | Placebo | | | Alcohol | | |
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Amphetamine	2.00	0.82	4	3.00	2.83	2	-	-	-	-	-	-
Ecstasy	3.56	3.13	9	3.67	4.58	9	-	-	-	-	-	-
Cocaine	3.36	3.32	11	.364	3.98	11	-	-	-	-	-	-
Cannabis	7.55	8.54	11	11.09	9.61	11	1.29	0.49	7	5.67	9.52	6
Alcohol	9.12	5.50	17	14.31	14.87	13	9.95	5.40	20	11.53	9.03	17
Cigarettes	21.92	11.40	12	17.00	11.99	8	3.11	2.98	9	11.50	12.80	8
Mushrooms	1	0	4	3	-	1	-	-	-	1	-	1
Ketamine	1.33	0.58	3	3.00	3.496	3	-	-	-	-	-	-
Poppers	1.57	0.98	7	4.67	7.53	6	2.17	1.17	6	3.50	1.91	4
Days since last use												
Amphetamine	8.00	8.49	2	5.80	6.36	2	-	-	-	-	-	-
Ecstasy	8.50	7.55	6	13.83	9.13	6	-	-	-	-	-	-
Cocaine	5.29	4.64	7	13.25	10.58	8	-	-	-	-	-	-
Cannabis	10.60	12.42	5	7.50	10.26	10	12.33	7.77	3	7.50	9.19	2
Alcohol	4.41	6.36	17	4.18	4.94	11	6.19	6.30	18	5.75	6.83	16

Table 4: Scores for cocaine and alcohol craving measures

| | Cocaine Users | | | | Nonusers | | | |
| | Placebo | | Alcohol | | Placebo | | Alcohol | |
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
DAQ Time 1	37.53	13.17	38.23	15.51	34.19	10.67	32.22	19.96
DAQ Time 2	39.18	14.22	46.00	22.68	35.67	14.20	34.89	18.81
DAQ Time 3	39.94	15.28	44.62	20.66	33.48	13.04	31.89	15.08
CCQ Time 1	114.94	34.93	106.83	23.17	87.67	23.99	86.39	21.53
CCQ Time 2	112.69	42.37	124.83	37.24	85.48	24.40	90.50	24.14
CCQ Time 3	126.81	41.62	123.83	31.58	84.43	28.04	92.67	27.71

Figure 1

Mean attentional Bias (ms) for cocaine-related pictures in the visual probe task by Group.

CP = Cocaine Placebo
CA = Cocaine Alcohol
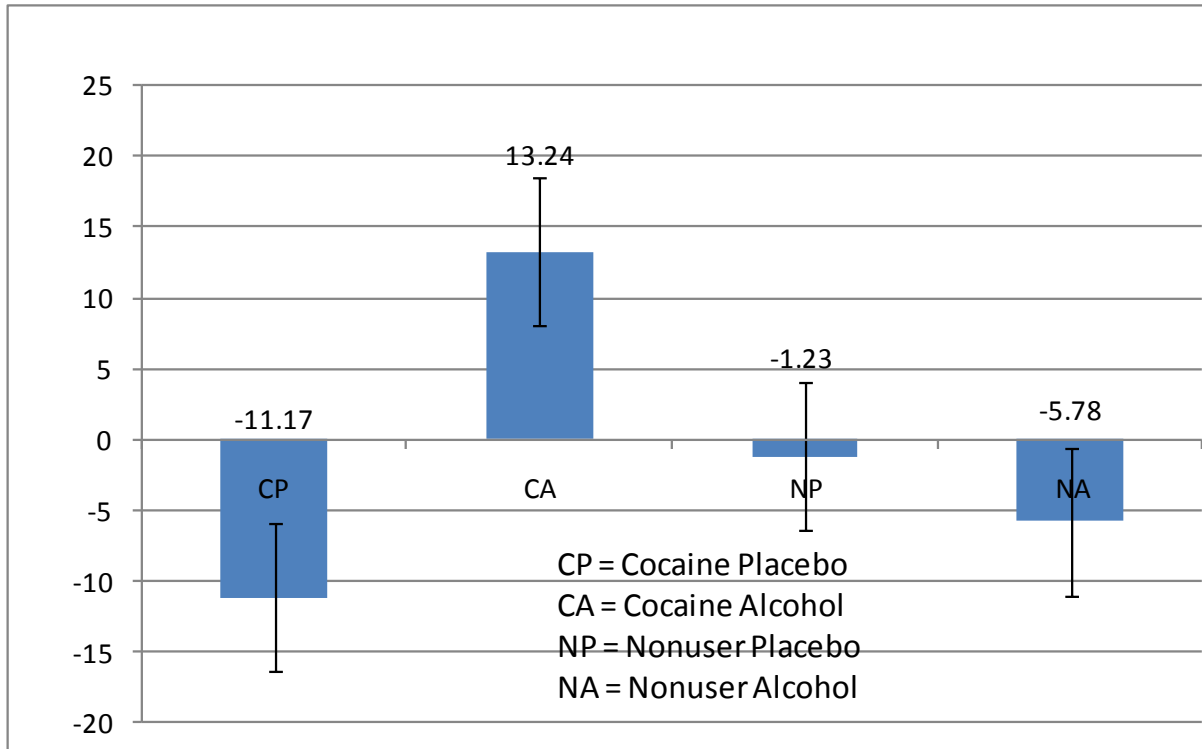NP = Nonuser Placebo
NA = Nonuser Alcohol

Figure 2

Mean attentional Bias (seconds) for cocaine related words in the modified Stroop by Group.