Psychological Medicine, Page 1 of 11. © Cambridge University Press 2011
doi:10.1017/S0033291711001139

ORIGINAL ARTICLE

Drug cue induced overshadowing: selective disruption of natural reward processing by cigarette cues amongst abstinent but not satiated smokers

T. P. Freeman[1]*, C. J. A. Morgan[1], T. Beesley[2] and H. V. Curran[1]

[1] *Clinical Psychopharmacology Unit, Clinical Health Psychology, University College London, London, UK*
[2] *Division of Psychology and Language Sciences, University College London, London, UK*

Background. Addicts show both reward processing deficits and increased salience attribution to drug cues. However, no study to date has demonstrated that salience attribution to drug cues can directly modulate inferences of reward value to non-drug cues. Associative learning depends on salience: a more salient predictor of an outcome will 'overshadow' a less salient predictor of the same outcome. Similarly, blocking, a demonstration that learning depends on prediction error, can be influenced by the salience of the cues employed.

Method. This study investigated whether salient drug cues might interact with neutral cues predicting financial reward in an associative learning task indexing blocking and overshadowing in satiated smokers ($n=24$), abstaining smokers ($n=24$) and non-smoking controls ($n=24$). Attentional bias towards drug cues, craving and expired CO were also indexed.

Results. Abstaining smokers showed drug cue induced overshadowing, attributing higher reward value to drug cues than to neutral cues that were equally predictive of reward. Overshadowing was positively correlated with expired CO levels, which, in turn, were correlated with craving in abstainers. An automatic attentional bias towards cigarette cues was found in abstainers only.

Conclusions. These findings provide the first evidence that drug cues interact with reward processing in a drug dependent population.

Received 23 March 2011; Revised 24 May 2011; Accepted 25 May 2011

Key words: Addiction, associative learning, attention, prediction error, reward, tobacco.

Introduction

Addiction is characterized by a lack of sensitivity to natural rewards and increased salience attribution to cues that predict drug reward or 'drug cues' (Goldstein & Volkow, 2002). Relapses following abstention are often attributed to drug cues (Shiffman *et al*. 1996), as these carry incentive salience (Robinson & Berridge, 1993) and bias attention (Field & Cox, 2008), an effect modestly related to increases in subjective craving (Field *et al*. 2009). However, an interaction between alternative reward processing and salience attribution to drug cues has not yet been demonstrated in addicted individuals. If the presence or absence of salient drug cues in an addict's environment could influence their ability to make inferences about the value of alternative rewards, this could impact dramatically on their choice to continue self-administering that drug or to pursue motivationally blunted alternatives and escape a cycle of addictive behaviour through prolonged abstinence.

Compared with satiation, nicotine abstinence disrupts reward processing according to effort-related speeding on a behavioural task (e.g. Al-Adawi & Powell, 1997; Powell *et al*. 2002*a*) and an increased tendency to discount financial rewards that are temporally delayed (Mitchell, 2004; Field *et al*. 2006). In addition, abstinence can exacerbate the attention-grabbing properties of drug-related words or pictures (e.g. Gross *et al*. 1993; Field *et al*. 2004; also see Mogg & Bradley, 2002) and attenuate the attention-grabbing properties of motivationally important words (Powell *et al*. 2002*b*). As such, we hypothesized that salient drug cues would interfere with smokers' ability to make accurate inferences about financial value during abstinence, but not satiation. In this study, we used previously established associative learning processes (overshadowing, blocking) to investigate this hypothesis since they have been shown to occur in cues

* Address for correspondence: T. P. Freeman, B.Sc., Clinical Psychopharmacology Unit, Clinical Health Psychology, University College London, Gower St, London WC1E 6BT, UK.
(Email: tom.freeman@ucl.ac.uk)

predicting rewarding outcomes and are highly dependent on the salience of the cues employed in the task.

Overshadowing (Mackintosh, 1976) occurs when one cue prevents a simultaneously presented cue from being associated with an outcome. For example, if a health inspector was investigating cases of food poisoning and noted that somebody had become ill after eating two foods together (e.g. ham and egg), they might consider each food to be equally important in causing the illness. Alternatively, if one food were particularly unusual or salient (e.g. ostrich egg) it could overshadow the other food (ham) and become judged as more important in causing the illness. Overshadowing has been shown to be highly dependent on cue salience. For example, in humans a visually salient cue will overshadow a less salient cue in predicting an outcome (Denton & Kruschke, 2006; Heckler *et al*. 2006). Overshadowing is thought to be caused by changes in selective attention rather than the predictive nature of cues, since it can take place after a single training conditioning trial (Mackintosh & Reese, 1979).

Blocking (Kamin, 1969) occurs when prior training that a cue predicts an outcome (A→outcome) interferes with learning that a new cue (B) predicts the same outcome when both cues are presented together (A + B→outcome). For example, a health inspector might have records that a patient became ill after eating (i) ham alone and later (ii) ham and egg together. In this case, learning that the egg was responsible for the illness would be blocked compared with a scenario in which the first record was omitted. Blocking has been used as an example of prediction error learning, since an outcome that is already predicted (no prediction error) can prevent further learning about that outcome (Rescorla & Wagner, 1972). However, salience can resemble validity in associative learning (Hall *et al*. 1977) and visual salience can 'protect' items from being blocked themselves or, conversely, can act to increase the magnitude of blocking when they block a less salient item (Denton & Kruschke, 2006; Heckler *et al*. 2006). These effects are likely to be caused by changes in selective attention, since blocked cues are attended to less than control cues during learning according to indices of eye tracking (Kruschke *et al*. 2005; Wills *et al*. 2007; Beesley & Le Pelley, 2011).

In line with the role of salience in associative learning, we predicted that, in abstinent smokers, smoking-related cues would overshadow neutral cues predicting the same financial reward and that blocking would be increased when a smoking cue blocked a neutral cue, but decreased when a neutral cue blocked a drug cue. Additional measures included a dot probe task to index attentional bias and subjective measures of craving and dependence.

Method

Design and participants

A between-subject design compared 24 controls (reporting never to have smoked tobacco more than once per month during lifetime), 24 satiated smokers ('smokers') and 24 smokers instructed to abstain for at least 12 h prior to testing ('abstainers'). Single blind conditions were used, such that the experimenter who administered the test battery was unaware of satiated/abstaining group membership, which was randomly assigned. Inclusion criteria for both smoking groups were reporting to: (i) have consumed at least 10 cigarettes per day for at least 1 year; (ii) smoke a first cigarette within 1 h of waking; (iii) not currently be using nicotine replacement therapy. Inclusion criteria for all three groups were: (i) normal or corrected to normal vision; (ii) fluent spoken English. Exclusion criteria for all three groups were a lifetime diagnosis of: (i) a learning impairment; (ii) a mental health problem; (iii) a substance abuse problem. All participants provided written, witnessed, informed consent. This study was approved by the UCL Psychology and Language Sciences Ethics Committee.

Drug Cue Reward Prediction Error Task (*DCRPET*)

This was a computer-based task. Participants were asked to imagine that they were a cleaner and had to learn to place household items (pictures of standard household objects or smoking items) in either a 'red room' or a 'green room' (trial structure is shown in Fig. 1). Correct choices were rewarded with money that accumulated during the course of the task. The 'cleaning' scenario was chosen in order to create a plausible framework in which both smoking and neutral items could predict reward, while avoiding any connotations of health or addiction (e.g. allergic reactions resulting from drugs; Matute *et al*. 1996). Stimuli were colour photographs of household items (12 neutral items, e.g. hammer, book, desk light, shaver) and four smoking items (cigarette pack, single cigarette, ashtray, lighter), all chosen to be white, grey or silver in colour in order to control for perceptual salience. Each time the experiment was run, these items were randomly assigned to the 12 neutral and four smoking cues used in the DCRPET (task design shown in Table 1).

Trials were randomized within each of six blocks per training stage. Items were presented either on their own or in pairs (pairs were counterbalanced for left/right display position). Each trial required an alternative forced choice between the red or green room. After a choice was made, visual feedback on the screen showed the amount of money available on that

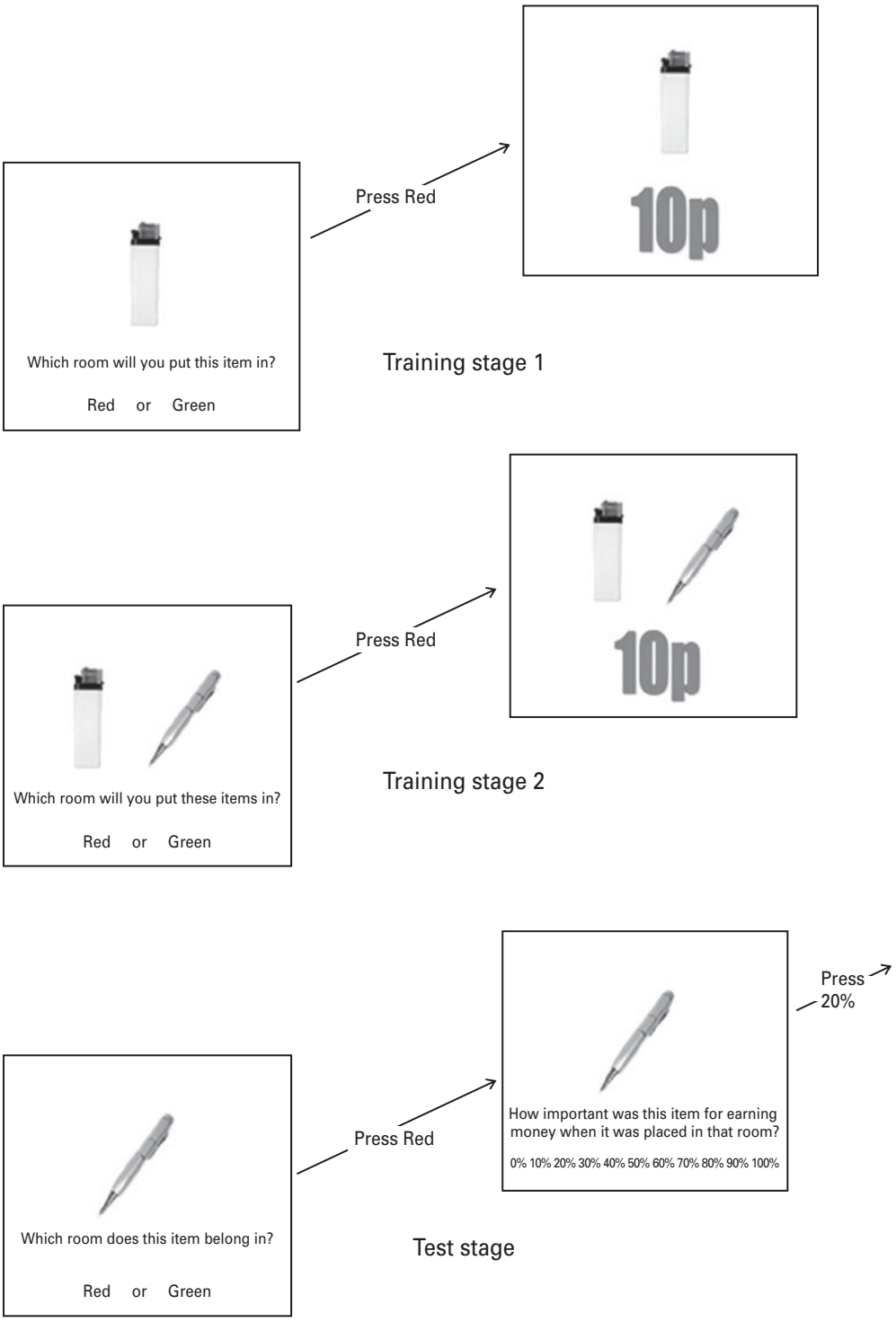

Fig. 1. Trial structure of the Drug Cue Reward Prediction Error Task. This example demonstrates a neutral cue being blocked by a drug cue. In training stage 1, it is learnt that the lighter belongs in the red room (**G**→red), and, in training stage 2, it is learnt that both the lighter and the pen belong in the red room (**G**+h→red). At the test stage, ratings of how important the pen was for earning money reflect the degree of blocking by the lighter.

trial (either 5p or 10p; financial value did not differ across items) in colour of the correct room. When responses were correct, visual feedback was accompanied by an auditory cash register 'ching-ching' sound. When choices were incorrect, the amount of money that could have been won was superimposed by a black cross and a low amplitude 'thud' sound was played.

Table 1. *Design of Drug Cue Reward Prediction Error Task*[a]

Salience manipulation	Training stage 1: 1 item predicts reward	Training stage 2: 2 items predict reward	Test stage: Which room, how important for earning money?
Overshadowing by/of a drug cue		a + **B** → Green	a **B**
Control for blocking		c + d → Red	c, d
Blocking	e → Green	e + f → Green	f
Blocking by a drug cue	**G** → Red	**G** + h → Red	h
Blocking of a drug cue	i → Red	i + **J** → Red	**J**
Filler trials	**U** → Green	**U** + v → Green	No test
	W + x → Red	–	
	y + z → Green	–	

[a] The task consisted of three stages (training stages 1 and 2 and the test stage). The correct choice of room for each trial type is shown following the arrow (red or green) and smoking cues are shown in bold upper case letters.

In the test stage, participants were instructed that they would be asked to judge individual items once for: (i) the correct room they belonged in (red/green); (ii) how important they were for earning money when placed in that room, from 0 to 100 in 10% intervals. Importance ratings had 10% added to them in order to weight 0% importance ratings towards the correct/incorrect choice. Incorrect choices were negatively scored (see Beesley & Le Pelley, 2011 for a similar method). Positive scores on this measure, therefore, reflected high perceived reward value for an item, while low or negative scores indicate that participants did not value that item in gaining reward. The scores for 'overshadowed' or 'blocked' scores can be compared with scores for 'control' cues in order to assess overshadowing and blocking: scores for overshadowed or blocked cues should be lower than those for control cues.

Dot probe

A computer-based task was used to assess attentional bias towards smoking-related stimuli. Participants were instructed that they would see two pictures on the screen, which would either be shown for a short or a long time. They were told that the pictures would disappear and an asterisk would appear either on the left or the right of the screen and that they were required to press the appropriate key (left or right) corresponding to the asterisk's location. Stimuli were colour photographs that were organized in pairs, such that 10 smoking-related items were paired with 10 neutral items matched for visual composition and complexity. Each pair of pictures was shown twice for 250 ms and twice for 2000 ms to index automatic and strategic processing respectively. Left/right screen position for the pair of pictures and the location of the probe were counterbalanced across stimulus presentation. A further 80 neutral items were used as fillers, again organized in pairs matched for perceptual characteristics, and counterbalanced for left/right screen position and probe location. A practice session of 10 neutral items was used prior to the test and a short break was provided halfway through the task.

Tobacco Craving Questionnaire-Short Form (*TCQ-SF*)

This 12 item short form of the 47 item TCQ (Heishman *et al*. 2003) has been shown to be as valid and reliable as the original scale. Each item is rated from 1 (strongly disagree) to 7 (strongly agree). Confirmatory factor analysis yields a four factor solution: emotionality; expectancy; compulsivity; purposefulness. In order to match the test battery across groups, this scale was adapted for controls by relating questions to tea/coffee drinking (e.g. 'I would be less irritable right now if I could drink a tea/coffee right now'). Data are not reported for controls.

Fagerstrom Test of Nicotine Dependence (*FTND*)

A scale of nicotine dependence shown to be a reliable indicator of smoking behaviour according to biochemical verification, the FTND (Heatherton *et al*. 1991) consists of six items scored between 0 and 3, with scores range from 0 (low dependence) to 10 (high dependence).

Wechsler Test of Adult Reading (*WTAR*)

The WTAR (Wechsler, 2001) provides an estimate of verbal IQ. Participants are required to read a list of 50 words aloud; each correct pronunciation scores 1 point.

Table 2. *Means* (S.D.) *for demographics, smoking behaviour and craving for controls* ($n=24$), *smokers* ($n=24$) *and abstainers* ($n=24$)

	Controls	Smokers	Abstainers
Gender			
Male	11	14	15
Female	13	10	9
Age	26.13 (4.97)	27.38 (6.72)	27.21 (4.38)
Years in education	18.04 (2.53)	17.21 (2.80)	16.54 (2.00)
WTAR	44.63 (4.59)	43.71 (5.74)	45.25 (4.08)
Expired CO (ppm)	1.33 (0.48)	11.79 (4.80)	3.25 (1.42)***
Years smoking		9.48 (5.89)	11.06 (4.51)
Cigarettes/day (*n*)		14.58 (4.40)	15.81 (8.30)
FTND		4.92 (1.98)	4.46 (1.84)
TCQ Total		47.63 (15.79)	55.58 (9.99)
Emotionality		10.58 (5.20)	12.25 (4.13)
Expectancy		14.04 (5.15)	18.13 (2.15)*
Compulsivity		9.71 (4.52)	10.25 (5.07)
Purposefulness		13.29 (4.41)	14.96 (2.58)

WTAR, Wechsler Test of Adult Reading; FTND, Fagerstrom Test of Nicotine Dependence; TCQ, Tobacco Craving Questionnaire.

* $p<0.05$, ** $p<0.01$, *** $p<0.001$.

Procedure

Prior to testing, an assistant used a handheld smokerlyser (Bedfont Scientific Limited, UK) to assess exhaled CO levels. A threshold of $\geqslant$11 ppm CO was used to exclude any abstainers suspected to have smoked within 12 h prior to testing, consistent with previously used cut-off criteria (e.g. Dawkins *et al*. 2007). In order to maintain blind conditions, both abstainers and smokers rinsed their mouths with mint mouthwash before testing began. Participants were then taken to a test laboratory where they completed the DCRPET, TCQ, N-back, dot probe and the WTAR. A number of other assessments were administered and will be reported elsewhere. Completion of the test battery took around 110 min.

Statistical analyses

All analyses were carried out using Statistical Package for Social Sciences (SPSS version 14; SPSS Inc., USA). One way analyses of variance (ANOVA) were used for demographic, craving and CO data (Kruskal–Wallis where data were non-parametric). Both training and test stage data from the DCRPET were analysed using repeated measures ANOVA. For analysis of blocking, the same control cue score was compared against each of the three blocked cue scores. *A priori* planned orthogonal contrasts were therefore used to compare: (i) the control cue score to all three blocked cues together; (ii) the neutral blocked cue to the other two blocked cues; (iii) the neutral cue blocked by a drug cue with the drug cue blocked by a neutral cue. Bonferroni-corrected *t* tests and non-parametric Mann–Whitney *U* tests were used to explore significant interactions or simple effects. For the dot probe task, participants' median reaction times to correctly identified probes were prepared in line with Mogg *et al*. (2007) using an inverse transformation to reduce the influence of skew and outliers (Ratcliff, 1993). Automatic and strategic attentional bias were investigated in repeated measures ANOVA models with validity (valid trial, invalid trial) as a within subject factor, with raw scores presented in tables and text for clarity.

Results

Participants and smoking behaviour (*Table 2*)

One participant in the abstainer group was excluded after providing a CO level $\geqslant$11 ppm and subsequently replaced, but all other abstainers gave levels in accordance with instructions not to smoke ($\leqslant$6 ppm). The three groups did not differ in any demographic variables and the two smoking groups did not differ in indices of smoking behaviour or level of dependence. Further, no participants in either smoking group reported current use of smoking pharmacotherapy (e.g. varenicline, bupropion). A Kruskal–Wallis test revealed group differences in expired CO ($\chi^2=56.322$, $p<0.001$). Bonferroni-corrected Mann–Whitney *U* tests (α level adjusted to 0.016) showed that CO levels were higher in smokers compared with both controls ($U_{48}=0.000$, $p<0.001$) and abstainers ($U_{48}=23.00$, $p<0.001$), and in abstainers compared with controls ($M_{48}=56.000$, $p<0.001$). Mann–Whitney *U* tests revealed that abstainers showed a trend for higher craving than smokers as indexed by total TCQ score ($U_{48}=195.500$, $p=0.055$) and significantly higher craving than smokers in the expectancy subscale of the TCQ ($U_{48}=149.500$, $p=0.004$). However, no group differences were found for the emotionality, compulsivity or purposefulness subscales.

DCRPET

Learning during training stages. Six (block; 1 to 6) $\times$ 3 (group) repeated measures ANOVA (RMANOVA) were used to assess learning to items during training stages 1 and 2. All models found significant effects of block (all *p*'s <0.001; reflecting increased accuracy over successive blocks) but no effects of group or

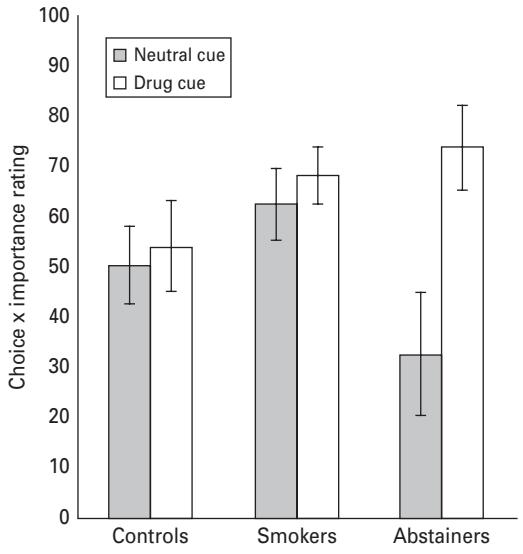

Fig. 2. Drug cue induced overshadowing according to choice × importance ratings for the neutral cue and drug cue in each group. Error bars show ±1 S.E.

interactions. Accuracy was high by block 6 (all items >85% correct), indicating that participants showed excellent learning of task contingencies.

Overshadowing (*Fig. 2*). In order to assess overshadowing, test scores for the two cues from the drug cue induced overshadowing pair were compared across groups. One smoker and one abstainer were excluded for individual scores that were >2.5 S.D. from the group mean. A 2 × 3 RMANOVA with item (neutral and drug) as a within-subject factor and group (controls, smokers, abstainers) as a between-subject factor found a significant item × group interaction ($F_{2,67}=3.833$, $p=0.027$) and a main effect of item ($F_{1,67}=6.978$, $p=0.008$), reflecting higher ratings for the drug cue than the neutral cue. In order to explore the interaction, paired *t* tests were conducted to compare ratings with the neutral and drug items in each group. Only one significant comparison emerged. In abstainers, the drug cue was rated higher than the neutral cue ($t_{22}=-3.208$, $p=0.004$), indicating that the drug cue significantly overshadowed the neutral cue in this group.

Blocking (*Table 3*). In order to assess blocking, ratings to all three blocked cues were compared with the mean of the two control cues. Since the same control cue score was used as a comparison for scores to each of the three blocked cue scores, a RMANOVA with *a priori* planned orthogonal contrasts compared: (i) the control cue score to all three blocked cues together; (ii) the neutral blocked cue to the other two blocked cues; (iii) the neutral cue blocked by a drug cue with the drug cue blocked by a neutral cue. One control was excluded for scoring >2.5 S.D. from the group mean. A significant main effect of contrast (i) was found ($F_{1,68}=4.088$, $p=0.047$), indicating a main effect of blocking, whereby all blocked cues were rated lower than the control cues. No significant effects were found for contrasts (ii) or (iii) and no significant item × group interactions emerged for contrasts (i), (ii) and (iii).

Dot probe (*Table 4*)

Analysis of reaction times to probes following images shown for a short (250 ms) exposure time revealed a significant group × validity interaction ($F_{2,69}=3.831$, $p=0.026$) but no other significant effects. Paired sample *t* tests split by group were used to explore this interaction and showed that reaction times were faster to probes following cigarette images than neutral images in abstainers ($t_{23}=2.545$, $p=0.018$) only. At the long (2000 ms) exposure time, no significant interactions or effects emerged.

Correlations

Pearson correlations were conducted between the degree of drug-cue induced overshadowing (choice × importance score to the drug cue – choice × importance score to the neutral cue), attentional bias at the short exposure time, craving (TCQ expectancy), nicotine dependence (FTND) and carbon monoxide level in the abstainer group only. Carbon monoxide level correlated positively with both TCQ expectancy craving ($r=0.501$, $p=0.013$) and level of drug-cue induced overshadowing ($r=0.471$, $p=0.023$). No other correlations reached significance.

Discussion

There were three main findings in this study. First, in abstinent smokers but not satiated smokers or controls, smoking-related cues overshadowed neutral cues in perceived reward value, despite the two types of cues having an identical associative history of rewards. Second, all three groups exhibited blocking and the use of drug cues as reward predicting cues did not interact with blocking in any group. Third, abstaining smokers but not satiated smokers or controls showed an attentional bias towards cigarette-related images displayed for a short duration.

The three groups did not differ in age, gender, years in education or pre-morbid IQ and the two smoking groups did not differ in any index of smoking behaviour. Mean Fagerstrom scores in both groups reflected

Table 3. *Group means* (*s.d.*) *for choice × importance ratings to the control cue and blocked cues* (*neutral cue blocked by a neutral cue, neutral cue blocked by a drug cue, drug cue blocked by a neutral cue*)

	Controls	Smokers	Abstainers
Control cue	4.85 (3.09)	4.27 (3.53)	4.63 (3.33)
Neutral cue blocked by a neutral cue	3.30 (5.27)	5.00 (3.67)	2.75 (5.51)
Neutral cue blocked by drug cue	4.22 (5.05)	2.71 (5.31)	2.63 (6.10)
Drug cue blocked by neutral cue	2.74 (6.74)	4.71 (4.40)	4.13 (5.18)

Table 4. *Reaction times to probes replacing images on valid and invalid trials following at short* (*250 ms*) *or long* (*2000 ms*) *exposure in controls, smokers and abstainers*

	Controls		Smokers		Abstainers[a]	
	Valid	Invalid	Valid	Invalid	Valid	Invalid
Short exposure	454.89 (96.58)	446.03 (106.62)	421.20 (56.35)	432.95 (62.38)	436.74 (79.81)	456.77 (73.37)
Long exposure	439.42 (65.35)	447.47 (86.11)	438.95 (63.91)	426.09 (78.84)	456.74 (74.58)	450.70 (104.55)

[a] Abstainers showed faster reaction times to probes following valid trials compared to invalid trials at a short exposure ($p = 0.018$), reflecting an attentional bias to drug cues.

moderate dependence (Vink *et al*. 2005). Carbon monoxide levels were reliably different across groups and confirmed that abstainers had refrained from smoking for at least 12 h prior to the study commencing. Abstainers showed higher craving than satiated smokers according to the 'expectancy' subscale of the TCQ-SF (Heishman *et al*. 2008), which relates to 'wanting' aspects of addiction (Robinson & Berridge, 1993).

DCRPET

Analysis of responses made during training stages 1 and 2 of this associative learning task showed that participants were able to learn correct responses to all items presented.

Choice × importance scores obtained during the test stage, reflecting the perceived reward value of individual items, were used to assess overshadowing and blocking. When comparing these test scores to two items presented as a pair with the same outcome (a smoking-related image and a neutral image), the cigarette image overshadowed the neutral image as indexed by higher reward value, in the abstaining smokers only. To the author's knowledge, this is the first study to find an interaction between exposure to salient drug cues and alternative reward processing in addicted individuals. It is noteworthy that carbon monoxide levels, which provide a biological measure of recent smoking behaviour, were positively related to both cigarette craving and drug-cue induced overshadowing, sharing around 25% of the variance in both cases. A significant effect of blocking was observed similarly across all three groups. This effect did not interact with group or item presented. These findings suggest that salient drug cues do not interact with associative blocking in a reward learning paradigm.

Attentional bias

Abstaining smokers, but not satiated smokers or controls, showed faster reaction times to a probe replacing cigarette-related images than neutral items shown for a short (250 ms) duration. An automatic bias amongst abstaining compared with satiated smokers has been previously been shown towards cigarette-related stimuli using eye tracking (Field *et al*. 2004); however, to our knowledge these results offer the first behavioural evidence of an increased automatic attentional bias due to tobacco deprivation using a dot probe paradigm. Automatic attentional bias has previously been shown amongst satiated smokers compared with controls (e.g. Ehrman *et al*. 2002; Mogg & Bradley, 2002; Bradley *et al*. 2004). However, the relationship between craving and attentional bias is not clear cut, since it has been previously found that lighter/less dependent smokers show stronger bias for smoking-related images than heavier/more dependent smokers (Hogarth *et al*. 2003; Mogg *et al*. 2005), consistent with

a transition from incentive salience to habit based responding after extensive heavy smoking (di Chiara, 2000). No bias was shown in either smoking group when images were shown for a longer (2000 ms) exposure in order to tap into strategic processing. Although attentional bias at a long exposure has been demonstrated behaviourally in satiated smokers (Bradley *et al*. 2003, 2004), gaze duration using eye tracking provides a more direct measure of strategic bias in smokers (e.g. Mogg *et al*. 2003; Kwak *et al*. 2007) and can be sensitive to the effects of tobacco abstinence (Field *et al*. 2004). It should also be noted that task demands have differed between studies; we employed a left/right forced choice response based on probe location similar to Ehrman *et al*. (2002), while others (e.g. Mogg *et al*. 2003) have incorporated choices that may not be detectable in peripheral vision (e.g. upwards or downwards arrow).

An attentional account of drug cue–reward interactions

Evidence for disrupted reward processing following tobacco deprivation in this study is in agreement with previous demonstrations that abstinence reduces reward responsivity (Al-Adawi & Powell, 1997; Powell *et al*. 2002*a*) and increases temporal discounting of reward (Mitchell, 2004; Field *et al*. 2006). Indeed, reduced reward thresholds to natural reinforcers are a hallmark feature of drug withdrawal (Koob & Le Moal, 2005). The current study found no differences between the three groups in the processing of rewards predicted by neutral cues alone according to test scores to neutral items only. Rather, aberrant reward processing was selective to competition between neutral and drug-related cues in abstaining smokers. This highlights the importance of interactions between drug-cue or drug salience and the motivation to act in pursuit of natural rewards. Overshadowing is highly dependent on the perceptual salience of cues employed in associative learning tasks (Mackintosh & Reese, 1979; Denton & Kruschke, 2006; Heckler *et al*. 2006) and, taken together with evidence for an automatic attentional bias in abstaining smokers only, these results suggest a role of attention in drug cue × reward processing interactions. This is in agreement with previous evidence that smoking-related images can increase neural activity in areas implicated in both reward anticipation and selective attention amongst smokers (Due *et al*. 2002).

Our findings that drug cues can modulate overshadowing but not blocking may be due to inherent differences between these processes. Overshadowing can occur after one conditioning trial (Mackintosh & Reese, 1979) and is thought to rely on the 'intrinsic salience' or physical aspects of the cues employed. In contrast, blocking may rely on 'acquired salience' since prior learning must be integrated with later conditioning during successive training sessions (Cassaday & Moran, 2010). These processes can be pharmacologically dissociated: abolished blocking due to amphetamine administration can be restored with D_2 antagonist pretreatment (Crider *et al*. 1982), while disrupted overshadowing following amphetamine treatment can be restored with co-administration of a D_1 but not D_2 antagonist (O'Tuathaigh & Moran, 2002). This suggests that D_1 and D_2 receptors control overshadowing and blocking respectively, in agreement with a role of prefrontal D_1 but not D_2 receptors controlling selective attention (Granon *et al*. 2000).

Kalivas *et al*. (2005) hypothesized that, in the healthy brain, an abundance of D_2 receptors on glutamatergic neurons projecting from the prefrontal cortex to the nucleus accumbens would allow a range of motivationally salient stimuli to initiate behaviours. However, during withdrawal from chronic drug treatment, D_1 receptors may be preferentially up regulated and as a result only motivationally strong stimuli (e.g. drug cues) might activate these D_1 receptors sufficiently to initiate behaviour (e.g. drug seeking). Tentatively, drug-cue induced overshadowing and automatic attentional bias amongst abstaining smokers might be explained by D_1 receptor up regulation in prefrontal cortex, confining selective attention to intrinsically salient drug cues.

Implications and limitations

The findings of this study extend previous demonstrating for salience attribution to drug cues, by providing evidence that drug cues can alter inferences of financial value to other non-drug cues predictive of the same reward. Previous treatment strategies have proposed that (i) the reward value of a drug should be decreased while (ii) that of alternative rewards should be increased (Volkow *et al*. 2004). However, these approaches have been considered in isolation and our results suggest that a synthesis of these approaches is needed. Pharmacological attempts to increase the value of natural rewards (such as dopamine agonists; Kosten *et al*. 2002) have been disappointing to date, but community-based reinforcement approaches have shown promising effects (Curran & Drummond, 2005). Further, it has been shown that the rate at which money is temporally discounted in smokers can predict choices between smoking or earning money in a laboratory model of abstinence reinforcement (Dallery & Raiff, 2007). Our results suggest that interventions aimed at drug cues, such as cue exposure therapy (O'Brien *et al*. 1990), disrupting reconsolidation

(Lee *et al*. 2005) or attentional bias training (Attwood *et al*. 2008), might have secondary effects on reward function in contexts where drug cues are present.

In terms of limitations, abstinent and satiated smokers were compared independently, so although the two groups did not differ in smoking behaviour or dependence levels, between-subject variation cannot be ruled out in interpreting effects due to abstinence. However, the repeated use of an associative learning task might lead to carry over effects in a within-subject design and there are only a limited number of discrete and conceptually different smoking cues that could potentially be used to create different task versions. Despite these limitations, the study had a number of important strengths. First, smokers were randomly allocated to an abstinent or satiated group. Second, all assessments took place under blind conditions and, third, a within-subject saliency manipulation was used, in contrast to previous investigations in humans that have investigated salience between subjects (Denton & Kruschke, 2006; Heckler *et al*. 2006).

Conclusions

In summary, despite showing no differences in learning during an instrumental learning task, abstinent smokers but not satiated smokers nor controls attributed higher reward value to cigarette-related items than neutral items that were equally predictive of reward. This drug cue induced overshadowing was correlated with expired CO, which, in turn, was correlated with craving in abstaining smokers. This study provides the first evidence that drug cues are able to interact with reward processing in a drug-using population and support a role of attention in this relationship.

Acknowledgements

This work was supported by an MRC/ESRC interdisciplinary studentship awarded to T.P.F. We thank James Bisby, Lorna Stewart and Hannah Powles for their assistance in screening participants in order to maintain blind conditions.

Declaration of Interest

None.

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