Salience Attribution in Addiction and Psychosis

Tom Parsons Freeman

Submitted for the degree of Doctor of Philosophy

University College London

December 2012

I, Tom P Freeman confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

……

Abstract

Salience attribution, the process by which particular stimuli come to selectively grab one's attention, is heightened towards drug-associated cues in substance users and irrelevant cues in psychosis. In **Chapter 1** I review this literature. Despite their theoretical link and the substantial co-morbidity of substance use in psychotic disorders, the extent to which these processes overlap is not well understood. The aim of this thesis was to investigate their relationship. The ability of drug cues to impact on associative learning processes was examined in **Chapter 2** using a newly developed task. Overshadowing by drug cues was found alongside smoking-related attentional bias in abstinent smokers but not in satiated smokers or controls. This overshadowing effect is replicated in **Chapter 3** among frequent ketamine users and polydrug-using controls. Ketamine users showed elevated psychotic-like symptoms, a reduction in associative blocking and a stronger impact of drug cues on blocking compared to polydrug controls. These results are indicative of a shared disruption of salience attribution in addiction and psychosis, which I investigated in **Chapter 4** among smokers with a diagnosis of schizophrenia. Associative blocking was reduced in these individuals compared to control smokers but both groups displayed an absence of blocking towards drug cues. The patient group also showed higher drug-cue attentional bias that correlated with positive psychotic symptoms. In **Chapter 5** I examined the role of dopamine in salience attribution in smokers. The dopamine D_2/D_3 agonist pramipexole (0.5mg) reduced urges to smoke and decreased attentional bias towards smoking-related images relative to monetary images when compared to placebo. In **Chapter 6** I discuss the theoretical and clinical implications of these findings. The effects of drug cues on associative learning provide a methodological advance, and these findings offer preliminary support for a link between disruptions of salience attribution in addiction and in psychosis.

Acknowledgements

I would like give the warmest thanks to my supervisor Val Curran for her continued support along every step of the journey. I feel incredibly lucky to have had her expert guidance during this time and look forward to working with her in the future. Val is one of the kindest people I know and takes a genuine interest in helping the people around her develop and progress. She creates a research environment that is welcoming, enriching, challenging and diverse. I couldn't have asked for anything better than this. I would also like to give a special mention to Celia Morgan. Celia's work has been an inspiration and her creativity, determination and hardiness to any challenge never ceases to amaze me.

It has been a pleasure to collaborate with James Stone, Tom Beesley, Ravi Das and Sunjeev Kamboj. I would like to thank Jon Roiser, Peter Dayan, Quentin Huys, Oliver Mason and David Shanks for valuable discussions and Sharinjeet Dhiman, Louise Noronha, Beatriz Orgaz, Chandni Hindocha, Fiona Pepper, Stephanie Minchin and Brigitta Brander, Jiye Shen, Billy Schmidt, Leah Markwick and Hannah Powles for their help with this work.

I am hoping to escape the PhD office alive following James Bisby and Lorna Stewart. To all those that made it out, all those that didn't and others who's time will come (James Harris, Fabi Lorencatto, Chia-Ying Chou, Alice Anokhina, Ravi Das; also Mike Down, John Weymer, Becky Chamberlain) thanks for being great company!

I would like to thank my family (Pam and Pete Freeman, Jeremy Parsons) for personal and academic sustenance (Parsons, 2012) and finally my partner Abigail Moss who has done an incredible job of putting up with me over the past three years. Her encouragement has been unconditional and I am very grateful for this.

The work presented in this thesis has given rise to the following publications:

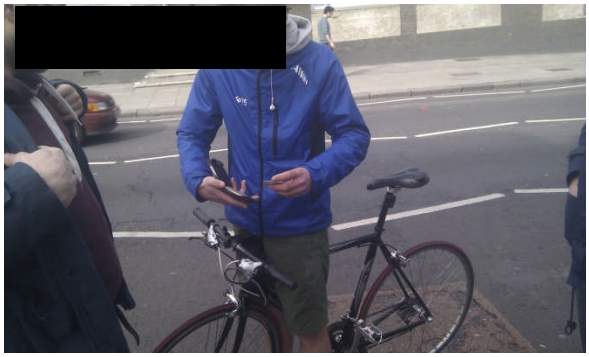
Freeman, T. P., Morgan, C. J. A., Beesley, T., & Curran, H. V. (2012). Drug cue induced overshadowing: selective disruption of natural reward processing by cigarette cues amongst abstinent but not satiated smokers. *Psychological medicine, 42*(1), 161.

Freeman, T. P., Morgan, C. J., Pepper, F., Howes, O. D., Stone, J. M., & Curran, H. V. (2012). Associative blocking to reward-predicting cues is attenuated in ketamine users but can be modulated by images associated with drug use. *Psychopharmacology,* doi:10.1007/s00213-012-2791-0

Freeman, T. P., Morgan, C. J., Brandner, B., Almahadi, B., & Curran, H. V. (2012). Dopaminergic involvement in effort-based but not impulsive reward processing in smokers. *Drug and Alcohol Dependence.* doi: 10.1016/j.drugalcdep.2012.10.016.

Preface: a salient personal experience

In February 2012 a friend of mine kindly offered to service and replace all of the parts on my bike as a birthday present. The finished job was impressive but included some unsavoury looking bright red tyres. Unfortunately the bike was stolen with chain cutters after just one ride! I wasn't very happy about this, and after the event I constantly found my attention being drawn towards similar looking bikes on the road. Given the size of London, it is incredible that one day I did actually spot the bike. I was with friends and we challenged the man riding the bike, and took a photo (see below).



The salience of my bike may have led to it being stolen, but also might have helped me get it back.

I finally got the bike back in June after a long-winded police process. Luckily, I no longer find that my attention is directed towards red bike tyres.

Contents

List of tables

List of figures

Chapter 1: Introduction to salience attribution in addiction and psychosis

1.1 Background

In 1993, Robinson and Berridge published a paper introducing an influential theory of drug addiction. Central to this 'incentive sensitization' theory were three factors: the concept of salience, the neurotransmitter dopamine, and the dissociation of motivational components of drug use or 'wanting' from hedonic aspects such as 'liking'. Robinson and Berridge proposed that drug-related stimuli are able to elicit 'wanting' and trigger drug seeking behaviour in addicted individuals due to Pavlovian conditioning between these cues and successively increasing or sensitised dopamine release achieved through repeated drug administration. This model has been extended to explain the 'attentional bias' shown towards drug-related stimuli in substance users, which in combination with craving might cause drug seeking to occur.

Although the incentive sensitization theory was primarily concerned with explaining drug addiction, it has been influential in our understanding other aspects of psychopathology. In their original proposal, Robinson and Berridge acknowledged that excessive salience attribution might in certain circumstances make the world become 'too bright' and cause psychotic experiences to occur (Robinson & Berridge, 1993). Indeed, research that led up to the development of the incentive sensitization theory was based on investigation of amphetamine sensitization as a model psychosis (Robinson & Becker, 1986). Recent developments of these ideas propose that irregular and context-independent dopamine release can allow salience to be attributed to irrelevant stimuli and thoughts. This may result in a state of aberrant salience that can only be resolved through the incorporation of these anomalous experiences into unusual beliefs that form the basis of delusions. Despite the common origins of these two lines of investigation they have generally been considered in

isolation. This is surprising given that the core psychological and neural elements of both theories (salience attribution, motivation and dopamine) remain common to contemporary accounts of drug addiction and psychosis. The aim of thesis is to further investigate the role of salience attribution these processes.

In this chapter I will first introduce the concept of 'salience' (section 1.2). Next, its role in drug addiction will be discussed. Addiction research has generally focused on the *specific* attribution of salience towards a *restricted* set of drug-associated stimuli (section 1.3). I will also consider it in broader terms with respect to the effects of attentional bias on *non-drug related stimuli* (section 1.4). In contrast to addiction, salience attribution in psychosis has generally been understood to occur *non-specifically* and towards cues that are *irrelevant* (section 1.5). Following on from this, I will introduce the literature addressing salience attribution with reference to comorbid substance abuse in psychotic disorders (section 1.6). Finally, the aims and hypotheses of this research will be presented (section 1.7).

1.2 What is 'salience'?

In the English language, salience can be defined as "*standing above or beyond the general surface or outline; jutting out; prominent among a number of objects*". Attention is thought to have a limited capacity (Broadbent, 1958) which necessitates that certain stimuli receive more processing than others. Salient stimuli are able to capture selective attention due to their basic characteristics, such as colour, orientation or intensity (Parkhurst, Law, & Niebur, 2002). In addition to these 'bottom-up' features, salience can be driven by 'top down' influences such as memory and current goals. Bottom up and top down influences typically interact with each other in order to allow for attention to be selectively allocated towards specific stimuli (Corbetta & Shulman, 2002) which is often but not always coincident with conscious awareness of selective attention (Koch & Tsuchiya, 2007)

The concept of salience has received a considerable amount of interest in terms of our understanding of abnormal behaviour. The application of 'salience' to mental illness notably developed from work in laboratory animals (Robinson & Berridge, 1993) and has progressed to the extent that 'salience dysregulation syndrome' was proposed as a new diagnostic title for use in DSM-V and ICD-11 (Van Os, 2009). Robinson and Berridge (1993) used the term 'incentive salience' to describe the 'attractiveness of external stimuli, events, places and their mental representations; their ability to capture attention' (page 280). Incentive salience is a psychological mechanism that is able to influence behaviour through its effects of on attention and motivation, such as eliciting approach towards a specific goal. In the case of drug addiction (Figure 1.1) attention and motivation may become compulsively directed towards drug-seeking behaviour. Release of dopamine following drug administration thus becomes increasingly large each time it occurs, and stimuli that are present at this time become assigned with heightened salience as a result. When these 'cues' are re-encountered, associative learning dictates that they activate the same sensitized dopamine release, attract

attention and drive goal-directed behaviour in order to seek out the drug; the process of salience attribution ensures that drugs and the cues that accompany their administration are 'wanted' independently of the hedonic effects they may be associated with.

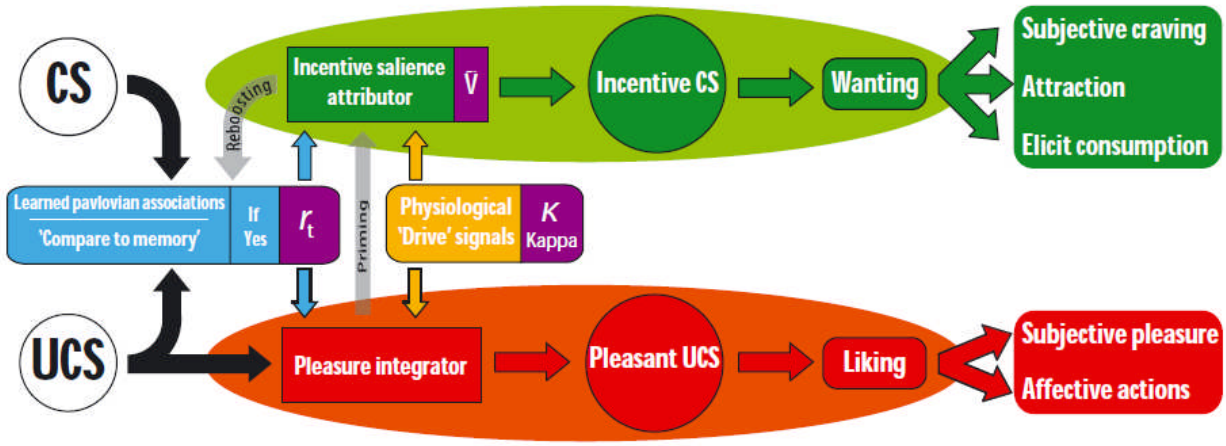


Figure 1.1: The incentive-sensitization theory (Robinson & Berridge, 1993; figure adapted from Berridge, 2012). (a) Under normal circumstances the attribution of pleasure or incentive acts to facilitate goal directed behaviour towards rewarding outcomes. Following sensitization of the dopamine system (b) incentive salience attribution becomes hypersensitive, causing cues associated with release of dopamine in this system (e.g. drug-associated stimuli) to be attributed with heightened salience and become powerful motivators of drug use.

Whilst incentive salience can account for observations in drug-addicted individuals who compulsively seek out their drug of choice, it does not explain aversive behaviour such as avoiding unpleasant outcomes. In light of findings linking aversive conditioning to dopamine release and salience attribution in a latent inhibition paradigm (Young, Joseph, & Gray, 1993) Robinson and Berridge suggested that dopamine might play a broad role in attributing 'motivational salience', a quality that might apply to both appetitive (incentive salience) and aversive stimuli (Berridge & Robinson, 1998). As such, aversive salience might share the

same perceptual-motivational characteristics as incentive salience. A role of dopamine in coding for motivational salience as opposed to incentive processes alone is supported by recent electrophysiological data (Bromberg-Martin, Matsumoto, & Hikosaka, 2010).

According to the incentive sensitization theory, associative learning is crucial in order for conditioned stimuli to elicit goal directed behaviour when they are encountered in future. However, according to this theory the role of dopamine is in the attribution of salience rather than promoting learning itself (Berridge, 2007) and the magnitude of this effect will be a product of learned associations and physiological drive. This implies that, for example, a smoker may find the sight of another person inhaling on a cigarette equally salient each time this occurs given equivalent levels of tobacco satiety. However, if they are deprived of nicotine this learned association will be amplified by their physiological state and excessive salience will be attributed to the cue (Field, Mogg, & Bradley, 2004), motivating them to seek the drug themselves.

In contrast to its role of motivation, others have argued instead that dopamine release and selective attention play a critical role in learning. For example, phasic (short latency, short duration) dopamine release has been proposed to act as a 'teaching signal' enabling people to accurately predict the occurrence of rewarding events (Schultz, Dayan, & Montague, 1997). According to this theory, rewarding occurrences initially elicit phasic dopamine release. However, after training this effect is replaced by the release of dopamine upon exposure to cues predictive of the event rather than the event itself. Consequently, dopamine release may code for learning, rather than motivation. If so, this effect may occur directly through the ability of dopamine release to code error in the prediction of an event (Rescorla & Wagner, 1972) or indirectly by influencing the amount of attention that is directed towards cues that are present at the time of learning (Mackintosh, 1975; Pearce & Hall, 1980). Whilst the role of sub-second dopamine release in human motivation and learning remain elusive, animal

data suggests that different populations of dopamine neurons may code for both learning and motivational salience (Bromberg-Martin et al., 2010). Moreover, whilst a causal role of attention in learning may be difficult to establish in humans, the sensitivity of certain paradigms to changes in the visual salience of cues and their relationship to changes in overt attention would suggest that they are driven by changes in salience and selective attention (see figures 1.1, 1.2 and 1.3).

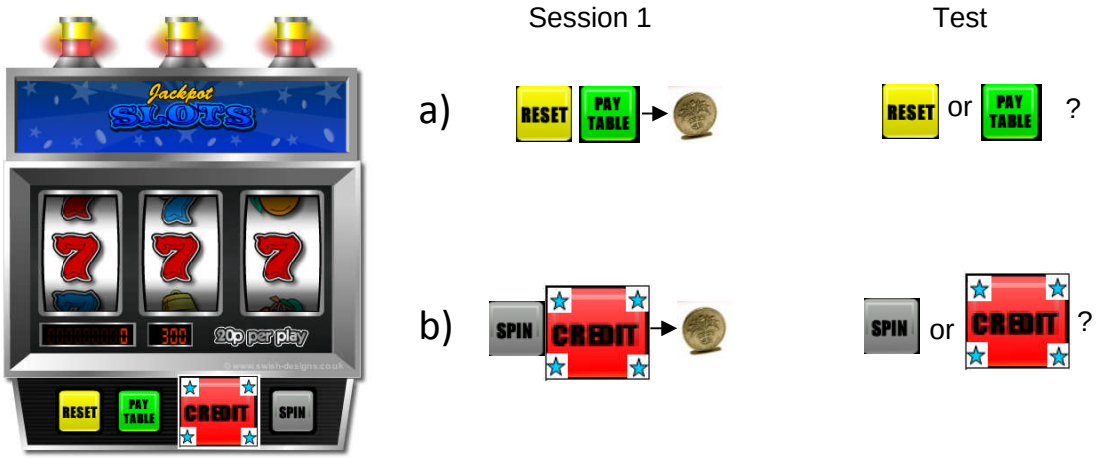


Figure 1.2: An illustration of 'overshadowing' (Mackintosh, 1976) using an appetitive Pavlovian conditioning design. In order to play this slot machine, individuals are required to press two buttons together in an attempt to win money. In one case (a) both buttons are equally salient but in the other case (b) one button is highly salient due to its bright colouring and large size. After winning in the first situation (a) both cues might have undergone equal learning with respect to the reward. However in the second case (b) the salient red button might overshadow any learning between the grey cue and reward. According to attentional theories of associative learning, the amount of attention directed towards a cue determines the rate of learning in processes such as overshadowing.

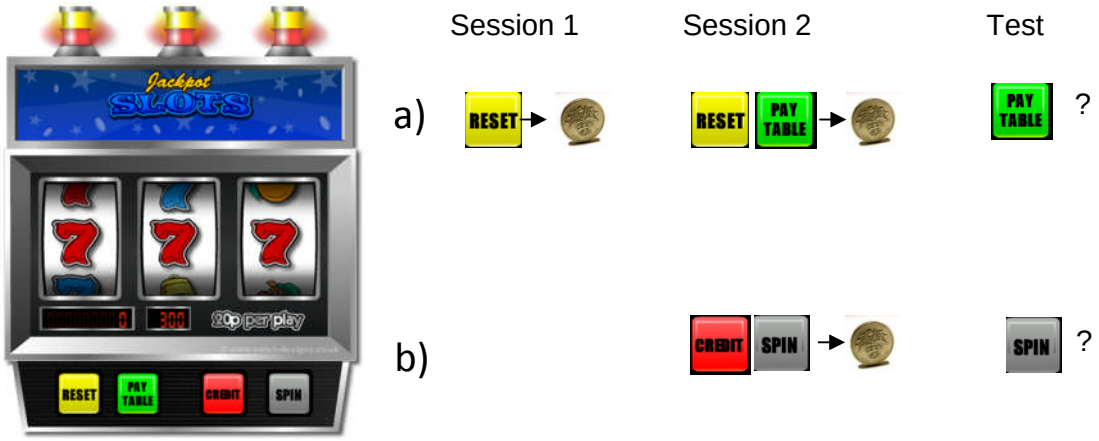


Figure 1.3: A demonstration of 'blocking' (Kamin, 1969). Pressing a single button is initially associated with a reward-based outcome in session 1 (a). Later, pressing this same button alongside a new button also results in reward in session 2. Blocking of this additional cue (shown in green) is reflected by a lower association between the cue and the outcome when compared to a control stimulus (b; shown in grey) that has received equivalent associative training. Blocking offers a classic demonstration that learning depends on 'prediction error' whereby no new learning occurs to a fully predicted event. However, if learning processes such as blocking are driven by changes in attention, manipulating salience (such that some cues are more salient than others) should affect the extent to which blocking occurs.

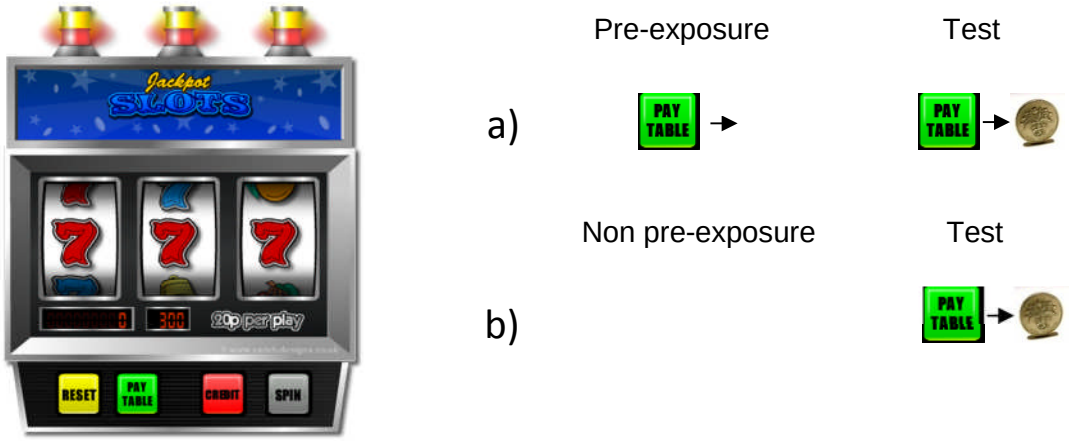


Figure 1.4: An example of 'latent inhibition' (Lubow & Moore, 1959). At test, pressing the green button results in a rewarding outcome. However learning of this contingency is typically slower after pre-exposure (a) in which this cue was initially associated with no event, when compared to a condition where it was not encountered at all (b). Thus, pre-exposure to a non-predictive stimulus can inhibit the ability to learn about this cue, which might be explained by an association between it and low predictive ability, implying that it is not deserved of attention in future.

In summary 'salience' refers to the ability of stimuli to gain preferential attentional processing and is often referred to in terms of dopamine release and motivational drive. However salience is also an important feature of associative learning whereby the degree of selective attention that is directed towards particular cues can determine rates of learning. This process can be thought of in a cyclical manner whereby *salience attribution leads to changes in attention, in turn altering associative learning, which acts to determine the salience of certain stimuli next time they are encountered.* Moreover, the expression of salience attribution may be modulated by state-dependent effects such as hunger, thirst or deprivation from a drug.

1.3 Attentional bias and aberrant salience attribution in drug users

The ability of drug-associated cues to 'grab attention' has been extensively replicated amongst users of a range of drugs of abuse (e.g. alcohol, tobacco, cannabis, opiates, ketamine) using a variety of paradigms (e.g. modified Stroop task, visual probe task, attentional blink task) and various indices (reaction times, errors, overt attention during eye tracking, event related potentials) [see reviews by (Field & Cox, 2008; Franken, 2003; Littel, Euser, Munafò, & Franken, 2012; Robbins & Ehrman, 2004). For example, one study (Mogg, Bradley, Field, & De Houwer, 2003) exposed tobacco smokers and controls to smoking-related images alongside matched neutral pictures side by side on a screen. In this visual probe task, reaction times to identify the orientation of probes appearing immediately after picture offset were recorded alongside fixations to both images using eye tracking. Mogg et al. found that smokers were more likely to initially fixate upon smoking-related images than control images and do so for longer than controls. Moreover, they were faster to respond to the probes appearing in the same location as smoking images than non-smoking images, whereas controls were not. Interestingly, duration of fixations and reaction time bias scores correlated positively with their tendency to be faster at 'approaching' rather than 'avoiding' these images in a separate task, providing a link between the ability of drug-associated cues to 'grab attention' and motivate behaviour (Robinson & Berridge, 1993).

Studies of salience attribution towards drug-associated cues in human populations have generally used tasks - such as the visual probe task - that measure bias in attention, or the tendency for drug associated stimuli to receive its preferential allocation. In an extension of the incentive-sensitization theory, Franken (2003) proposed that attentional bias plays a central role in causing substance use (Figure 1.5). According to this theory, attentional bias

acts to enhance craving, which in turn could increase bias in a cyclical process that ultimately culminates in drug use. This is supported by a positive correlation between these measures according to a meta-analysis of 68 studies, with a stronger relationship observed for direct measurement using eye tracking and event related potentials (Field, Munafo, & Franken, 2009). Further support for the role of attentional bias in drug use has come from a number of independent studies documenting its ability to predict clinical outcomes. This relationship has generally been in the predicted direction, with those individuals showing higher attentional bias at baseline having a lower chance of achieving successful abstinence from drugs of abuse including alcohol (Garland, Franken, & Howard, 2012) tobacco (Janes, Pizzagalli, & Richardt, 2010; Powell, Dawkins, West, Powell, & Pickering, 2010; Waters et al., 2003) and heroin (Marissen et al., 2006). Moreover, high attentional bias at baseline can predict poor adherence to and outcomes from substance abuse treatment in users of alcohol (Cox, Hogan, Kristian, & Race, 2002), cocaine (Carpenter, Schreiber, Church, & McDowell, 2006) and methamphetamine (Hester, Lee, Pennay, Nielsen, & Ferris, 2010).

In contrast, one study (Carpenter, Martinez, Vadhan, Barnes-Holmes, & Nunes, 2012) found that high attentional bias on a Stroop task was associated with *better* adherence to treatment and fewer positive drug screens in cocaine treated individuals. However this relationship was only found for late treatment weeks (13-34) when financial incentive for compliance was withdrawn. In addition, some evidence has shown that tobacco smokers with higher levels of dependence (Mogg, Field, & Bradley, 2005) or greater cigarette consumption (Hogarth, Mogg, Bradley, Duka, & Dickinson, 2003) show a relative reduction in attentional bias compared to lighter or less dependent smokers. This would suggest attentional bias is not responsible for the maintenance of addictive behaviour in some individuals and that it may only be a relevant index of dependence for certain groups of drug users. Conversely, other findings indicate that higher cigarette consumption or dependence is associated with a

stronger attentional bias (Vollstädt-Klein et al., 2011). Although there are some disparities, taken together, the evidence does suggest that salience attribution is an important process in drug addiction that could be targeted to improve clinical outcomes in treatment of substance users.

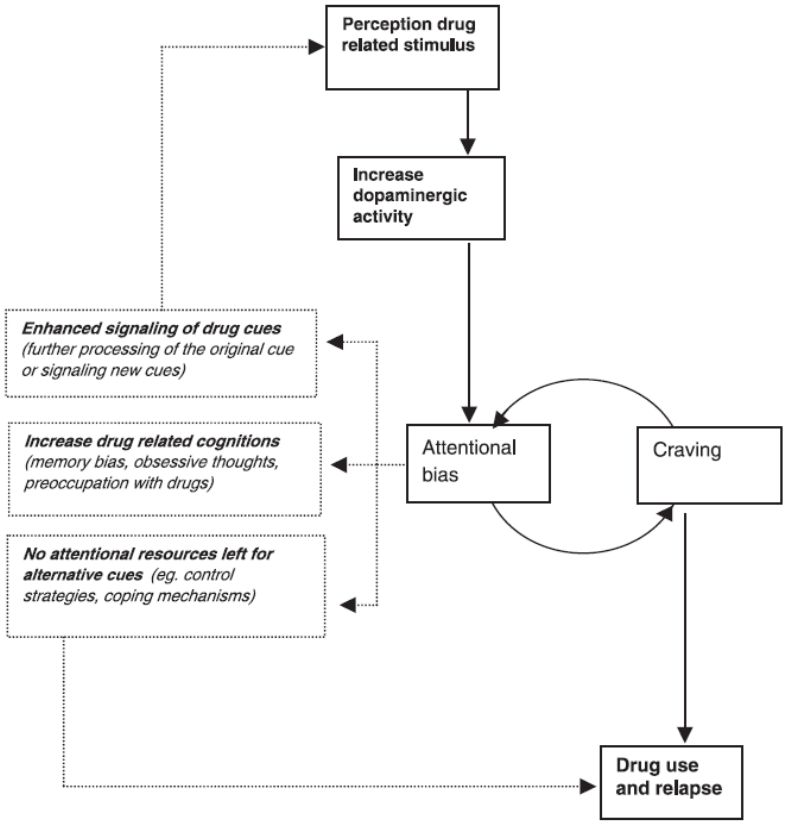


Figure 1.5 A neuropsychopharmacological model of drug addiction (Franken, 2003). Dopamine release serves to enhance attentional bias to drug cues, which increases craving and causes drug use to occur. The link between attentional bis and craving is cyclical; moreover attentional bias can enhance signalling of new drug cues and enhance drug-related cognition. Due to the limited capacity of selective attention, attentional bias will cause a reduction in available resources to attend to other non-drug cues.

Sceptics have argued that the ability of drug cues to attract maintained selective attention may be an epiphenomenon of substance use since its abolishment in experimental paradigms may

not prevent drug seeking behaviour (Hogarth, Dickinson, & Duka, 2009; Hogarth, Dickinson, Janowski, Nikitina, & Duka, 2008). However, this does not negate the idea that salience attribution can cause drug seeking to occur in general, in less experimentally constrained circumstances. Some experimental evidence does show that a causal relationship can exist between attentional bias and drug use. For example, after training social drinkers to attend towards alcohol cues, Field and Eastwood reported an increase in their urges to drink and consumption of replica beer in a 'taste test' (Field & Eastwood, 2005). Moreover some studies have found reductions in drug use or slower latency to relapse at follow up after attentional bias training in alcohol-using populations (Fadardi & Cox, 2009; Schoenmakers et al., 2010). Whilst these approaches are in their infancy and may need refinement before they are a feasible addition to clinical practice, they provide some evidence that manipulating salience attribution towards drug cues – as measured by attentional bias – may influence clinical outcomes in substance users.

Robinson and Berridge (1993) and Franken (2003) predicted that attentional bias is caused by the release of dopamine upon exposure to drug-associated cues. In support of this hypothesis, a single 2mg dose of the D_2 antagonist haloperidol abolished drug-related attentional bias in heroin-dependent individuals (Franken, Hendriks, Stam, & Van den Brink, 2004) and BOLD activation in response to smoking-related cues in dorsal anterior cingulate and right dorsolateral prefrontal cortices (Luijten et al., 2012). Further, attenuating dopaminergic function through acute tryptophan and phenylalanine depletion can dampen attentional bias in smokers (Hitsman et al., 2008) which was also found in another study amongst females only (Munafò, Mannie, Cowen, Harmer, & McTavish, 2007). Added to this, the D_2/D_3 agonist pramipexole produced effects on attentional bias in stimulant users that were dependent on the nature of their drug use, acting to exacerbate a pronounced bias in those with high compulsivity but eliminating it in those with less compulsive use (Ersche et al., 2010).

Surprisingly however, none of these studies have found any changes in subjective craving alongside these effects, as might be expected from theoretical accounts (Franken 2003; Robinson and Berridge, 1993).

Robinson and Berridge (1993) viewed incentive salience and 'wanting' as essentially the same process of sensitised dopamine release. However 'wanting' may not always be subject to introspection as indexed by self-report, which could account for dopaminergic effects on 'wanting' (attentional bias) but in the absence of changes in subjective craving. Franken (2003) proposed that craving should be influenced by the magnitude of attentional bias (following dopamine release) and that these two factors might synergistically act to increase one's propensity to use the drug. An absence of change in craving in the above studies is somewhat problematic for this theory, although they could be explained by a subtle effect on attentional bias which might precede effects on craving (Franken, 2003).

However an important question which remains to be addressed is whether manipulations of the dopamine system that *do* alter subjective craving can produce corresponding changes in attentional bias. For example, Munafò et al. (2007) found that acute tryptophan and phenylalanine depletion decreased attentional bias in females but conversely increased craving in males. These contrasting effects arose in different groups, which were of very small size (n=5) and clearly need replication in adequately powered studies. However if similar effects were found in the same individuals after dopaminergic manipulation, this would be problematic for current accounts of salience attribution in addiction (Franken, 2003; Robinson & Berridge, 1993).

1.4 Beyond attentional bias

Unsurprisingly, research on salience attribution in substance users has tended to focus on responses towards stimuli associated with drug use itself. However, within the broader framework of attention, motivation, goal directed behaviour and learning, this bias might be expected to impact upon other processes that are not directly associated with drug seeking or consumption. The definition of salience is inherently relative: salient cues and thoughts are defined as such by their contrast to others. This might imply that salience has some kind of limited capacity, such that when a drug and its associated cues are highly salient, a loss of salience occurs by necessity to other stimuli and internal representations.

In contrast to the incentive sensitization theory, Franken's model suggested that attentional bias would not always lead to drug use directly. Specifically, this bias could enhance drug-related cognition, which might create a bias in memory, obsessive thoughts and preoccupation with the drug. For example, when compared to social drinkers a group of alcoholics were found to remember more alcohol-related images but had equal recall of positive images; moreover this memory bias correlated with cue-elicited increases in subjective craving (Franken, Rosso, & van Honk, 2003). In addition to these effects on drug-related cognition, a lack of available resources for non-drug cues would be expected to occur which might impair cognitive control and coping mechanisms (Franken, 2003). In agreement with this position, drug-related but not neutral stimuli are able to impair working memory performance in cocaine users at high levels of working memory load (Hester & Garavan, 2009).

The combination of enhanced selective attention towards drug-related stimuli and a reduction in available resources to attend to other cues might be expected to give rise to robust changes in associative learning. Following the demonstration of blocking (Kamin, 1969) it became

clear that associative learning is not simply a reflection of the amount of training that occurs between a stimulus and an outcome, but is also dependent on relations between different stimuli that are present at the time of learning. Given that the extent to which stimuli are selectively attended to during learning can give rise these 'cue competition' effects (Mackintosh, 1975; Pearce & Hall, 1980) it might be predicted that a bias towards salient, drug-related stimuli in conjunction with a reduction in the capacity of attention might gear learning processes towards the drug and away from non-drug cues.

For example, it was recently shown that exposure to alcohol-related cues created a bias towards local rather than global processing in a subsequent target identification task, with this effect becoming more pronounced in individuals who rated a strong level of drive to consume alcohol (Hicks, Friedman, Gable, & Davis, 2012). These findings appear to show that exposure to drug-related cues may create a 'myopia' in which resources for non-drug stimuli are lacking. This is also supported by early evidence showing that *in vivo* drug cue exposure in smokers (Sayette & Hufford, 1994) and alcoholics (Sayette et al., 1994) increased reaction times to respond to a tone in a secondary task. Furthermore, the use of alcohol-related words in an artificial grammar learning task was also able to impair learning of inferential rules in heavy but not light drinkers (Pothos & Cox, 2002) which might reflect an enhanced focus on the appetitive properties of these words and a resulting loss of ability to learn during the task. Biases in learning with regards to drug-related cues rather than other stimuli could produce gross changes in an individual's ability to predict and respond to salient events.

Goldstein and Volkow hypothesized that addicted individuals show an increase in salience attribution towards drug-related cues but are hyposensitive to non-drug reinforcers (Goldstein & Volkow, 2002). Moreover, exposure to drug-related cues might act to exacerbate hyposensivity to natural rewards (Volkow et al., 2010). Using a paradigm which might be indicative of this process, Goldstein and colleagues presented cocaine users with a Stroop

task employing cocaine-related and neutral words, offering different levels of financial incentive for correct responses. The findings did not reveal any interactions between word type and reward magnitude in behavioural (reaction time and accuracy) or fMRI data in people with cocaine use disorder (Goldstein et al., 2009a; Goldstein et al., 2010). In other words, cocaine users' responsivity to financial reward was not impacted by the presence of drug cues in this dual-task procedure. Thus, a possible role of drug-related cues on incentive salience attribution still remains to be established.

One potential way to examine these effects would be to exploit the well-documented bias of attention traditionally used in a visual probe paradigm (Figure 1.6a) in a modified associative learning task (Figure 1.6b). The rate of associative learning about a given cue is thought to be a result of the amount of selective attention that is paid to it (Mackintosh, 1975; Pearce and Hall, 1980). When two cues are competing for attention, this means that a salient cue that is attention-grabbing may reduce the amount of attention that is paid to another cue that is co-present. In associative learning, the relationship between the less salient of the two cues would be overshadowed (Mackintosh, 1976). This might suggest that in drug-related contexts that often promote relapse, overshadowing of non-drug rewards may also occur.

In a blocking paradigm, the second stage of training typically places two cues alongside each other, with one of these cues having been pre-trained as predictive and the other being a novel but redundant cue e.g. (Haselgrove & Evans, 2010). During blocking paradigms, analysis of eye movements has revealed that people fixate less upon a blocked cue than the pre-trained cue that it is presented with (Beesley & Le Pelley, 2011; Kruschke, Kappenman, & Hetrick, 2005; Wills, Lavric, Croft, & Hodgson, 2007). Furthermore, the extent to which gaze is less directed towards the blocked cue correlates with the reduction of learning that occurs after the blocking procedure (Kruschke et al., 2005; Wills et al., 2007) as well as future learning about that cue in new cue-outcome relationships (Beesley & Le Pelley, 2011).

Furthermore, levels of blocking and overshadowing can be determined by the perceptual salience of the cues employed (Denton & Kruschke, 2006; Heckler, Kaminski, & Sloutsky, 2006), with highly salient cues overshadowing less salient cues, producing a stronger blocking effect and being resistant to being blocked themselves. This suggests that a general tendency to direct less attention at particular cues as a result of attentional bias might be associated with a reduction in new learning, whilst conversely biases in attention towards certain stimuli should enhance learning about those stimuli in new relationships.

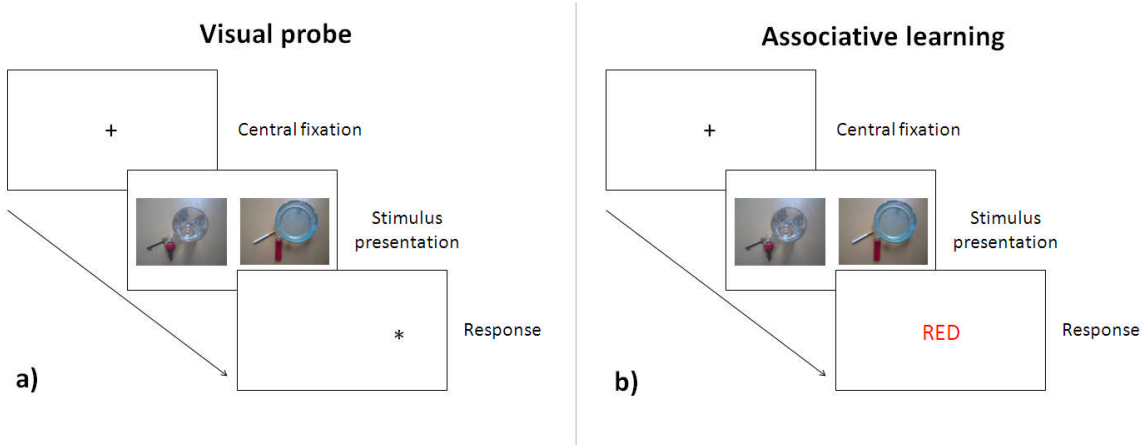


Figure 1.6: Indexing biases in visual selective attention. (a) In a visual probe task, a drug-related image is presented alongside a neutral one. Faster reaction times in responses to a probe when it appears in the same location as the drug-related compared to the neutral image are indicative of attentional bias. (b) Associative learning tasks can employ a similar design whereby two cues are trained to predict an unconditioned stimulus (e.g. some pairs are associated with a 'red' response and others with 'green', with correct responses being financially rewarded). After sufficient training, ratings towards the individual cues within these pairs can be taken. If attention was biased towards the drug cue during training, learning about the relationship between the less salient neutral cue and the outcome it was associated with might be reduced or overshadowed, resulting in a loss of its predictive value of reward.

1.5 Salience attribution in psychosis

It was recently proposed that the introduction of 'salience dysregulation syndrome' to DSM-V and ICD-11 could improve upon current diagnostic criteria used for psychotic disorders (Van Os, 2009). Van Os argued that these criteria would have more specificity to the profile of symptoms than those that are currently used. Moreover they would reflect change along a continuum of symptoms occurring at a lower level in the general population, and would therefore be easier for family members and society to relate to. Perhaps most importantly this could also reduce stigma for individuals who are diagnosed with the condition. The process referred to by Van Os was a state of aberrant salience that is thought to give rise to psychosis (Kapur, 2003).

Kapur's theory (figure 1.7) states that in healthy individuals, dopamine firing in response to behaviourally relevant cues and internal representations serves an adaptive role in guiding motivation and behaviour (Berridge & Robinson 1998). However in psychosis, dysregulated and context-independent dopamine release might allow for the aberrant assignment of salience to irrelevant external objects and internal representations. A state of aberrant salience can be gaged from the subjective reports of patients describing their pre-psychotic state, which were often characterised by profound changes in perception and attention, with some reports that patients plugged their ears or closed their eyes in an attempt to reduce the intensity of these experiences (Chapman, 1966; Freedman & Chapman, 1973).

Delusions are thought to arise as 'top down' cognitive explanations for a state of aberrant salience, serving to provide 'insight relief' by finally offering an explanation for these anomalous experiences. In this framework, hallucinations are seen as aberrantly salient internal representations such as perceptions or memories (e.g. one's 'internal voice' may come to resemble an external voice giving running commentary on one's behaviour).

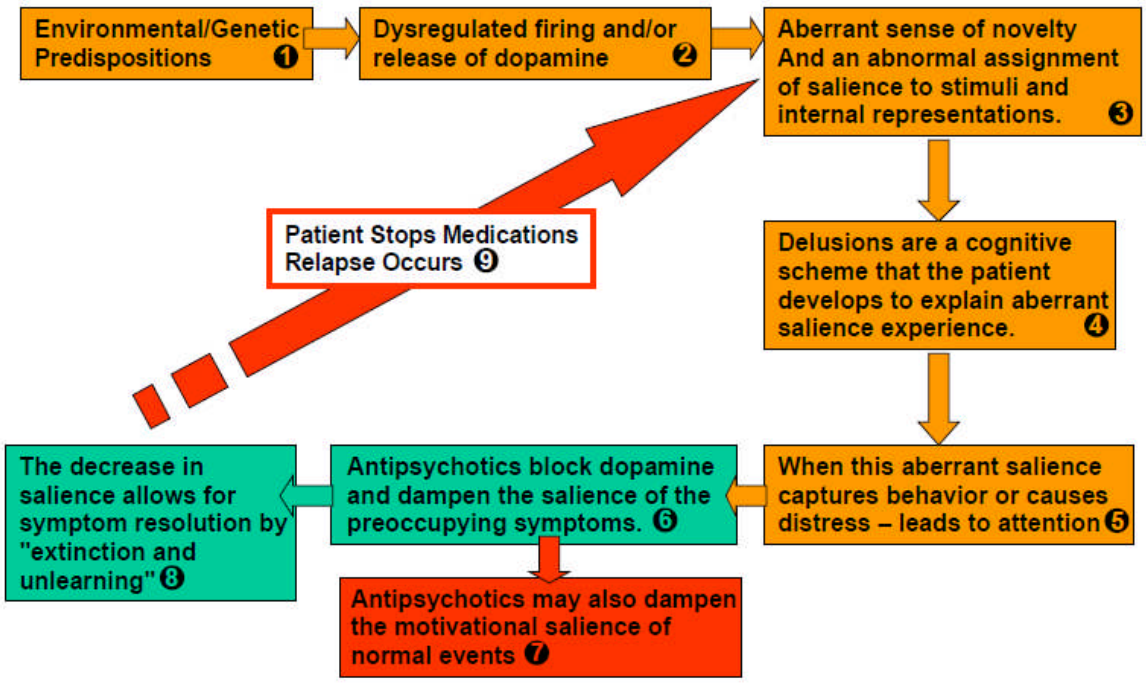


Figure 1.7: A model of aberrant salience in psychosis (Kapur 2003). The orange boxes show the pathway from dysreglated dopamine release to psychotic beliefs. Preoccupation with these beliefs can be tempered with antipsychotic treatment as shown in green. However this may also dampen motivational salience generally and relapse may occur if dosing is stopped.

Kapur argued that dopamine receptor antagonist drugs produce their 'antipsychotic effects' by acting upon the attribution of salience rather than the nature of the beliefs themselves. This is supported by qualitative data from patients during antipsychotic drug treatment, reporting that it acted to reduce behavioural impact, cognitive preoccupation and emotional involvement with the symptoms, but little change in conviction in them (Mizrahi et al., 2006). Because antipsychotics do not directly target these maladaptive beliefs, they will retain the same content unless they are treated with psychological therapy or undergo a gradual process of extinction learning. Hence, when medication is stopped a patient is likely to relapse into a psychotic episode characterised by the same delusional beliefs experienced during their previous episodes. The effects of an acute drug challenge (e.g. with the psychotomimetic

NMDA-R antagonist, ketamine) in remitted patients with schizophrenia corroborates this since 70% reported a re-emergence of a symptom they had previously experienced during an acute episode (Lahti, Weiler, Tamara, Parwani, & Tamminga, 2001).

In contrast to the literature on salience in drug addiction which has tended to use a small number of well-defined and validated paradigms, research on aberrant salience in psychosis have used a variety of different approaches and novel tasks. One study found that when classifying the affective properties of negative, positive or neutral words, patient with delusions were more likely to show a negative response bias than either patients not suffering from delusions or healthy controls, indicative of the aberrant assignment of salience to neutral material (Holt et al., 2006). This bias correlated with the severity of delusional symptoms, although this correlation was carried out in the whole sample of patients rather than separately in the group showing active delusions and response bias. Another study found that the tendency to fall victim to a speech illusion when listening to white noise increased from controls to relatives of patients with schizophrenia, and was highest in patients with schizophrenia, who also showed a pronounced tendency to interpret speech with affective meaning (Galdos et al., 2011). However the possibility that these individuals were actually experiencing auditory hallucinations rather than a speech illusion cannot be excluded.

Other studies have used paradigms that directly assess responses to motivationally salient events that might not be adequately captured by affective changes in the aforementioned tasks. Jensen et al. found enhanced BOLD activation in the striatum of patients diagnosed with schizophrenia in response to cues predicting the absence of shock compared to controls, which might indicate aberrant salience attribution to a non-predictive cue (Jensen et al., 2007). However, the patient group showed lower levels of acquisition during conditioning as

evidenced by skin conductance, and self-reported uneasiness did not reveal any evidence of conditioning in this group, which could provide an alternative explanation for these findings.

Another study found that patients with schizophrenia were able to learn to learn contingencies in a task leading to rewarding and neutral outcomes equally as well as controls. However, they showed less of a distinction between reward-based and non-reward based trials and an apparent speeding towards non-reward predictive stimuli relative to controls (Murray et al., 2007). Patients in this study also showed a lack of distinction between unexpected rewarding and unexpected neutral events according to BOLD activation in the midbrain, indicating enhanced attribution of salience to irrelevant stimuli and augmented salience of motivationally relevant stimuli. However no relationship between performance and symptoms emerged in either of these two studies, which might imply that they were not relevant to psychosis at all.

Using the Salience Attribution Task, which indexes reaction time speeding and explicit ratings towards relevant and irrelevant stimulus dimensions, Roiser and colleagues found higher ratings for the reward prediction of irrelevant stimulus dimensions in patients with schizophrenia with delusions versus those without (Roiser et al., 2009) and Ultra High Risk (UHR) individuals versus healthy controls (Roiser, Howes, Chaddock, Joyce, & McGuire, in press). Although 'adaptive' ratings towards relevant stimuli were lower in medicated patients than in controls, they did not differ across those suffering from delusions and those without, or between the UHR and control groups, suggesting that they might be secondary effects of antipsychotic medication (Kapur, 2003). Evidence from this task also supports a role of dopamine in aberrant salience, due to an opposite relationship between dopamine synthesis capacity and hippocampal activation to irrelevant stimulus features in the UHR group versus controls, although levels of dopamine synthesis did not differ between the groups. Furthermore, another study using an adaptation of this task found that the introduction of

dopamine agonist medication increased both 'aberrant' and 'adaptive' salience in people with Parkinson's disease (Nagy et al., 2011) supporting a common role of dopamine in these two types of salience attribution.

Further evidence for the irrelevant attribution of salience in relation to psychosis comes from our superstitious conditioning task (Freeman et al., 2009). The development of this task was based on the hypothesis that delusion formation might operate in an analogous way to the development of superstitious beliefs and behaviours. For example, pigeons exposed to food at random, response-independent intervals developed superstitious behaviours such as head twisting and turning on the spot, due to their occurrence at the time of reward delivery (Skinner, 1948). In the development of psychosis, associative learning between thoughts or behaviours and rewards might be expected occur at random due to chaotic dopamine firing (King, Barchas, & Huberman, 1984; Shaner, 1999). We explored this using a ketamine model of psychosis. We found that chronic ketamine users showed an elevated tendency to make superstitious choices between stimuli that were associated with reward value at random when compared to polydrug controls (Freeman et al., 2009). Moreover in healthy volunteers, baseline superstitious conditioning was predictive of the extent to which a high (150ng/ml) or low (75ng/ml) dose of ketamine subsequently induced paranoia and delusory thinking, although ketamine did not acutely increase superstitious conditioning or delusory thinking for either dose at a group level.

Two other processes that are reflective of aberrant salience attribution and have been studied with relevance to psychosis are 'blocking' (Kamin, 1969) and 'latent inhibtion' (Lubow & Moore, 1959), see figure 1.8. In tasks that index these processes, aberrant salience is reflected by elevated rates of learning to irrelevant stimuli, according to past regularities defined in these tasks. The disruption of these processes was central to an influential model of schizophrenia proposed by Gray, Hemsley and colleagues (Gray, Feldon, Rawlins, Hemsley,

& Smith, 1991). According to this theory, the positive symptoms of schizophrenia may reflect a disruption of integration between previous experience and levels of recognition, learning and action towards environmental stimuli. Central to this model is the existence of a 'comparator' which acts to constantly assess whether information experienced is consistent with one's predictions. This comparator is anatomically defined as the subiculum, projecting from the hippocampal formation to the nucleus accumbens. Gray and colleagues argued that destruction of this pathway would cause an individual to tag irrelevant stimuli as important and causal in events that are highly predictable to healthy individuals, giving rise to positive symptoms of schizophrenia.

Latent inhibition is a translational model of psychosis and was conceived as an index of motivational salience due to its relationship with dopamine release in aversive conditioning (Berridge & Robinson, 1998; Young et al., 1993). Latent inhibition can be disrupted by repeated amphetamine exposure in animals (Solomon, 1981) and after a single low dose in humans (Gray, Pickering, Hemsley, Dawling, & Gray, 1992; Kumari et al., 1999; Thornton et al., 1996). In agreement with Gray et al.'s hypothesis, latent inhibition may impaired in acute but not chronic schizophrenia e.g. (Baruch, Hemsley, & Gray, 1988; Rascle et al., 2001). However other studies have failed to find to find a loss of latent inhibition in people with a diagnosis of schizophrenia (Swerdlow, Braff, Hartston, Perry, & Geyer, 1996) and its absence in acute but not chronic schizophrenia may be more reflective of shorter illness duration rather than specific symptoms (Gray, Pilowsky, Gray, & Kerwin, 1995; Vaitl et al., 2002). More recently, research has turned to the paradigm of learned irrelevance which presents both 'to-be conditioned' stimuli at pre-exposure in an uncorrelated manner, prior to conditioning at test (Orosz et al., 2011)

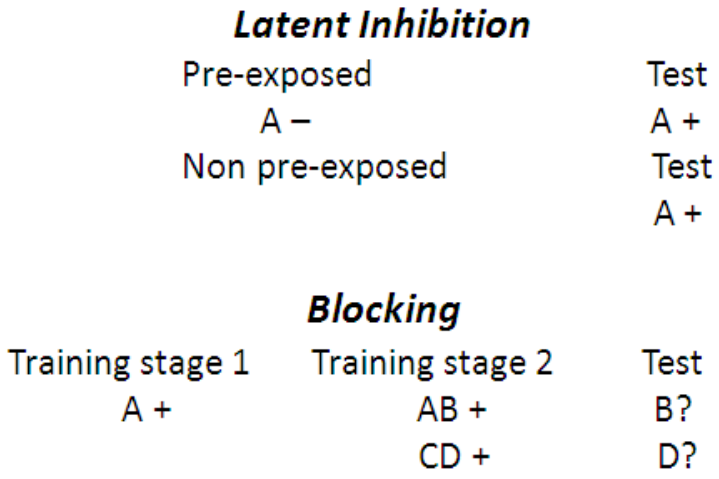


Figure 1.8: The role of latent inhibition and blocking in psychosis. During latent inhibition, pre-exposure of stimulus A with no outcome (A-) should inhibit learning about a relationship between A and an outcome (A+) when compared to a non-pre-exposed condition when A is not encountered before test. In people with schizophrenia this may not occur, and learning about A during test is less affected by pre-exposure. In blocking paradigms, learning about the relationship between cue B and an associated outcome is reduced when it is co-trained with an established predictor of that outcome (A+), in comparison to an equivalent cue (C or D). In schizophrenia the irrelevant cue B may nevertheless become associated with the outcome, in contrast to healthy individuals who show a blocking of this learning.

Blocking is also attenuated in people with a diagnosis of schizophrenia and again has been found to be related to the acute phase of the illness and positive but not negative symptoms (Jones, Gray, & Hemsley, 1992; Jones, Hemsley, Ball, & Serra, 1997). Blocking correlated negatively with subclinical positive symptoms in one study, however the correlation only emerged when considering the scores of controls and patients together (Moran, Al-Uzri, Watson, & Reveley, 2003) , and in another study using the same task, reduced blocking in patients with schizophrenia was correlated with negative and depressive symptoms (Moran, Owen, Crookes, Al-Uzri, & Reveley, 2008). Moreover, a loss of blocking was found in

people with relatively high levels of subclinical negative symptoms in a student population (Haselgrove & Evans, 2010). Others have found that lower levels of blocking relates to both positive (ideas of reference) and negative (poor attention and rapport) symptoms (Bender, Müller, Oades, & Sartory, 2001). Given that 'schizophrenia' can be a heterogeneous diagnosis it is not surprising that patterns of symptom dimensions may not be uniform across different groups of patients. For example, a reduction in blocking was related to the severity of delusions in paranoid patients, but to alogia and affective flattening in non-paranoid individuals (Oades, Zimmermann, & Eggers, 1996).

Gray's theory of psychosis might be seen as a more specified variation of the aberrant salience hypothesis. Both theories place a central role of exaggerated and non-context dependent dopamine release in the onset of psychotic symptoms and both suggest that this will cause irrelevant stimuli to become attention grabbing and drive learning. However, Gray proposed that the problem might be "*difficulty in integrating different experiences with the same or similar stimuli when these require some form of contextually dependent differentiation*' (Gray, 1998) (page 261)." As such, 'aberrant salience attribution' in Gray's model only occurs in contexts where the associative history of the stimulus or stimuli present at the time dictate that certain stimuli are irrelevant and should be ignored. In a related manner, Fletcher and Frith view erroneous prediction errors as responsible for the development of psychosis across hierarchical levels of processing in the brain (Fletcher & Frith, 2008). Hence, in common with aberrant behaviourally indexed prediction error (e.g. lack of blocking) the distinction between expected and surprising events might be less evident according to brain activation in people with psychosis (Corlett et al., 2007; Murray et al., 2007) and following administration of psychotomimetic drugs such as ketamine (Corlett et al., 2006).

Despite the common origins underlying Gray's theory of schizophrenia and the aberrant salience hypothesis, they have been investigated almost exclusively separately apart from some exceptions (Schmidt & Roiser, 2009; Smith, Li, Becker, & Kapur, 2006). This is a shame because although findings have been mixed with regards to latent inhibition/blocking and positive psychotic symptoms, their link to schizophrenia is generally well replicated, and this has been shown across different samples when using the same task (Bender et al., 2001; Moran et al., 2003; Moran et al., 2008; Oades et al., 1996). Moreover, evidence showing that blocking is sensitive to cue salience (Denton & Kruschke, 2006; Heckler et al., 2006) and correlates with changes in overt attention during learning (Kruschke et al., 2005; Wills et al., 2007) would suggest that blocking offers an excellent index of the ability of salient stimuli to 'grab attention' in people with a psychotic illness.

1.6 Salience attribution and comorbid substance abuse and psychosis

Schizophrenia and substance abuse are highly comorbid, with prevalence estimates ranging widely across studies from between 10 and 70% (Mueser et al., 1990). Alcohol tends to be the most commonly abused drug, with elevated rates also seen for cannabis and cocaine. It is estimated that around 50% of people with schizophrenia have comorbid substance abuse and this is associated with poorer clinical outcomes in a range of domains such as medication compliance, psychotic symptoms, additional health risks and housing (Dixon, 1999). According to meta-analysis of studies worldwide, 65% of people with schizophrenia smoke tobacco, five times higher than in controls from the general population (Dixon, Haas, Weiden, Sweeney, & Frances, 1991).

Although nicotine may have the potential to alleviate a number sensory and cognitive processes that may be deficient in schizophrenia (Kumari & Postma, 2005) smoking is a major cause of coronary heart disease in these individuals which in turn is the leading cause of premature death in this population (Hennekens, Hennekens, Hollar, & Casey, 2005). One study investigating the records of 1200 people with schizophrenia found that smoking in middle age was associated with a 12-fold higher chance of death within the next 5-10 years (Kelly et al., 2011). The enormity of this problem has led to the proposal that comorbid substance abuse should be considered as a new indication for antipsychotic drug development (Awad, 2012). Whilst the relationship between substance abuse/tobacco smoking and schizophrenia has been extensively researched, the role of salience attribution in this relationship has received very little investigation up until now.

Chambers and colleagues put forward what is probably the most comprehensive theory of comorbid substance abuse in schizophrenia discussing a potential role of salience attribution (Chambers, Krystal, & Self, 2001). This ‘primary addiction hypothesis’ draws on basic

research showing that neurodevelopmental models that are able to reproduce a pathophysiology relevant to schizophrenia are also able to elicit changes similar to those seen following repeated drug administration in animal models of addiction. As such, this hypothesis states that a primary neurodevelopmental abnormality (originating in the hippocampal formation and prefrontal cortex) will not only manifest itself as schizophrenia but at the same time can make that individual biologically vulnerable to the incentive-motivational effects of drugs of abuse, even if they have never been exposed to these drugs prior to the illness.

According to this theory, dysregulation of excitatory hippocampal and prefrontal afferents to the nucleus accumbens leads to hyper-responsivity to dopamine release in the nucleus accumbens. This disruption of contextual and inhibitory influences in the brain could give rise to the symptoms of schizophrenia due to the attribution of salience to irrelevant stimuli, by abolishing processes such as latent inhibition and blocking as proposed by Gray et al. (1991). Meanwhile, the dopamine system might become sensitised in the absence of drug exposure. This, in addition to a loss of inhibitory control, might render the individual particularly vulnerable to incentive motivational stimuli and compulsive behaviours. Specifically, Chambers and colleagues suggested that the motivational salience of drugs and their associated cues should be heightened in people with schizophrenia. However they also suggested that this pathophysiology might also give rise to other motivational disturbances such as pathological gambling (Potenza & Chambers, 2001) This theory has the advantage of explaining elevated use of a range of substances that may be problematic for individual theories of self-medication based on specific symptoms (Khantzian, 1997). It is not entirely clear from this account why people might abuse substances more readily than they engage in other compulsive behaviours. One explanation for this might be a propensity for individuals to seek out more the most immediate and intense rewards (Krystal et al., 2006), namely drugs

of abuse. This explanation would also fit with the greater dopamine release associated with drugs of abuse than with natural rewards or non-drug related compulsive behaviours.

Another theory states conversely that repeated drug exposure might increase the risk of psychosis and substance abuse. Tsapakis, Murray and colleagues (O'Daly et al., 2005; Tsapakis, Guillin, & Murray, 2003) suggested that this could account for many observations of comorbid substance abuse schizophrenia. In particular they suggested that drugs of abuse (particularly amphetamine and cannabis) which are able to elicit sensitization of the dopaminergic system might increase an individual's risk of developing psychosis or bring forward the time of onset of psychosis. Evidence for dopaminergic abnormalities are far from clear in cannabis users, with mixed evidence regarding its ability to induce dopamine release in human users (Barkus et al., 2011; Bossong et al., 2008; Stokes et al., 2010; Stokes, Mehta, Curran, Breen, & Grasby, 2009) and one study reporting a reduction in dopamine synthesis capacity in frequent users compared to controls (Bloomfield et al., 2012) in contrast to the elevation seen in people with schizophrenia (Howes et al., 2012). Nevertheless cannabis may be an independent risk factor for the development of a psychotic disorder (Moore et al., 2007) and can bring forward the onset of psychosis by an average of 2.7 years (Large, Sharma, Compton, Slade, & Nielssen, 2011). With reference to salience attribution, Tsapakis and colleagues argued that sensitised dopamine release during acute schizophrenia might account for spurious associative learning in general but also towards stimuli associated with drug use. Thus, both this account and that of Chambers et al. (2001) would predict that enhanced attribution of salience to irrelevant stimuli might be accompanied by an increase of attention towards drug-related cues (Figure 1.9b).

When considering the hypothesis that repeated drug use might result in psychosis and in addictive behaviour alike, it is worth noting that these psychosis-like effects might also contribute to the development of maladaptive patterns of drug use independent of reward and

reinforcement. Viewing the parallels between the sensitisation of dopamine release in latent inhibition and drug addiction, Joseph and colleagues suggested that the ability of disrupted latent inhibition to make familiar stimuli appear salient might provide some explanation for the abuse potential of certain drugs. In other words, given that dopamine release occurs towards motivationally relevant stimuli and events generally, dopamine-augmenting drugs of abuse might be self-administrated in order to make 'a boring life more interesting' or 'widening the gates of consciousness' through enhanced salience attribution to familiar stimuli (Joseph, Young, & Gray, 1996). This account does not discuss any change in the salience of drug-associated stimuli. However it might relate to why psychotomimetic effects of drugs such as ketamine (Pomarol-Clotet et al., 2006) may be cited as reasons for continued use in people who chose to self-administer the drug, such as "melting into the surrounding", "visual hallucinations", "out-of-body experiences" and "giggliness" (Muetzelfeldt et al., 2008).

I am not aware of any theories that have explicitly predicted that salience attribution towards drug-related cues should be lower in schizophrenia than for controls. However some empirical work might tentatively hint towards this possibility. Theories of aberrant salience attribution and related processes in schizophrenia have been predominantly concerned with explaining positive psychotic symptoms (Gray et al., 1991; Kapur, 2003; Shaner, 1999). However it would appear unlikely that aberrant salience attribution might impact upon psychotic symptoms alone. For example, if motivational salience is assigned in a context-independent manner (Kapur, 2003) irrelevant stimuli and thoughts will come to the attention of the individual and might ultimately lead to delusional beliefs. However, the lack of normal synchrony between dopamine release and environment stimuli or internal representations might also entail a loss of the ability to achieve goal directed behaviour – perhaps including the attribution of salience to drug-associated stimuli (Figure 1.9c).

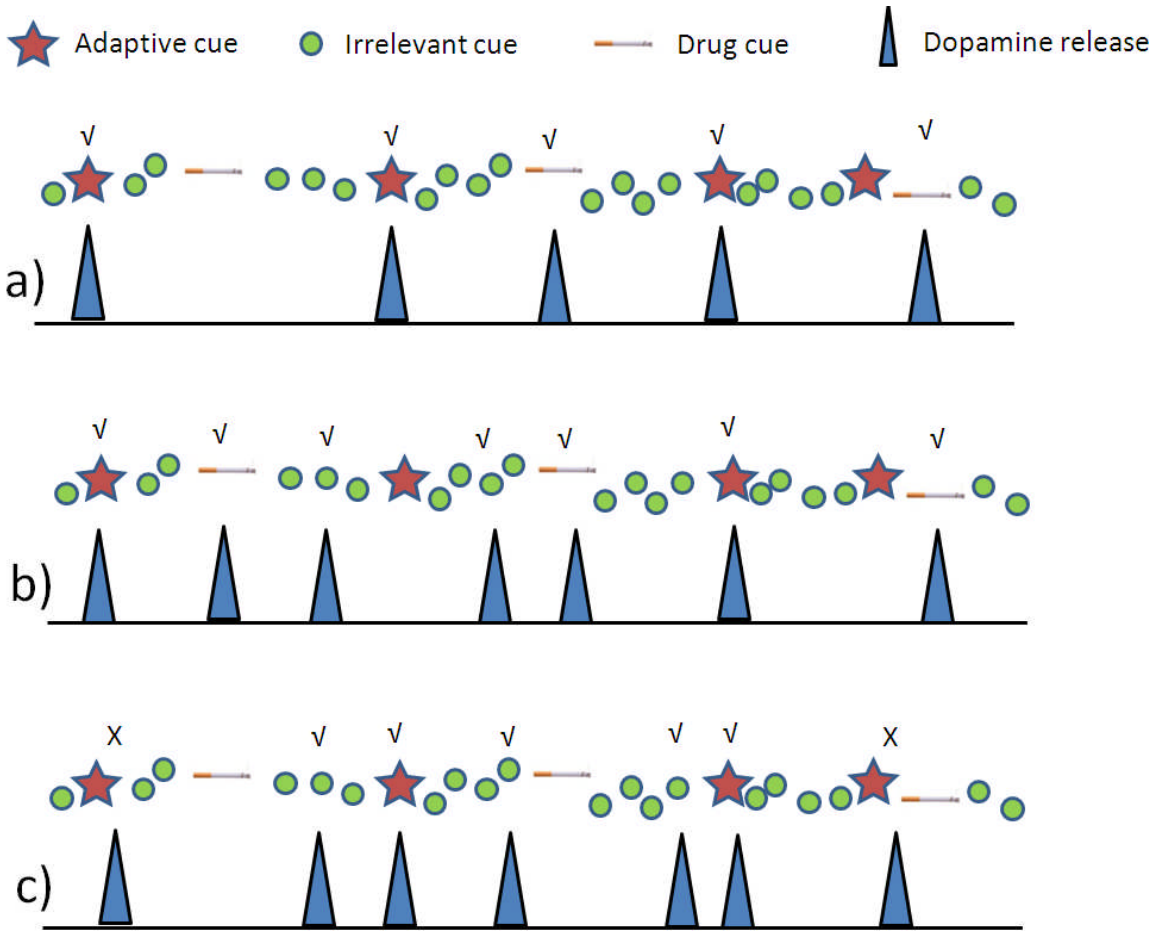


Figure 1.9: The role of dopamine in salience attribution in comorbid psychosis and substance abuse (a) In an otherwise healthy smoker, both 'adaptive stimuli' and drug cues grab attention, shown by tick marks above each type of cue (b) In psychosis aberrant salience attribution occurs to irrelevant cues. In addition, this may enhances the salience of drug cues, either directly (e.g. Tsapakis et al., 2003) or independently (Chambers et al., 2001). (c) Another possibility is that dysregulated dopamine release leads to aberrant salience, but 'false negatives' would reduce the amount of salience attributed to drug-related stimuli, demonstrated by cross marks above 'missed' stimuli.

Although this was not part of Kapur's theory, evidence from the Salience Attribution Test suggests that aberrant salience attribution correlates with negative symptoms, both in patients with schizophrenia and in controls (Roiser et al., 2009). These results have been confirmed in independent samples of healthy volunteers and a sample of people with Parkinson's

disease (Housden, O'Sullivan, Joyce, Lees, & Roiser, 2010; Schmidt & Roiser, 2009). Roiser and colleagues suggested that fluctuations in the timing of dopamine release might on the one hand lead to 'false positives' – attribution of salience to irrelevant stimuli, relating to psychotic symptoms, and at the same might result in 'false negatives', whereby an appropriately timed dopamine release is missed. In other words, context-independent dopamine release might on the one hand bring irrelevant stimuli to attention, leading to a state of aberrant salience. At the same time, this out of context firing should entail that some stimuli are not attributed with salience when in fact they were of potential motivational value, which in turn could give rise to negative symptoms such as avolition, anhedonia and social withdrawal.

These findings are also supported by evidence from other paradigms. For example as discussed above, a loss of blocking has been linked to negative symptoms as well as positive symptoms in people diagnosed with schizophrenia (e.g. Bender et al., 2001; Moran et al., 2008; Oades et al., 1996). This evidence could also indicate that a tendency to attribute predictable situations as novel and deserved of further learning might also be associated with a tendency to misattribute salience generally, perhaps leading to an inability to attribute motivational salience to cues predictive of drug reward. If the development and maintenance of drug addiction is largely a result of salience attribution towards specific drug-related stimuli, a 'noisy', chaotic state of dopamine release might impair this relationship and people with schizophrenia who use substances might be expected to attribute drug-related stimuli with less salience than people without this illness but with similar levels of drug use history.

Although this hypothesis might seem unlikely given the strong relationship between schizophrenia and substance use, it would be in agreement with different explanations for

enhanced drug use in this population[1]. For example, a self-medication hypothesis could suggest that drug use in schizophrenia might be an attempt to remove/reduce unpleasant symptoms, impairments or processes as a form of negative reinforcement (Khantzian, 1997). Elevated drug use in order to alleviate certain psychological states is supported by a large scale study (Swendsen, Ben-Zeev, & Granholm, 2011) employing Ecological Momentary Assessment (EMA) in community dwellers with a diagnosis of schizophrenia. It was found that elevations in psychotic symptoms were predictive of later substance use, and this relationship was also true in the reverse direction, whereby substance use (particularly cannabis) increased the severity of later psychotic symptoms This does support the idea that substance use in schizophrenia may be an attempt to self-medicate symptoms that emerge during the course of the illness, although not a particularly successful one in the case of cannabis. On the other hand, an alternative explanation might be that the elevation in psychotic symptoms just prior to substance use might have been accompanied by an increase in salience attribution towards drug-associated cues, priming drug-seeking behaviour.

Kapur (2003) emphasised the role of antipsychotics in dampening motivational salience in general, which would result in a loss of preoccupation with all rewarding and aversive stimuli. As a result, people with schizophrenia might be expected to use substances in order to alleviate this dysphoric state, rather than due to the enhanced salience of drug-related stimuli. On the basis of evidence that atypical antipsychotics such as clozapine are associated with lower rates of substance abuse and tobacco smoking, and have a lower affinity to D_2 receptors than typical antipsychotic drugs, Green et al. (1999) argued that substance use in schizophrenia could be linked to the re-establishment of levels of reward from life that are seen in healthy individuals, consistent with the idea that drug addiction may in general be

[1] The literature examining possible reasons for this comorbidity is extensive and this thesis does not aim to address every explanation. Rather, the aim is to establish whether an association between salience attribution and substance abuse exists in psychotic disorders.

reflective of a homeostatic mechanism to correct reward dysfunction that arises upon cessation of drug use (Koob and LeMoal, 2001).

Despite a range of theoretical approaches to understanding the role of salience attribution in substance use and psychotic disorders, there has been very little research investigating the neurocognitive basis of drug use, in contrast to the wealth of research conducted in substance use generally (e.g. the work described in section 1.3). In terms of tobacco smoking, people with schizophrenia do not differ from controls in the extent to which they show increases in subjective craving when exposed to smoking-related cues (AhnAllen & Tidey, 2011; Fonder et al., 2005; Tidey, Rohsenow, Kaplan, Swift, & Adolfo, 2008) although their responses may be more variable (Tidey et al., 2008). In contrast, cocaine abusers with schizophrenia showed a greater increase in subjective craving compared to a group characterised by cocaine dependence alone (Smelson et al., 2002). However these groups differed in their cocaine use, with the comorbid group reporting less frequent use in general but having used it more recently, and showed higher craving at baseline. Moreover, cue reactivity falls short of the requirements of salience attribution in that it does not require changes in selective attention (Field & Cox, 2008).

Interestingly, the only study to my knowledge comparing attentional bias between drug users with and without diagnosis of schizophrenia found the opposite effect to that predicted by Chambers et al. (2001) and others (Tsapakis et al., 2003). This study found evidence for attentional bias in cocaine abusers without a diagnosis of schizophrenia but no evidence of bias in comorbid individuals (Copersino et al., 2004). Furthermore, the same result was found when medicated patients were removed from statistical analysis. It should be noted however that whilst both groups were diagnosed with a cocaine use disorder, levels of cocaine use were not reported and subjective cocaine craving was lower in the schizophrenia group which might provide an alternative explanation for these findings (Field et al. 2009b).

The attribution of salience towards drug associated stimuli in schizophrenia presents a clear gap in the literature, and the hypothesis that salience attribution towards drug-related stimuli might differ in schizophrenia remains to be adequately tested. Moreover, the prediction that these processes share common neurobiological basis presents an outstanding theoretical question that might inform clinical approaches to treating people with schizophrenia who do and do not have substance use problems.

1.7 Aims of this thesis

1.7.1 Research questions and hypotheses

1) Can exposure to drug-related cues influence the attribution of salience to non-drug stimuli, and what is the role of dopamine in this process?

Based on theoretical accounts of salience attribution and a limited capacity of selective attention it is predicted that when substance users are exposed to drug-related cues, they will attribute less salience to non-drug cues directly and through associative learning processes. It is predicted that changes in craving (e.g. due to abstinence or dopaminergic manipulations) will produce corresponding changes in bias in associative learning.

2) Is there a relationship between salience attribution processes linked to addiction and those linked to psychosis?

Based on evidence for aberrant salience attribution in psychosis and in addiction, alongside the high co-morbidity of these two disorders, it is predicted that people with schizophrenia will show heightened attribution of salience towards drug-related cues compared to controls.

.

1.7.2 Methodological aims

In order to carry out the research proposed in this thesis, a novel paradigm will be developed which will aim to incorporate aspects of salience attribution that are common to both addiction and psychosis. The ability of drug-related cues to grab selective attention should entail that associative learning processes will be influenced by this bias. In particular, if attention is directed towards a drug cue and concomitantly away from other stimuli that are present, new learning may favour the drug-related stimulus at the expense of the neutral stimulus as predicted by hypothesis 1. This task will be first be developed and tested in a study of abstinent smokers, satiated smokers and non-smokers (Chapter 2).

Blocking is an associative learning paradigm is linked to changes in selective attention and is pathologically altered in schizophrenia[2]. This process therefore offers a strong experimental platform with which to investigate a potential interaction of salience attribution processes related to psychosis (blocking) and those related to drug use (attentional bias). The incorporation of drug and neutral cues into an associative learning will be employed alongside existing tasks indexing attentional bias (the visual probe and modified Stroop tasks) and clinical and psychometric indices of symptoms and psychopharmacology. If the effects of drug cues in this task co-vary with levels of blocking in general, this should imply that there is a relationship between these two processes. The pattern of results obtained should be able to determine whether psychosis is associated with enhanced attribution of salience to drug-related stimuli or vice versa.

As a preliminary step this task will be assessed in chronic ketamine users (chapter 3) who have previously been shown to have elevated 'basic' symptoms which resemble those shown

[2] Latent inhibition is another candidate process. However, if drug cues were incorporated into the pre-exposure stage of a latent inhibition task, a lack of latent inhibition might be due to the attention-grabbing properties of the cue at baseline rather than what is learned about the cue during pre-exposure. This could make it problematic to experimentally isolate 'latent inhibition' effects.

by schizophrenia-prone individuals who later transitioned to psychosis (Morgan et al., 2012). Ketamine is a dependence forming drug, with frequent users showing enhanced attentional bias towards images of ketamine and money (Morgan, Rees, & Curran, 2008) As such, frequent users of ketamine could offer a tentative and preliminary model of substance abuse and psychosis co-morbidity, and the results of this study will be used to update hypothesis 2 above.

Next, chapter 4 will assess whether smokers with schizophrenia show differential attribution of salience towards drug cues when compared to smokers from the general population, in order to test hypothesis 2.

Finally, the role of dopamine on salience attribution will be examined in chapter 5. In this study, eye tracking will be used to investigate salience attribution towards smoking-related and other reward-based images. In addition, other tasks will be used to investigate non-drug reward processing and salience attribution with relevance to drug addiction.

Chapter 2: Salience attribution and associative learning in smokers

2.1 Introduction

Learning is influenced by the characteristics and relevance of stimuli we encounter (Mackintosh, 1975, Pearce & Hall, 1980). For example if a child was simultaneously exposed to a light and a bell before lunch was served at school, both cues (light and bell) might be seen as an equally important signals of food. If the bell was extremely loud however, its intensity might 'overshadow' any role of the light in the prediction of food (Mackintosh, 1976). Alternatively, consider a child who is exposed to a light and a bell predicting food at a new school. Again, both cues might be seen as equally important as each other. However, if the child had previously experienced that a light alone signalled food, 'blocking' should reduce the amount of associative learning that takes place between the bell and food (Kamin, 1969).

Associative learning is thought to be influenced by the amount of attention directed towards individual cues during training (Mackintosh, 1975, Pearce and Hall, 1980). Support for this possibility comes from paradigms that have manipulated the properties of cues used in associative learning tasks such that some are more perceptually salient than others. The results of these studies have shown that when two cues of differing salience predict the same outcome, the cue of lower salience is overshadowed by the more salient cue (Heckler et al., 2006; Kruschke et al., 2006). Moreover, differences in salience influence blocking: A more salient cue will block a less salient cue more effectively than an equally salient cue; conversely a highly salient cue is less able to be blocked by a less salient cue than one of equal salience (Heckler et al., 2006; Kruschke et al., 2006).

Tobacco smokers show a bias in attention towards smoking-related cues, and this bias can be exacerbated during abstinence (Field et al., 2004; Gross, Jarvik, & Rosenblatt, 1993). If

selective attention contributes to overshadowing and blocking, and is particularly biased towards smoking-related images during abstinence, abstaining smokers might be expected to show an overshadowing of neutral cues and as well as modulation of blocking by drug related stimuli. If these effects act to impinge on the attribution of salience to non-drug stimuli, they might potentiate deficits in incentive motivational processes. For example when compared to satiety, nicotine abstinence can dampen the attention grabbing properties of motivationally salient words (Powell, Tait, & Lessiter, 2002), reduce effort-related speeding on a behavioural task e.g. (Al-Adawi & Powell, 1997; Powell, Dawkins, & Davis, 2002) and increase the tendency to discount rewards that are temporally delayed (Field, Santarcangelo, Sumnall, Goudie, & Cole, 2006; Mitchell, 2004; Yi & Landes, 2012)

However it is not yet known whether exposure to drug cues can impinge on the motivational salience of non-drug cues through associative learning processes such as blocking and overshadowing. The present study therefore aimed to determine this with individuals who were smokers and were either satiated or temporarily abstinent from cigarettes. 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.

2.2 Methods

2.2.1 Design and participants

A between subject design compared 24 Controls (reporting never to have smoked tobacco >1 time a month lifetime), 24 satiated smokers ('Smokers') and 24 smokers instructed to abstain for at least 12 hours 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 ten cigarettes per day for at least one year, (ii) smoke a first cigarette within an hour of waking, and (iii) not currently 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 a (i) learning impairment, (ii) mental health problem or (iii) substance abuse problem. All participants provided written, witnessed, informed consent. This study was approved by the UCL Psychology and Language Sciences Ethics Committee (Appendix 1 and 2).

2.2.2 Assessments

Drug Cue Reward Prediction Error Task (DCRPET)

This was a novel computer based task designed specifically for the current study. 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 shown is shown in figure 2.1). 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, whilst avoiding any connotations of health or addiction (e.g. allergic

reactions resulting from drugs) (Matute, Arcediano, & Miller, 1996). Stimuli were color photographs of household items (12 neutral items, e.g. hammer, book, desk light, shaver) and 4 smoking items (cigarette pack, single cigarette, ashtray, lighter), all chosen to be white, grey or silver in color in order to control for perceptual salience. Each time the experiment was run these items were randomly assigned to the 12 neutral and 4 smoking cues used in the DCRPET (task design shown in table 2.1).

Trials were randomized within each of 6 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 that trial was worth (either 5p or 10p; financial value did not differ across items) in color 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.

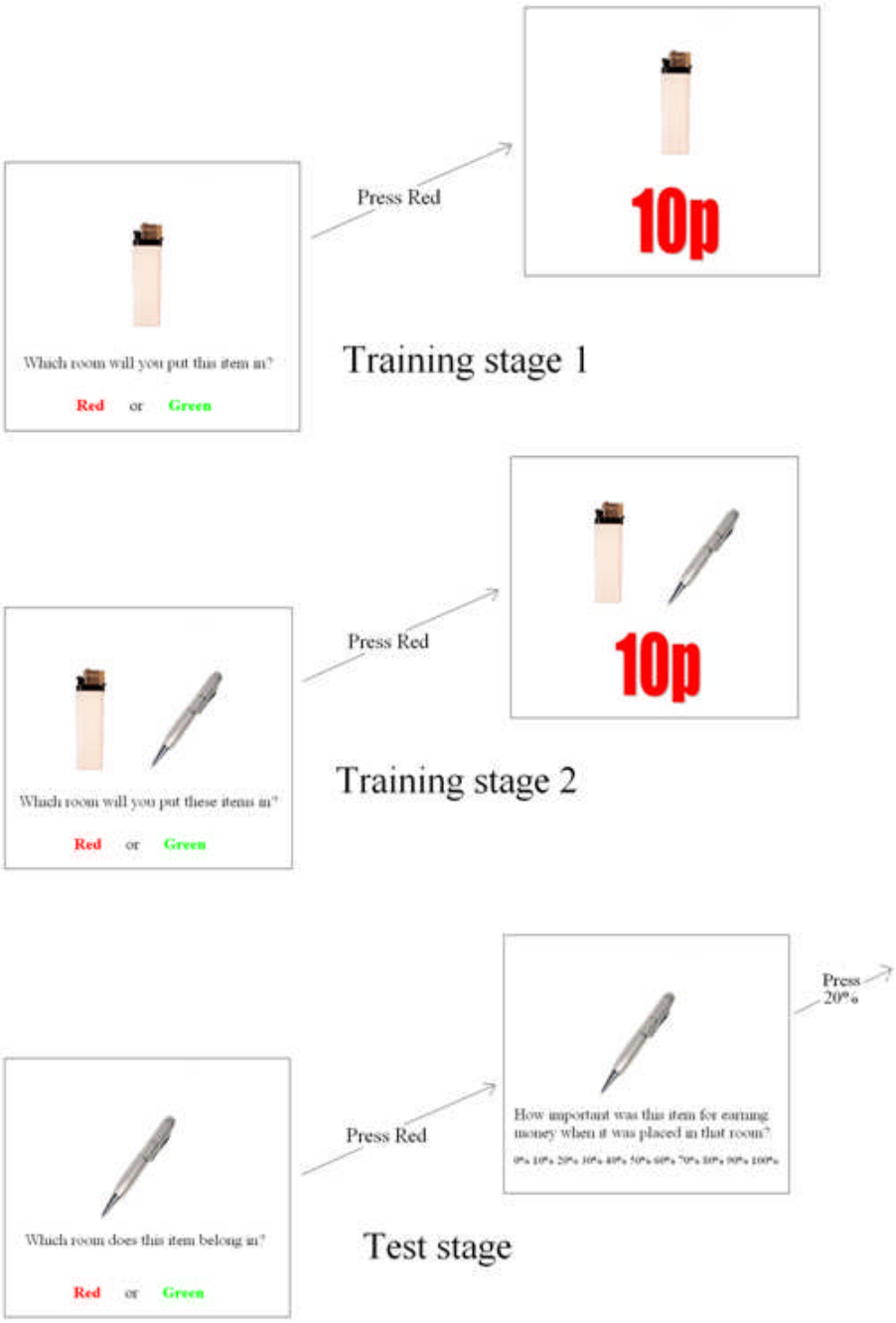


*Figure 2.1: trial structure of the DCRPET. This example demonstrates a neutral cue being blocked by a drug cue. In training stage 1, trial and error learning allows participants to associate this cue with the red room (**I**→Red), and in training stage 2, it is again associated with the red room alongside a novel but redundant cue (**I**+j→Red). At the test stage low associative strength between this novel cue (shown here as a pen) and the outcome would imply that it had been blocked with regards to the outcome.*

Table 2.1: Design of the DCRPET. The task consisted of 3 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.

Salience manipulation	**Training stage 1:**	**Training stage 2:**	**Test stage**:
	1 item predicts reward	2 items predict reward	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 of a drug cue	g→Red	g+**H**→Red	**H**
Blocking by a drug cue	**I**→Red	**I**+j→Red	j
	U→Green	**U**+v→Green	
Filler trials	W+x→Red	-	No test
	y+z→Green	-	

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) and (ii) how important they were for earning money when placed in that room, from 0 to 100 in 10% intervals. Data were analysed for accuracy, importance, and also composite scores in which importance scores (with 10% added in order to weight guesses) were positively scored for correct choices and negatively scored for incorrect choices (see Beesley & Le Pelley, 2011 for a similar method). Higher scores are reflective of stronger associative learning and valuation of the reward-

based outcomes, lower scores might be expected for blocked cues or cues that were overshadowed. The scores for blocked cues were compared to scores for 'control' cues which had undergone the same associative training with the outcome but had not been subjected to blocking.

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 coloured 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 250ms and twice for 2000ms 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 trials 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) (Heishman, Singleton, & Pickworth, 2008)

This 12 item short form of the 47 item TCQ (Heishman, Singleton, & Moolchan, 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' and '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 is not reported for controls.

Fagerstrom Test of Nicotine Dependence (FTND)(Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991) A scale of nicotine dependence shown to be a reliable indicator of smoking behaviour according to biochemical verification, the FTND 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) (Wechsler, 2001)

The Wechsler Test of Adult Reading provides an estimate of verbal IQ. Participants are required to read a list of 50 words aloud; each correct pronunciation scores 1 point.

2.2.3 Procedure

Prior to testing, an assistant used a handheld smokerlyzer (Bedfont Scientific Limited) to assess exhaled CO levels. A threshold of ≥11ppm CO was used to exclude any Abstainers suspected to have smoked within 12 hours prior to testing, consistent with previously used cut off criteria (Dawkins, Acaster, & Powell, 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, dot probe, and the WTAR.

2.2.4 Statistical analyses

All analyses were carried out using Statistical Package for Social Sciences (SPSS version 14). One way ANOVAs 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's. Extra within subject factors of Cue (a**B**, cd, e, g, **I** , a**B**, cd, ef, g**H, I**j) and Block (1-6) were included for accuracy data from training stages 1 and 2. For analysis of blocking, the same control cue score (collapsed scores from c and d) was compared against each of the three blocked cue scores. *A priori* planned orthogonal contrasts were therefore used to compare: (i) the control cue to all three blocked cues together (f, **H**, j) (ii) the neutral blocked cue (f) to the remaining two blocked cues (**H**, j) (iii) the drug cue blocked by a neutral cue (**H**) with the neutral cue blocked by the drug cue (j). 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 using an inverse transformation based on a previous study (Mogg, Garner, & Bradley, 2007) 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.

2.3 Results

Participants and smoking behaviour (Table 2.2)

One participant in the Abstainer group was excluded after providing a CO level ≥11ppm and subsequently replaced, but all other Abstainers gave levels in accordance with instructions not to smoke (≤6ppm). The three groups did not differ in any demgraphic 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 cessation pharmacotherapy (e.g. varenicline, bupropion). A Kruskal Wallis test revealed group differences in expired CO, ($\chi^2_2 = 56.322$, $p < 0.001$). Bonferroni corrected Mann Whitney U tests (α level adjusted to 0.016) showed that CO levels were higher in Smokers compared to both Controls ($U_{48} = 0.000$, $p < 0.001$) and Abstainers ($U_{48} = 23.00$, $p < 0.001$), and in Abstainers compared to 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.

Table 2.2: Smoking behaviour and group demographics. WTAR: Wecshler Test of Adult Reading; FTND: Fagerström Test of Nicotine Dependence; TCQ: Tobacco Craving Questionnarie Short Form.

	Controls	**Smokers**	**Abstainers**
Gender (M/F)	11/13	14/10	15/9
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)
N cigarettes/day		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)
TCQ Emotionality		10.58 (5.20)	12.25 (4.13)
TCQ Expectancy		14.04 (5.15)	18.13 (2.15)*
TCQ Compulsivity		9.71 (4.52)	10.25 (5.07)
TCQ Purposefulness		13.29 (4.41)	14.96 (2.58)

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

Drug Cue Reward Prediction Error Task

Learning during training stages (Figure 2.2)

A significant Cue x Block interaction $F_{35,70} = 3.076$, $p = 0.001$, η_p^2=0.036 and significant effects of Cue $F_{7,70} = 12.110$, $p < 0.001$, η_p^2=0.118 and Block $F_{7,70} = 12.110$, $p < 0.001$, η_p^2=0.432 were found. Exploration of the interaction by assessing effects Block in RMANOVA models for each Cue (α adjusted to 0.00625) revealed significant effects of Block for all novel cues in training stages 1 and 2 (e, g, **I**, ab, cd, all *F*'s > 7.435, all *p*'s < 0.001) but not for blocking cues (ef, g**H**, **I**j; all *F*'s < 3.044, all *p*'s > 0.01).

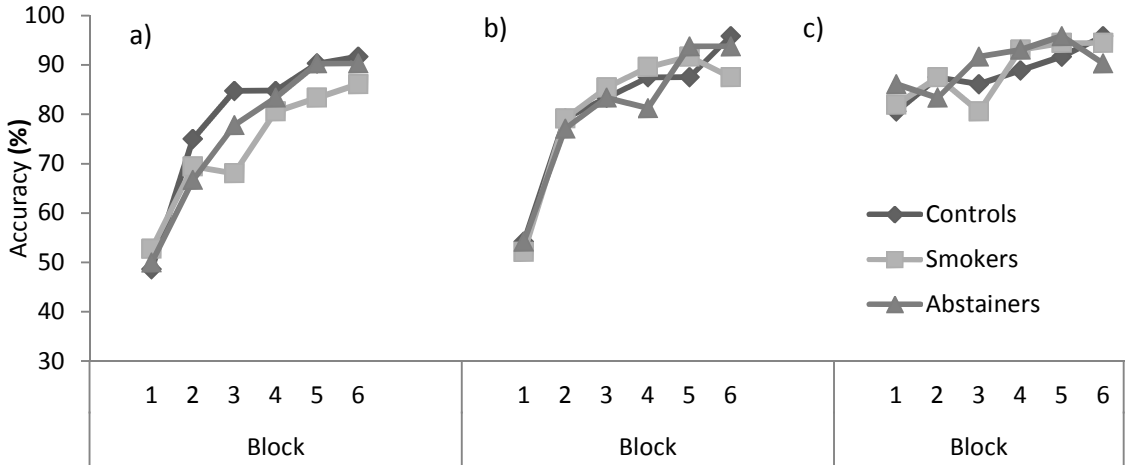


*Figure 2.2: Learning cue-outcome contingencies during the training stages of the DCRPET. a) In training stage 1, accuracy to stage 1 cues (e, g, **I**)increased progressively across blocks to ceiling level. b) Pairs of novel cues in stage 2 (a**B**, cd) again underwent progressive learning in training stage 2. c) Crucially, accuracy during stage 2 to pairs consisting of one pretrained (i.e. blocking) cue and one novel but redundant (i.e. blocked) cue (ef, g**H**, **I**j) began at ceiling level, implying that cue-outcome learning was transferred across training stages. Since there was no prediction error for these cue pairs, learning between the blocked cue and the outcome should be retarded, reflected by low accuracy at the test stage.*

Test stage

Accuracy (Table 2.3): A trend for an effect of cue emerged for overshadowing $F_{1,69} = 2.949$, $p = 0.090$, $\eta_p^2 = 0.041$, indicating higher accuracy to the drug cue compared to the neutral cue. No significant effects emerged for analysis of overshadowing or blocking.

Importance (Table 2.3): A significant effect of cue emerged for analysis of overshadowing ($F_{1,69} = 5.207$, $p = 0.026$, $\eta_p^2 = 0.070$) indicating higher importance ratings to the drug cue compared to the neutral cue. No other effects were found.

Accuracy x importance

For analysis of overshadowing, one Smoker and one Abstainer were excluded for individual scores that were > 2.5 standard deviations from the Group mean. A Cue x Group interaction ($F_{2,67} = 3.833$, $p = 0.027$, $\eta_p^2 = 0.103$) and a main effect of Item ($F_{1,67} = 7.384$, $p = 0.008$, $\eta_p^2 = 0.099$) were found, 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 to 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 that the drug cue significantly overshadowed the neutral cue in this group (Figure 2.3)

Table 2.3: Accurcy and importance scores from the test stage of the DCRPET.

	Controls	Smokers	Abstainers
a accuracy	91.67±28.23	91.67±28.23	79.17±41.49
B accuracy	87.50±33.78	100.00±0.00	95.83±20.41
cd (control cue) accuracy	87.50±30.40	87.50±26.58	85.42±23.22
f accuracy	75.00±44.23	91.67±28.23	79.17±41.49
H accuracy	70.83±46.43	91.67±28.23	83.33±38.07
j accuracy	79.17±41.49	75.00±44.23	70.83±46.43
a importance	50.42±17.32	57.08±26.12	49.58±26.29
B importance	55.83±23.02	58.33±26.15	70.00±21.26
cd (control cue) importance	48.13±19.38	48.54±20.03	52.92±19.33
f importance	47.92±18.88	46.67±24.61	46.67±21.80
H importance	54.58±28.59	47.92±27.34	49.58±27.42
j importance	49.58±24.22	43.75±23.92	49.58±27.10

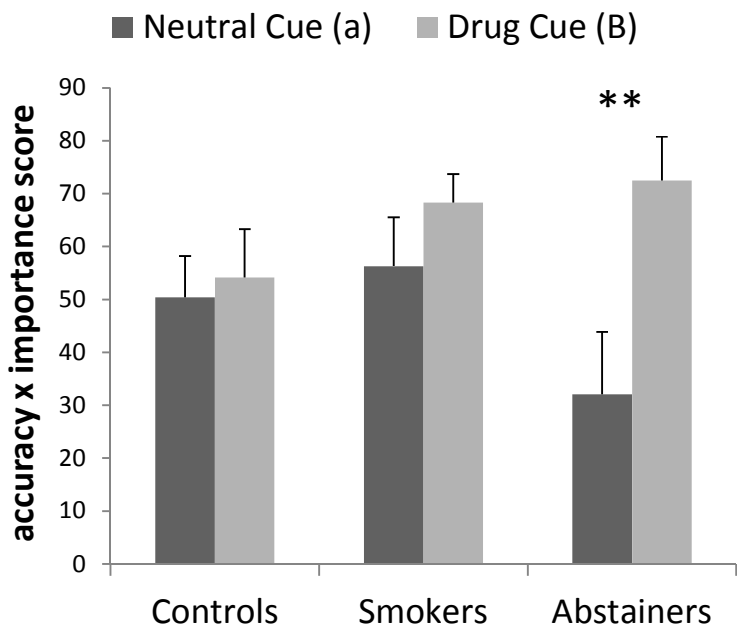


Figure 2.3: Drug-cue induced overshadowing according to choice x importance ratings for the neutral cue and drug cue in each group. Error bars show SEM.

For analysis of blocking (Figure 2.4) one control was excluded for scoring >2.5 standard deviations from the group mean. A significant main effect of contrast (i) was found ($F_{1,68}$ = 4.088, p = 0.047, η_p^2 = 0.057) indicating a main effect of blocking in all groups, 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 x Group interactions emerged for contrasts (i), (ii) and (iii).

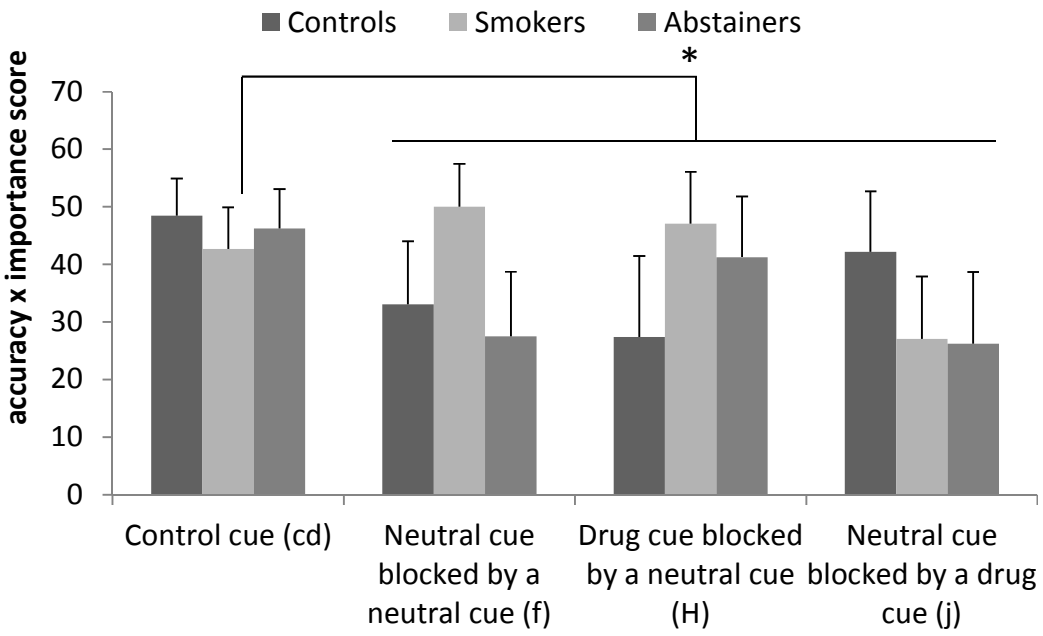


Figure 2.4: Blocking according to choice x importance ratings. A main effect of blocking was found across the groups. However no interactions emerged for contrasts examining the effects of drug cues on blocking. Error bars show SEM

Dot probe (Table 2.4)

Analysis of reaction times to probes following images shown for a short (250ms) exposure time revealed a significant Group x Validity interaction ($F_{2,69}$ = 3.831, p = 0.026, η_p^2=0.100) 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 (p=0.018) but not in satiated smokers (p=0.221) or controls (p=0.174). At the long (2000ms) exposure time, no significant interactions or effects emerged.

Table 2.4: Attentional bias on the dot probe task. 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.

	Controls		**Smokers**		**Abstainers**	
	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)

Correlations

Pearson correlations were conducted between the degree of drug-cue induced overshadowing (choice x importance score to the drug cue – choice x 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.

2.4 Discussion

There were three main findings in this study. Firstly 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. Secondly all three groups exhibited blocking, and the use of drug cues as reward predicting cues did not interact with blocking in any group. Thirdly, abstaining smokers but not satiated smokers or controls showed an attentional bias towards cigarette related images displayed for a short duration.

Analysis of responses on the DCRPET during training stages showed that participants were able to learn correct responses to all items presented. At the test stage, when comparing these test scores to two items presented as a pair with the same outcome (a smoking related image and a neutral image) accuracy and importance scores revealed a tendency for drug cues to overshadow neutral cues in all groups. However, choice x importance scores revealed an interaction with group, whereby drug cues overshadowed neutral cues in 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. 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 according to choice x accuracy ratings. 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 in the populations tested here. However, blocking was only evident when analysing composite accuracy x importance scores rather than these scores independently and had a small effect size. Thus, it is possible that interactions with drug cues and blocking might arise using a different task design or scenario.

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 (250ms) duration. Automatic attentional bias has previously been shown amongst satiated smokers compared to controls (Bradley, Field, Mogg, & De Houwer, 2004; Ehrman et al., 2002; Mogg et al., 2003). One study using eye tracking found an increase in bias of maintained attention during abstinence but no change in initial orienting (Field et al., 2004) 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.

No bias was shown in either smoking group when images were shown for a longer (2000ms) 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., 2004; Bradley, Mogg, Wright, & Field, 2003), gaze duration using eye tracking provides a more direct measure of strategic bias in smokers e.g. (Mogg et al., 2003) 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) whilst others (Mogg et al., 2003) have incorporated choices that may not be detectable in peripheral vision (e.g. upwards or downwards arrow).

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 and mean FTND scores in both groups reflected moderate dependence. Carbon monoxide levels were reliably different across groups and confirmed that abstainers had refrained from smoking for at least 12 hours prior the the study commencing. Abstainers showed higher craving than satiated smokers according to the 'expectancy' subscale of the TCQ-SF (Heishman et al., 2008) which reflects anticipated pleasure from smoking.

Overshadowing is highly dependent on the perceptual salience of cues employed in associative learning tasks (Denton and Kruschke, 2006; Heckler et al. 2006) and abstaining smokers showed an attentional bias towards drug-related images on the dot probe task. Although scores from these tasks did not correlate with each other, this does tentatively suggest when drug-related cues are highly salient, other cues that are predictive of reward may be attended to less, resulting in a loss of associative learning between those cues and the motivational outcomes they coincide with. This provides a novel explanation for the loss of motivational salience that might occur with respect to non-drug cues in drug-related contexts. The overshadowing of neutral cues in this reward prediction paradigm adds to previous evidence for disrupted reward processing following tobacco deprivation (Al-Adawi & Powell, 1997; Field et al., 2006; Mitchell, 2004; Powell, Dawkins, et al., 2002; Yi & Landes, 2012).

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 D2 antagonist pretreatment (Crider, Solomon, & McMahon, 1982) whilst disrupted overshadowing following amphetamine treatment can be restored with co-administration of a D1 but not D2 antagonist (O'Tuathaigh & Moran, 2002) These findings suggest that D1 and D2 receptors control overshadowing and blocking respectively, in agreement with a role of prefrontal D1 but not D2 receptors in controlling selective attention (Granon et al., 2000). Another consideration is that drug cues might only influence blocking in conditions where it is already perturbed, such as in acute schizophrenia (e.g. Jones et al., 1992).

In terms of limitations, abstinent and satiated smokers were compared independently as separate groups, 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, this design was chosen over a within-subject design because the repeated use of an associative learning task might lead to carry over effects in a within-subject design. Further, there are only a limited number of discrete and conceptually different smoking cues that could potentially be used to create the different task versions needed for repeated measures.

Despite these limitations, the study had a number of important strengths. Firstly, smokers were randomly allocated to abstinent or satiated group, secondly, all assessments took place under blind conditions, and thirdly, a within subject saliency manipulation was used, in contrast to previous investigations in humans that have investigated salience between subjects (Denton and Kruschke, 2006; Heckler et al., 2006).

In summary, abstinent smokers but not satiated smokers nor controls showed an overshadowing of neutral cues that were equally predictive of reward. The magnitude of this effect in abstaining smokers was correlated with expired CO, which in turn was correlated with tobacco craving. This study provides the first evidence that drug cues are able to interact with the salience of cues that do not predict a drug-related outcome and support a role of attention in this relationship.

Chapter 3: Salience attribution in ketamine users with symptoms of dependence and subclinical delusional beliefs

3.1 Introduction

Blocking refers to the reduction in new learning that typically occurs towards outcomes with well-established causes. A loss of blocking is thought to be an important cognitive abnormality in psychosis (Fletcher & Frith, 2008; Gray et al., 1991) by allowing irrelevant stimuli to influence perception and learning processes, making highly predictable events appear novel and surprising. In animals, blocking is attenuated by chronic amphetamine treatment, an effect that can be prevented by co-administration of haloperidol (Crider et al., 1982). However in humans, acute amphetamine administration has not produced an adequate model of the loss of blocking seen in acute schizophrenia (Gray et al., 1997; Jones et al., 1997). Although blocking is disrupted in schizophrenia, the pharmacological basis of this process remains to be established.

Repeated exposure to the N-methyl-D-aspartate (NMDA) receptor antagonist ketamine can model many of the positive, negative and cognitive symptoms that characterise schizophrenia (Corlett, Honey, Krystal, & Fletcher, 2010; Morgan & Curran, 2006). For example, regular use of ketamine is associated with elevated schizotypy and depression (Curran & Morgan, 2002; Morgan, Muetzelfeldt, & Curran, 2009) and these symptoms have been linked to a reduction in blocking in the general population and people with schizophrenia (Bender et al, 2001; Haselgrove & Evans, 2010; Moran et al., 2003; 2008). Intriguingly daily ketamine users show elevations in subclinical 'basic symptoms' that closely resembled a group of prodromal individuals who later transitioned to psychosis (Morgan et al., 2012). In terms of associative learning, ketamine users adopt superstitious conditioning more readily than controls (Freeman et al., 2009), and when employing a causal learning task in healthy

volunteers, Corlett et al. (2006) found that an acute dose of ketamine impaired their ability to distinguish between expected and unexpected events according to BOLD signal in right prefrontal cortex (rPFC). Based on these observations, I would predict that an attenuation of blocking should be observed in ketamine users.

Users of many dependence-forming substances including ketamine show a bias of attention towards drug-related words or images (Morgan et al., 2008) and this process is thought to play a causal role in drug seeking. Crucially however, attentional bias towards drug cues may deplete attentional resources such that processing of other, non-drug cues may be compromised (Franken, 2003). Limitations in the capacity of attentional processing are thought to explain why redundant cues are blocked or overshadowed during cue competition (Pearce & Hall, 1980), and exposure to drug cues might therefore limit addicts' ability to learn about other motivationally important cues in their environment. This effect could contribute to competition between drug and non-drug rewards in addicted individuals, which can be potentiated during craving and withdrawal (Goldstein & Volkow, 2011). For example, abstaining smokers correctly assign less importance to reward predicting cues when they competed with drug cues for attention during training (chapter 2). This effect of drug cue induced overshadowing was accompanied by an attentional bias to smoking images and was absent in satiated and control groups.

In the present study, we administered the DCRPET to a group of ketamine users and a polydrug control group in order to assess blocking and overshadowing to neutral and drug-related cues. Firstly, based on previous observations that ketamine users show elevated schizotypal and depressive symptoms, we predicted that blocking would be attenuated in ketamine users. Secondly, based on the ability of drug cues to command selective attention we predicted that the extent of blocking would depend on whether drug cues acted as

‘blocking’ or ‘blocked’ stimuli, and that drug cues would overshadow neutral cues in ketamine users.

3.2 Methods

3.2.1 Design and participants

A between subject design was used to compare 18 ketamine users (ketamine use at least once a week and for at least 3 years) with 16 polysubstance using controls (use of drugs other than ketamine). This design was chosen to provide sensitivity to ketamine-related effects by controlling for the polydrug use typical of those who regularly the drug (e.g. Curran & Morgan, 2002), rather than a normative sample from the general population. All participants provided written, witnessed, informed consent. This study was approved by the UCL Graduate School Ethics Committee (Appendix 3 and 4). The following measures were administered:

3.2.2 Assessments

Drug Cue Reward Prediction Error Task (DCRPET)

The task was similar to that presented in chapter 2. However, cues were pictures of ketamine related stimuli (white crystalline powder in a clear bag, on an opaque surface, on a credit card, and a folded sheet of magazine used to wrap ketamine) or neutral laboratory items matched for perceptual characteristics (e.g. pestle and mortar, copper sulphate, latex gloves, bunsen burner, metal wire, test tube stand, flask). Furthermore, training stages contained 8 blocks rather than 6 in order to ensure high accuracy by the end of training. Finally, test scores were obtained for the blocked cue 'l' rather than using it as filler trial in chapter 2. The task design is shown in (Table 3.1).

Table 3.1: Design of the DCRPET. Single cues (training stage 1) and then pairs of cues (training stage 2) were trained for their association with outcomes (red or green) during the task. Neutral cues are shown in normal text and drug cues are shown in bold capitals; pictorial cues were randomly assigned to cues each time the experiment was run.

Selective learning mechanism	**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	**B**
Control for blocking		c+d →Red	d
Blocking	e→Green	e+f→Green	f
Blocking of a drug cue	g→Red	g+**H**→Red	**H**
Blocking by a drug cue	**I**→Red	**I**+j→Red	j
	K→Green	**K**+l→Green	l
Filler trials	w+x→Green	-	No test
	y+z→Red	-	

Drug history: A comprehensive history of self-reported ketamine use was assessed using weekly calendar charts. Each calendar consisted of a 7 x 2 table with 'AM' and 'PM' sections for each day of the week and participants indicated the amount they typically consumed by marking an X for every gram in individual cells of the calendar. A new calendar was used for each time period at which one's level of use changed, from when ketamine was first tried to the current amount. Other drugs that were currently used at least once a month were reported according to number of days per month, amount used per

session, years used and days since last use in both groups, and urine analysis was used to confirm recent use.

Schizotypal Personality Questionnaire (SPQ)(Raine, 1991): A 74 item self-rated inventory of schizotypal personality. Data are presented according to a three factor model of schizotypy consisting of Cognitive/Perceptual, Interpersonal and Disorganised subscales (Raine, Reynolds, Lencz, & Scerbo, 1994).

Peters' Delusion Inventory (PDI)(Peters, Joseph, & Garety, 1999): A self-rated scale of delusional ideation. The PDI consists of 21 items and a 'Yes/No' score is obtained according to the number of items endorsed. These items are additionally rated for the 'Preoccupation', 'Conviction' and 'Distress' they are associated with.

Beck Depression Inventory (BDI-II)(Beck, Steer, & Brown, 1996). A 21 item self-rated inventory of depression over the previous week.

Leeds Dependence Questionnaire (LDQ)(Raistrick et al., 1994). A 10 item scale designed to assess degree of drug dependence and administered here with reference to ketamine. Each item is scored from 0 to 3, giving a maximum score of 30.

Spot the word (Baddeley, Emslie, & Nimmo-Smith, 1992). This task was used to measure premorbid intelligence. Scores correlate strongly with verbal IQ, and 1 point is awarded for each of 60 items, giving a maximum score of 60.

3.2.3 Procedure

Participants completed the assessments in the following order: drug history, spot the word, BDI, PDI, SPQ, DCRPET.

3.2.4 Statistical analysis

All analyses were conducted using Statistical Package for Social Sciences (SPSS) version 18. χ^2 tests and ANOVA models were used to assess effects of Group (Mann Whitney U tests where data violated assumptions of parametric analysis). Extra within subject factors of Cue (a**B**, cd, e, g, **I**, **K** a**B**, cd, ef, g**H, I**j, **K**l,) and Block (1-8) were included for accuracy data from training stages 1 and 2. For test stage data, responses to cues that were equivalent with each other on the task (c and d, j and l) were combined to form single scores. Overshadowing was examined using RMANOVA's with a between subject factor of Group and a within subject factor of Cue (a, **B**). In order to assess blocking the control cue score (c and d collapsed) was used as a baseline. *A priori* planned orthogonal contrasts were used to compare, (i) the control cue to all three blocked cues together (f, **H**, jl) (ii) the neutral blocked cue (f) to the other two blocked cues (**H**, jl) (iii) the drug cue blocked by a neutral cue (**H**) with the neutral cue blocked by the drug cue (jl). Post hoc t-tests were Bonferroni-corrected and the Greenhouse-Geisser correction was used where data violated the assumptions of sphericity.

3.3 Results

Demographics, psychological wellbeing and drug use (Table 3.2)

Groups did not differ in gender or verbal intelligence as measured by 'spot the word' scores, but ketamine users were older and had spent fewer years in education than controls. Ketamine users scored higher than controls on the BDI, the Cognitive/Perceptual, Interpersonal and Disorganized subscales of the Schizotypal Personality Questionnaire, and on the Yes/No, Distress, Preoccupation and Conviction subscales of Peters' Delusion Inventory. They reported to have been taking the drug for 10.39 (±3.58) years, and estimated that they were currently using 9.27 (±8.40) grams over 4.67 (±1.88) days in an average week, with last use 1.72 (±1.45) days ago. The mean lifetime number of grams consumed was estimated at 4431.17 (±2865.46) grams and Leeds Dependence Questionnaire scores were on average 14.83 ±6.68, reflecting moderate to high dependence (Raistrick et al., 1994). The ketamine group consisted of more current users of cocaine and cannabis, had been using cannabis and alcohol for more years, and consumed more units of alcohol per session than controls, but no other significant group differences were found. No participants reported use of any drugs within 24 hours prior to testing, suggesting that the observed effects were due to chronic rather than acute on chronic exposure.

Table 3.2: Demographic data, psychosis-like symptoms and other drug use in controls and ketamine users. BDI: Beck Depression Inventory, SPQ: Schizotypal Personality Questionnaire; PDI: Peters' Delusion Inventory.

	Controls	Ketamine users	χ^2_{1} / t_{32}
Gender (male/female)	9/7	13/5	0.95
Age	26.25 ±5.60	30.50 ±6.00	2.13*
Years in education	17.50 ±3.44	14.09 ±3.03	3.03**
Spot the word	49.25 ±4.84	48.83 ±6.77	0.20
BDI	5.56 ±8.40	16.44±11.52	3.113**
SPQ cognitive/perceptual	2.00 ±2.63	11.50 ±8.14	†39***
SPQ interpersonal	4.56 ±3.41	11.83 ±8.84	†74.5*
SPQ disorganized	3.50 ±5.11	9.83 ±3.63	4.20***
PDI yes/no	1.88 ±3.18	8.06 ±4.65	4.47***
PDI distress	3.69 ±6.14	18.00 ±13.33	†36.5***
PDI preoccupation	3.69 ±7.12	19.93 ±17.06	†29.5***
PDI conviction	5.50 ±10.82	26.06 ±16.31	4.27***
Alcohol currently used (Y/N)	16/0	17/1	0.92
Alcohol days per month	8.16 ±6.03	13.59 ±10.97	†97.50
Alcohol years used	10.75±6.76	17.88 ±5.62	3.30**
Alcohol amount per session (units)	5.38 ±3.44	7.93 ±4.95	#†84.50
Alcohol last use (days)	4.50 ±4.41	3.06 ±4.89	0.89
Cocaine currently used (Y/N)	1/15	9/9	7.81**
Cocaine days per month	2.00	4.22 ± 4.55	0.46
Cocaine years used	7.00	10.11 ±4.65	0.64
Cocaine amount per session (g)	0.50	1.03 ±1.14	0.44
Cocaine last use (days)	3	13.00 ±9.1	1.05
MDMA currently used (Y/N)	1/15	5/13	2.70
MDMA days per month	1.00	2.20 ±1.64	0.67
MDMA years used	5.00	11.60 ±4.22	1.43
MDMA amount per session (g)	0.15	0.39 ±0.34	0.65
MDMA last use (days)	24.00	11.60 ±9.13	1.24
Cannabis currently used (Y/N)	3/13	12/6	7.89**
Cannabis days per month	10.33 ±12.86	22.92 ±11.09	1.71
Cannabis years used	9.00±1.73	17.33 ±6.05	2.30*
Days taken to smoke 3.5g cannabis	10.67 ±10.02	5.71 ±6.61	1.06
Cannabis last use (days)	15.00 ±14.53	3.42 ±6.71	2.137

*p<*0.05;** 0.01;***0.001;* †Non parametric Mann-Whitney U statistic reported; #two ketamine users were unable to provide an estimate of units consumed due to varying habits.

Drug Cue Reward Prediction Error Task (DCRPET)

Learning in training stages 1 and 2 (Figure 3.2)

A significant Cue x Block interaction emerged ($F_{16, 500} = 4.198$, $p < 0.001$ η_p^2=0.116) as well as main effects of Cue ($F_{6,500} = 7.740$, $p < 0.001$, η_p^2=0.195) and Block ($F_{4,500} = 53.091$, $p < 0.001$, η_p^2=0.624). No other significant effects or interactions emerged. The Cue x Block interaction reflected progressive learning from chance to ceiling level for single cues and pairs of cues that were novel, as evidenced by significant linear effects of Block (e, g, **I**, **K**, a**B**, cd; all $F_{1,32}$'s > 17, all p's <0.001), but no effect of Block for pairs of cues consisting of one pretrained cue and one redundant cue (ef, g**H**, **I**j, **K**l; all Block $F_{1,32}$'s < 3, all p's >0.05). Thus, accuracy was high in both groups and transferred across stages (Figure 3.2).

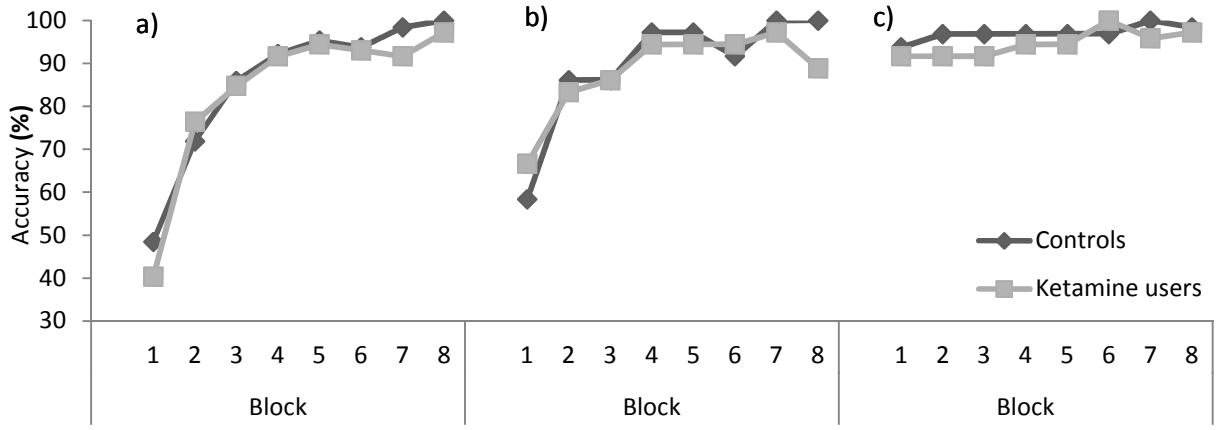


Figure 3.1: Learning cue-outcome contingencies during the training stages of the DCRPET. Both groups showed progressive learning for novel cues presented in training stage 1 (a), novel cues in training stage 2(b) and pre-trained/novel cue pairs in training stage 2 (c).

Test stage

Due to a recording error, 5 participants (4 controls and 1 ketamine user) had data missing for 1 of the 8 cues in the test stage. This 4.25% of test stage data was replaced by substituting the group mean.

Accuracy (Table 3.3)

Overshadowing: For accuracy scores, a significant effect of Cue emerged ($F_{1,32}$ =4.541, p = 0.041; η_p^2 = 0.124) indicating that accuracy was higher for the drug cue (**B)** than the neutral cue (a) in both groups.

Blocking: Significant Group x Cue interactions were found for the contrast comparing the control cue vs. all blocked cues ($F_{1,32}$ =6.342, p = 0.017; η_p^2 = 0.165) and the contrast comparing the drug cue blocked by a neutral cue (**H**) vs the neutral cue blocked by a drug cue (jl) ($F_{1,32}$ =5.022, p = 0.032; η_p^2 = 0.136). No other significant interactions or main effects emerged. The first interaction reflected higher accuracy in ketamine users compared to controls for all blocked cues combined (t_{32} = 2.308, p = 0.022), but no group differences to the comparison cue, indicating a reduction in blocking in the ketamine using group. The second interaction reflected higher accuracy to the drug cue blocked by a neutral cue in ketamine users compared to controls (t_{32} = 2.563, p = 0.015) but no group differences in responses to the neutral cue blocked by a drug cue. These data indicate that group differences in blocking by/of drug cues is reflected as a resistance to blocking of drug cues in ketamine users.[3]

[3] Given that previous findings have linked attenuated blocking to age, schizotypy and depression independent of ketamine use, we repeated these analyses in models that substituted age, schizotypy (SPQ total score), delusional ideation (global PDI score) or depression (BDI total score) for Group in all 34 participants based on median split. None of the orthogonal contrasts were significant in these models and no contrasts showed significant interactions with age, schizotypy or depression. The only effect to emerge in these analyses was a main effect of depression ($F_{1,32}$ =4.334, p = 0.045) indicating higher accuracy to all cues in those with more

Table 3.3: Accuracy and importance scores from the test stage of the DCRPET.

	Controls	Ketamine users
a accuracy	87.50±34.16	88.24±32.22
B accuracy	100.00±0.00	100.00±0.00
cd (control cue) accuracy	96.88±12.50	86.11±28.73
f accuracy	75.00±44.72	94.44±23.57
H accuracy	73.33±44.22	100.00±0.00
jl accuracy	90.00±20.00	88.89±21.39
a importance	41.25±9.96	52.35±17.12
B importance	40.67±14.62	65.00±14.31
cd (control cue) importance	44.69±13.91	54.17±10.31
f importance	46.25±18.02	47.78±19.42
H importance	30.67±10.48	58.89±18.26
jl importance	47.33±8.15	50.83±15.16

Importance (Table 3.3)

Overshadowing: Importance scores revealed a main effect of Group ($F_{1,32}$ =6.161, p = 0.018; η_p^2 = 0.161) reflecting higher scores to both cues amongst ketamine users compared to controls (Table 3).

severe depression. This shows that group differences in these factors observed alone cannot explain the results obtained.

Blocking: the only significant effect to emerge was an interaction between Group and the contrast comparing a drug cue blocked by a neutral cue (**H**) vs. the neutral cue blocked by a drug cue (jl) ($F_{1,32}$ =9.937, p = 0.004; η_p^2 = 0.237). This interaction reflected higher importance ratings to the drug cue blocked by a neutral cue in ketamine users compared to controls (t_{32} = 3.296, p = 0.002), but no group difference for the neutral cue blocked by a drug cue.

Choice x accuracy

Overshadowing (Figure 3.3): For accuracy x importance scores, a main effect of Cue was found ($F_{1,32}$ =4.818, p = 0.036; η_p^2 = 0.131), reflecting higher scores to the drug cue (**B**) compared to the neutral cue (a). Furthermore, a main effect of group was found, indicating that higher scores were given by ketamine users compared to controls ($F_{1,32}$ =4.713, p = 0.037; η_p^2 = 0.128).

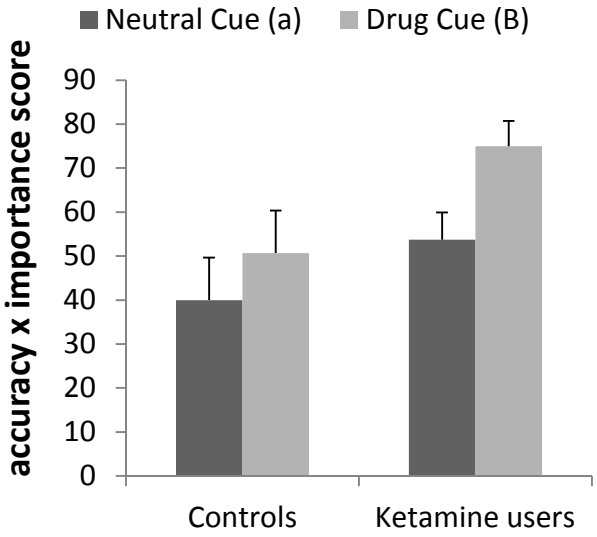


Figure 3.2: *Overshadowing in controls and ketamine users. Both groups showed overshadowing of a neutral cue by a drug cue, whilst scores were generally higher in ketamine users compared to controls. Error bars show SEM.*

Blocking (Figure 3.4): Group x Cue interactions were found for the contrast comparing the comparison cue vs. all blocked cues ($F_{1,32}$ =5.587, p = 0.024; η_p^2 = 0.149) and the contrast comparing the drug cue blocked by a neutral cue (**H**) vs. the neutral cue blocked by a drug cue (jl) ($F_{1,32}$ =7.532, p = 0.010; η_p^2 = 0.191). In addition, a main effect of group ($F_{1,32}$ =4.454, p = 0.043; η_p^2 = 0.122) was found, indicative of higher scores in ketamine users compared to controls. The first interaction reflected higher scores in ketamine users compared to controls for all blocked cues combined (t_{32} = 2.800, p = 0.009), but no group differences to the comparison cue, indicating a reduction in blocking in the ketamine using group. The second interaction reflected higher scores to the drug cue blocked by a neutral cue in ketamine users compared to controls (t_{32} = 4.067, p < 0.001).

Correlations

Correlations were carried out between (i) the magnitude of blocking overall (accuracy x importance score) and the magnitude of blocking of a drug cue (accuracy x importance score) and (ii) levels of dependence (LDQ), grams of ketamine used per week, years of ketamine use, total grams used, BDI scores, SPQ cognitive perceptual, SPQ interpersonal and SPQ disorganized subscales, PDI yes/no, PDI distress, PDI preoccupation, PDI conviction. No significant correlations emerged (all p's > 0.05).

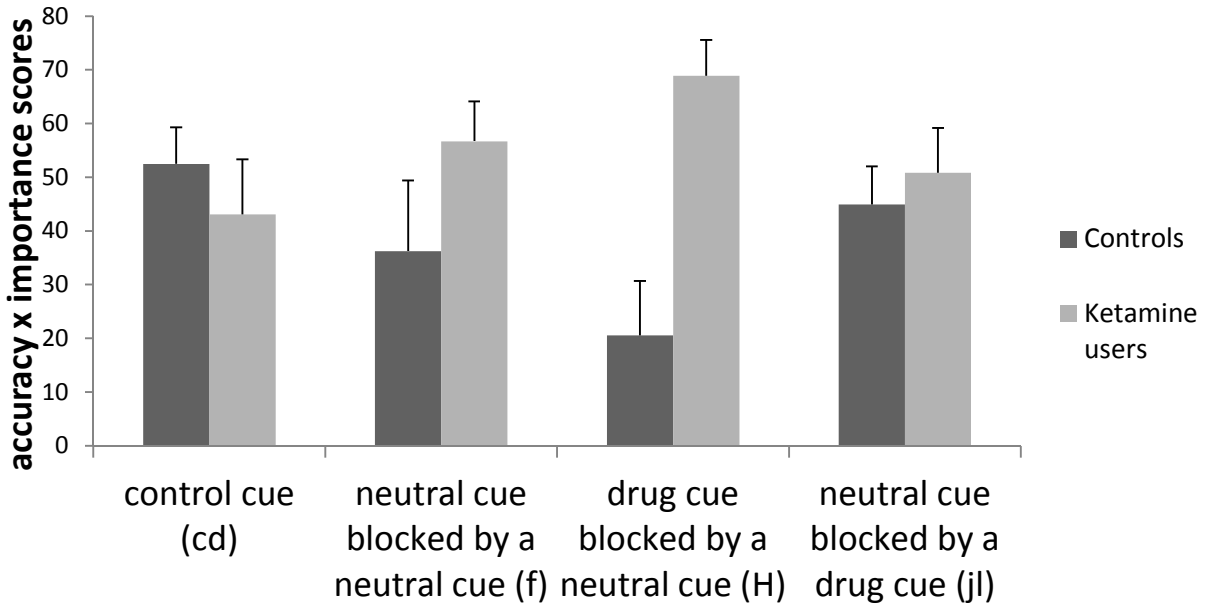


Figure 3.3: Blocking in controls and ketamine users. Controls showed less blocking overall when compared to ketamine users. In addition, the use of drug cues as blocking or blocked cues interacted with the magnitude of the effect in ketamine users but not controls. Specifically, drug cues were especially resistant to the blocking effect in ketamine users. Error bars show SEM.

3.4 Discussion

This study compared the performance of a group of ketamine users with polydrug using controls on a task indexing associative learning processes (blocking and overshadowing) occurring to neutral and drug-related cues following reward-based Pavlovian conditioning. The groups did not differ in accuracy to cues during training, but ketamine users displayed a reduction in blocking compared to controls, evidenced by higher scores to redundant, blocked cues. Ketamine users also showed a modulation of blocking by drug cues, seen as a resistance to blocking of drug cues by neutral cues.

Blocking is an associative learning process accompanied by changes in selective attention (Krushke et al., 2005; Wills et al., 2007) and a failure to show blocking may cognitively underpin schizophrenia (Gray et al., 1991; Fletcher & Frith, 2009). As predicted we found a reduction in blocking in ketamine users compared to controls, an effect that cannot be attributed to non-specific cognitive impairment because (i) the groups did not differ in accuracy scores during learning (ii) blocking was evidenced by *higher* accuracy to blocked cues in ketamine users compared to controls. Ketamine users in this study also showed elevated delusional ideation, schizotypy and depression replicating previous findings (Curran & Morgan, 2002; Morgan et al., 2012; Morgan et al., 2009) and in line with observations that schizotypy and depression coincide with attenuated blocking (Bender et al., 2001; Haselgrove & Evans, 2010; Moran et al., 2003; 2008). Importantly schizotypy, delusional ideation and depression alone could not account for these effects of blocking in the whole sample and neither could age, which is also related to the emergence of blocking (Crookes & Moran, 2003).

These findings are the first to our knowledge linking glutamate to blocking, and are in agreement with abnormal associative learning in this population (Freeman et al., 2009) and in

healthy volunteers following acute ketamine, according to rPFC responses to prediction error during causal learning. In addition, both Corlett et al. (2006) and Freeman et al. (2009) found that individual differences in associative learning amongst drug-free, healthy individuals can predict the extent to which they experience psychotic-like symptoms following an acute dose of ketamine. Collectively, these results are supportive of a link between glutamatergic dysfunction and associative learning in schizophrenia (Corlett et al., 2010). Glutamate is elevated in anterior cingulate cortex following acute ketamine administration, and correlates positively with post-infusion psychotic symptoms (Stone et al., 2012). Furthermore increased cortical glutamate is evident in rats following chronic ketamine treatment (Kim et al., 2011). However, the extent to which this occurs in human ketamine users and contributes to the psychopathology observed in this population is yet to be established. Use of other drugs and pre-existing differences in ketamine users are important shortcomings of assessing the effects of repeated NMDA-R antagonist exposure in humans. Longitudinal designs offer one partial solution to these issues (Morgan et al., 2009)

On average, ketamine users had been using the drug for over 10 years, and were currently taking more than 9 grams across 4-5 days each week, showing moderate to high dependence. In common with many drugs of abuse, images associated with ketamine command selective attention amongst frequent users (Morgan et al., 2008) and in this study we investigated whether drug cues might modulate the degree of blocking in ketamine users based on similar observations in studies manipulating the peceptual salience of cues in blocking tasks (Denton & Kruschke 2006, Heckler et al., 2005). Blocking in ketamine users differed according to whether the blocking or blocked cues were drug related or netural, an effect that was absent in controls. Specifically, a drug cue was more resistant to being blocked by a neutral cue in this group, evidenced by ceiling accuracy, and was also given higher importance ratings. To

our knowledge, these results provide the first evidence that drug cues modulate associative blocking. Our results are in agreement with the findings of Denton & Kruschke (2006) showing that a visually salient cue was less prone to blocking by a less salient cue, compared to a condition where both cues had equal (low) salience. Thus, as demonstrated in animal work (Feldman, 1975; Hall, Mackintosh, Goodall, & Martello, 1977) and contrary to the predictions of Rescorla &Wagner (1972), salience appears to resemble validity in associative learning, perhaps due to biases in selective attention during cue competition.

In contrast to these effects, drug cues did not enhance blocking of neutral cues in this study. One possible explanation for this is that there were a fewer number of drug cues compared to neutral cues in training stage 1, perhaps signalling that they were poor predictors of the outcome and should not be attended to (Mackintosh, 1975). Previous studies have encountered similar effects whereby categories of cues appear to gain or lose associative strength based on the task design (Denton & Kruschke, 2006; Heckler et al., 2006). Our choice to use conceptually distinct drug-related images in this study limited the number of salient cues we could use to address our hypotheses, and future studies should use balanced factorial and/or between subjects task designs to address whether the effects of cue salience differ for blocking or to-be blocked cues in humans.

It was previously hypothesized that drug cues should not undergo blocking with respect to drug receipt (Redish, 2004) however this hypothesis has not been supported to date (Panlilio, Thorndike, & Schindler, 2007). In contrast, we examined the effect of drug cues on associative learning about alternative rewards, and the use of an associative learning task may offer a more sensitive behavioural instrument than reaction time or imaging designs to detect interactions between drug-related and alternative rewards (Goldstein, Alia-Klein, et al.,

2009). Distal as well as proximal cues may be linked to drug use (Conklin, Robin, Perkins, Salkeld, & McClernon, 2008) however our findings suggest that exposure to drug cues can impact on one's ability to learn new information about non-drug outcomes, due to a bias in selective learning.

The ability of drug cues to attract attention may have a broader role in addiction than cue-induced drug seeking alone, which is consistent with evidence that experimental abolishment of overt attentional bias does not prevent cue-induced drug seeking in smokers (Hogarth et al., 2008) and that working memory is impaired in the presence of drug cue distracters amongst cocaine users (Hester & Garavan, 2009). These effects might account for drug-related learning and preoccupation that far exceeds what is necessary to simply obtain the drug, as well as impaired learning about alternative rewards. In terms of treatment strategies, these findings suggest that contingency management might be less effective in high-risk, drug associated contexts and this may be more pronounced during craving/withdrawal, when competition between drug and non-drug rewards is heightened (Goldstein & Volkow, 2011).

Ketamine users gave higher importance ratings to both overshadowing cues (neutral and drug), which could reflect increased appetitive processing of money-related and drug cues (Morgan et al., 2008). However in terms of cue-outcome accuracy both groups showed drug cue induced overshadowing, in contrast the findings of chapter 2 where this effect occurred in abstinent smokers but not abstaining smokers or controls. Given that overshadowing is thought to reflect 'intrinsic' or bottom-up salience (Cassaday & Moran, 2010), overshadowing in this study may have been caused by the perceptual characteristics of the cues. In contrast, blocking is thought to be caused by the acquired salience of cues, reflecting top-down salience (Cassaday & Moran, 2010). This distinction is intriguing when considering that drug-cue effects on blocking have only emerged in a group showing a reduction of this effect generally (ketamine users), but not in groups for whom this effect was

intact (controls, satiated smokers and abstaining smokers in chapter 2). Although blocking is often attenuated in people with schizophrenia, the role of salience attribution in the elevated levels of substance abuse and tobacco smoking in this population is not well understood. The findings obtained here tentatively suggest that salience attribution with relevance to psychosis (blocking) co-varies with salience attribution towards drug-related cues (lack of blocking to drug cues). This would suggest that individuals showing high levels of aberrant salience attribution to irrelevant stimuli might be especially prone to the incentive-motivational properties of drug-related stimuli (e.g. Chambers et al., 2001; Tsapakis et al., 2003).

In terms of limitations, the possibility that pre-existing differences contributed to these results is an inevitable shortcoming of this cross-sectional design. Furthermore, the ketamine group had used cannabis and alcohol longer, consisted of more current cocaine and cannabis users, were older and had spent fewer years in education. They did not, however differ in estimated premorbid verbal IQ or gender and were generally similar in other drug use. Polydrug using individuals may offer the most appropriate control group for assessing chronic effects of ketamine in a cross sectional design (e.g. Curran & Morgan, 2002). However, these individuals do not provide normative data reflecting a general population and an additional non-drug using group would be one way in order to address this issue. In addition, given that ketamine is typically consumed as a white crystalline powder, the images we used resembled other drugs such as MDMA and cocaine and may therefore not have elicited ketamine-specific responses. However if this was the case, the effects produced by these cues would still be attributable to their association with drug use, which was the primary aim of the task. Finally, using accuracy scores as the main outcome measure did not allow for sufficient variance with which to link task performance to specific symptoms. However, accuracy scores have the advantage of providing an objective and unambiguous index of selective learning.

In conclusion, this study demonstrated that a group of ketamine users showing elevated delusional ideation, schizotypy and depression showed a reduction in blocking compared to controls, and a modulation of blocking by drug cues, whereby drug cues were resistant to being blocked by neutral cues. Drug cues also overshadowed neutral cues in both groups. These findings support glutamatergic involvement in blocking and the ability for drug-related material to bias selective reward learning mechanisms in addiction.

Chapter 4: Salience attribution in smokers with a diagnosis of schizophrenia

4.1 Introduction

People with schizophrenia are five times more likely to smoke tobacco and five times less likely to achieve successful cessation than smokers from the general population (De Leon and Diaz, 2005) and tobacco smoking carries a high risk of mortality in these individuals, particularly in middle age (Kelly et al., 2011). On average, people diagnosed with schizophrenia have a 15 year reduction in life expectancy and coronary heart disease, which is strongly linked to smoking, is the predominant cause of premature death in this population (Hennekens et al., 2005). The association between tobacco smoking and schizophrenia is therefore of considerable public health interest.

According to a primary addiction hypothesis proposed by Chambers et al. (2001) substance abuse and schizophrenia are independent manifestations of a common neurodevelopmental abnormality arising from the hippocampal formation and prefrontal cortex. The resulting loss of inhibition over dopamine release in the nucleus accumbens could on the one hand give rise to the symptoms of schizophrenia due to the attribution of salience to irrelevant stimuli (Gray et al., 1991) and on the other hand independently enhance the incentive-motivational properties of drugs and their associated cues, resembling a sensitized state that would only normally be achieved through chronic drug exposure (Robinson & Berridge, 1993). The idea that a sensitization of the dopamine system could explain the link between schizophrenia and drug abuse has been suggested by others (O'Daly et al., 2005; Tsapakis et al., 2003). Moreover, the results reported in chapter 3 would tentatively suggest that salience attribution processes relevant to addiction and to schizophrenia might co-vary with each other, further supporting this hypothesis. If so, smokers with a diagnosis of schizophrenia might be expected to show a reduction in blocking in general when compared to controls, in agreement

previous findings (Bender et al., 2001; Jones et al., 1992, 1997; Moran et al., 2003, 2008; Oades et al., 1996) and would also exhibit a stronger resistance to the blocking effect concerning drug-related stimuli.

One previous study found that drug-related attentional bias was present in cocaine abusers, but not in people with schizophrenia who abused cocaine (Copersino et al., 2004). These findings appear to go against the idea that salience attribution towards drug-related cues might be heightened in this population. One explanation for this might have been related to loss of signal to noise in terms of context-dependent dopamine release (e.g. Kapur, 2003) which may prevent the formation of adaptive associations cues and reward (e.g. false negatives; Roiser et al., 2009) including drug-related stimuli. However, the comorbid schizophrenia and cocaine using group showed lower scores in cocaine craving in this study, which might have accounted for these findings given the relationship between attentional bias and craving (Field et al., 2009b).

This study aimed to address the role of salience attribution in smoking among people with schizophrenia compared to healthy smokers from the general population. Based on the primary addiction and sensitisation hypotheses (Chambers et al., 2001; O'Daly et al., 2005; Tsapakis et al., 2003) it was predicted that smokers with a diagnosis of schizophrenia should 1) exhibit heightened attentional bias to smoking cues, 2) show an attenuation of blocking and 3) a greater disruption of blocking by drug cues, when compared to control smokers. It was also predicted that the groups would not differ in cue reactivity, based on previous studies (Ahnallen & Tidey, 2012; Fonder et al., 2005; Tidey et al., 2008).

4.2 Methods

4.2.1 Design and participants

A between subjects design compared 15 smokers with a diagnosis of schizophrenia (SWDS) with 15 'healthy' control smokers (CS). Inclusion criteria were age 18-75, smoking ≥ 5 cigarettes per day, normal or corrected to normal vision, and fluent spoken English. SWDS were required to have a current diagnosis of schizophrenia, and controls were excluded if they reported any current or history of a major Axis 1 disorder, or a current or history of psychotic disorder in any immediate family member. This study was approved by the NRES (SWDS, appendix 5 and 6) and UCL Psychology and Language Sciences Research Ethics Committes (CS, appendix 1 and 7) and was conducted in accordance with the Declaration of Helsinki.

4.2.2 Assessments

Modified Stroop Task

This task required participants to name the colour of words that were either neutral or smoking-related (88 words each, presented on separate test cards in counterbalanced order) Stimuli were taken from a previous study (Dawkins, Powell, West, Powell, & Pickering, 2006). Response times to name each set of 88 words and the number of errors were recorded. Longer response times and more errors on smoking compared to neutral words are indicative of attentional bias.

Drug cue reward prediction error task (short version, Table 4)

This task was similar to that described in study 1. The task was modified to make it simpler, focusing on i) blocking, ii) blocking of a drug cue, iii) overshadowing. The task design is shown in table 4.1. A further change was that 'importance' scores were rated without numbers, since some participants in study 2 reported finding these confusing in terms of '%' ratings. In order to address this concern, responses were adapted into a visual analogue scale displayed onscreen, anchored from 'not at all' to 'very much so'. Responses were indexed using a row of 11 keys marked with blank stickers, parallel to the VAS line displayed onscreen. Responses were scored from 0 to 100% as in chapters 2 and 3.

The short version of the task employed 10 neutral cues and 2 drug-related cues, which were randomized to their corresponding letter in the task at the start of each experiment. Training phases 1 and 2 each consisted of 6 blocks.

Smoking Visual Analogue Scales

The following visual analogue scales were administered "How much do you want to smoke a cigarette right now?" and "How much would you enjoy a cigarette if you smoked right now", on 100mm scales anchored from "Not at all" to "Very much so". These scales were administered at three time points: 1) pre cue exposure, 2) post cue exposure, and 3) post testing session (approximately 30 minutes after testing had begun; prior to clinical assessment). The cue exposure video which lasted 2 minutes was taken from a previous study (Kamboj et al., 2012), and depicts a white male smoking a cigarette from start to finish.

Table 4.1 Design of the DCRPET short version

Salience manipulation	**Training stage 1:**	**Training stage 2:**	**Test stage**:
	1 item predicts reward	2 items predict reward	Which room, how important for earning money?
Blocking	a→red	a+b→Red	b
Blocking of a drug cue	c→green	c+**D**→Green	**D**
Control for blocking		e+f→Green	e + f
Overshadowing		g+**H**→Red	g+**H**
Filler trials	i+j→Red	i+j→Red	No test
	k+l green	k+l green	

Subjective Attentional Bias Questionnaire (Waters, A. personal communication, Appendix 8)

This scale indexes subjective experiences of having one's attention drawn to cigarettes and smoking cues. The scale consists of 8 items rated from 0 (not at all) to 4 (extremely).

Motivation To Stop Scale (MTSS)(Kotz, Brown, & West, 2012)

A single item index of ones' motivation to quit smoking that combines desire and intention to quit. Scores range from 1 (I don't want to stop smoking) to 7 (I REALLY want to stop

smoking and intend to in the next month). Scores have been shown to provide a linear prediction of smokers' likelihood of engaging in a quit attempt within the next 6 months.

Fagerström Test of Nicotine Dependence (FTND; Heatherton et al., 1991)

This widely used scale consists of six items rated between 0 and 3, with scores ranging from 0 (low dependence) to 10 (high dependence).

National Adult Reading Test (NART) (Nelson, 1991)

This task requires participants to read 50 irregular words. Full scale IQ was estimated according to the following formula: 128 – 0.83 x error score.

Clinical Assessment

Clinical assessment for smokers with schizophrenia was based on the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984b) and the Scale for the assessment of Negative Symptoms (SANS) (Andreasen, 1984a). Current diagnosis of schizophrenia was confirmed using ICD-10 criteria (WHO, 1993). SWDS completed the Oxford Liverpool Inventory of Feelings and Experiences (O-LIFE) (Mason, Linney, & Claridge, 2005) as an index of schizotypy.

4.2.3 Procedure

SWDS were recruited and assessed during their regular clozapine clinic visits. Following initial identification and screening, a suitable test day was arranged based on a future clinic appointment. After their clinic appointment which typically lasted 15 minutes, testing commenced in a quiet room. In order to control for the effect of this delay on tobacco satiation, CS were asked to refrain from smoking for at least 15 minutes before they arrived for testing. Following assessment of breath carbon monoxide (Bedfont Micro Smokerlyzer, UK), both groups completed the protocol in the following order: cue reactivity, modified Stroop task, Drug Cue Reward Prediction Error Task, National Adult Reading Task, Subjective Attentional Bias Questionnaire, Fagerstrom Test of Nicotine Dependence, post testing visual analogue scales. After the test battery, smokers with schizophrenia were assessed on the Scale for the Assessment of Positive Symptoms and Scale for the assessment of Negative Symptoms, and control smokers completed the Oxford Liverpool Inventory of Feelings and Experiences. Participants were paid for their time (£7.50 per hour, plus up to an additional £5 depending on task performance).

4.2.4 Statistical Analysis

All analyses were carried out using Statistical Package for Social Sciences (SPSS version 19). Independent sample t-tests (Mann Whitney-U tests where data violated assumptions of homogenous variance) and chi-squared tests were used to compare groups on demographic and questionnaire-based variables. RMANOVA models with a between subject factor of Group were used for the remaining analyses and included within subject factors of Time (pre exposure, post exposure)/(post exposure post session) for VAS ratings, and Stimulus (smoking, neutral) for Stroop interference and error scores. For the DCRPET task, control cue scores (e, f) were collapsed and compared with blocked cues in separate RMAONVA models assessing (i) blocking, (ii) blocking of a drug cue. Overshadowing was analysed by comparing scores to the neutral cue g with the drug cue **H**. As in chapters 2 and 3, analysis was carried out on 1) accuracy, 2) importance, 3) accuracy x importance scores. Response time data from the Stroop task was missing for one participant with schizophrenia, and VAS scores were missing for one control; analyses of these tasks were carried out with (n-1) fewer degrees of freedom. Post hoc t tests were two-tailed and bonferroni corrected.

4.3 Results

Participants and demographics (Table 4.2)

The groups did not differ significantly on any demographic (gender, age, estimated full-scale IQ) or smoking related variables (years smoked, cigarettes per day, time since last cigarette, expired carbon monoxide, salivary cotinine, Fagerstrom Test of Nicotine Dependence, Motivation to Stop Smoking, number of people who had previously tried to quit, and the number and duration of quit attempts in these people).

Visual Analogue Scales (Figure 4.1)

Smoking cue exposure (Pre Exposure to Post Exposure)

No significant main effects or interactions emerged for analysis of pre and post exposure scores on "How much do you want to smoke a cigarette right now?" or "How much would you enjoy a cigarette if you smoked right now?"

Changes across the testing session (Post Exposure to Post Session)

Analysis of "How much do you want to smoke a cigarette right now" revealed a main effect of Time ($F_{1,27}$=4.662, p = 0.040, η_p^2=0.147), indicating an increase from Pre to Post ratings in both Groups. When examining "How much would you enjoy a cigarette if you smoked right now", trends were found for a Time x Group interaction ($F_{1,27}$=3.871, p = 0.059, η_p^2=0.125) and a main effect of Time ($F_{1,27}$=3.060, p = 0.092, η_p^2=0.102). Post hoc t tests revealed a significant increase from Pre to Post in the SWDS (p=0.010) but not CS (p=0.892). However, inspection of Figure 4.1 indicates that this increase appeared to normalise the scores of both groups rather than elevating those in SWDS above CS.

Table 4.2: Demographics, smoking behavior and symptom scores

	Schizophrenia	Controls	χ^2_1 / $t_{(28)}$
Gender (M/F)	11/4	12/3	$\chi^2_{(1)}$=0.186
Age	37.20 ±9.37	35.53±8.57	$t_{(28)}$=0.508
NART full scale IQ	109.80 ±10.57	115.33±4.17	U=77.000
Years smoked	18.37 ±8.50	17.83±8.79	$t_{(28)}$=0.169
Cigarettes per day	18.43 ±12.70	15.10±8.53	$t_{(28)}$=0.844
Last smoked (minutes)	60.33 ±34.61	62.00±64.83	$t_{(28)}$=0.088
Expired carbon monoxide (ppm)	13.21 ±8.99	13.67±6.72	$t_{(27)}$=0.154
Salivary cotinine (ng/mL)	662.11 ±544.51	569.75 ±446.47	$t_{(25)}$=0.480
FTND	5.53 ±2.75	4.13±2.10	$t_{(28)}$=1.568
MTSS	3.64 ±1.82	3.29±1.94	$t_{(26)}$=0.502
Tried to quit (Y/N)	12/3	12/3	$\chi^2_{(1)=}$0.000
Quit attempts (n)	3.04 ±2.37	3.71±4.6	$t_{(22)}$=0.442
Maximum quit time (days)	338.63 ±671.78	277.17±327.22	$t_{(22)}$=0.285
Daily clozapine dose (mg)	435 ±178.24		
SAPS global score	7.80 ±3.99		
SANS global score	6.60 ±3.58		
O-LIFE Unusual Experiences		4.73 ±3.24	
O-LIFE Cognitive Disorganisation		5.60 ±2.80	
O-LIFE Introvertive Anhedonia		3.27 ±2.37	
O-LIFE Impulsive Non-conformity		3.73 ±2.40	

NART: National Adult Reading Test; FTND: Fagerström Test of Nicotine Dependence; MTSS: Motivation to Stop Scale; SAPS: Scale for the Assessment of Positive Symptoms; SANS: Scale for the Assessment of Negative Symptoms; O-LIFE: Oxford-Liverpool Inventory of Feelings and Experiences. MTSS was analysed with n=14 in each group due to two smokers responding "I don't know"; Expired carbon monoxide was analysed with n=29 due to one participant in the schizophrenia group being unable to hold their breath; cotinine was analysed with n=27 due to three samples containing insufficient saliva (one smoker with schizophrenia, two control smokers).

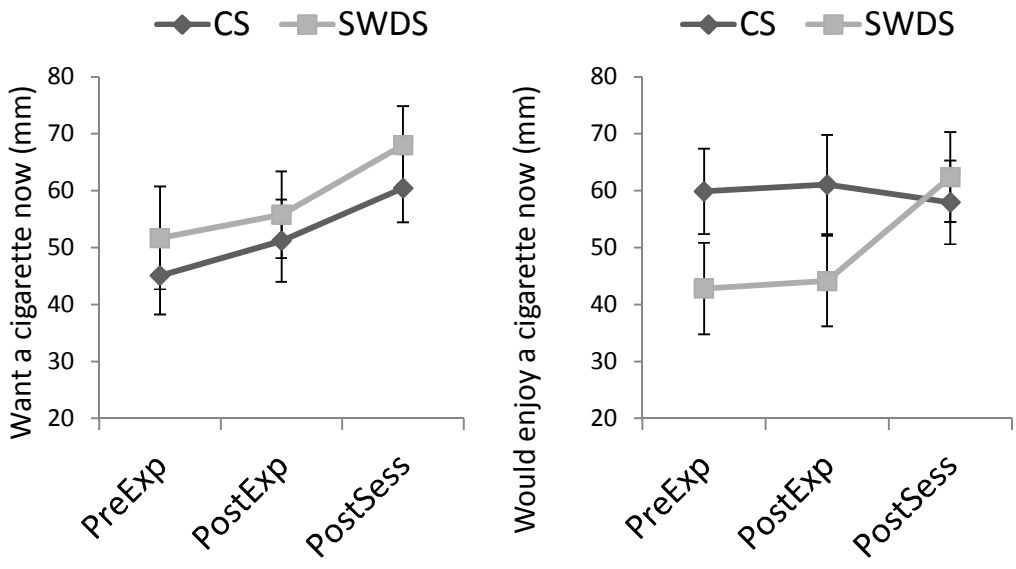


Figure 4.1: Smoking VAS scores. No significant effects emerged for the cue reactivity procedure (pre exposure to post exposure).'Want a cigarette' scores increased from post exposure to post session in both groups. In contrast 'would enjoy a cigarette' scores did not change across the session in CS, but increased from the post exposure to post session in SWDS, to the same level as CS.

Subjective Experiences of Attentional Bias

Subjective Attentional Bias questionnaire scores were 14.53 ±6.15 for controls and 16.67 ±4.98 for SWDS; these means were not significantly different (t_{28}=1.044, p = 0.305).

Modified Stroop Task (Figure 4.2)

For response time, a trend for a Type x Group interaction ($F_{1,27}$=3.527, p = 0.071, η_p^2=0.116) and main effects of Group ($F_{1,27}$=9.608, p = 0.004, η_p^2=0.262) and Type ($F_{1,27}$=15.374, p < 0.001, η_p^2=0.363) were found. The interaction reflected a stronger interference effect (slower responses to drug words than neutral words) in SWDS (p=0.004) than in CS (p=0.091), whist main effects indicated slower naming time in the schizophrenia group compared to controls,

and for smoking words compared to neutral words. For errors, only a trend for a main effect of Type was found ($F_{1,28}$=2.995, p = 0.095, η_p^2=0.097) which reflected a tendency for slightly more errors on smoking words than neutral words in both SWDS (1.73 ±2.28 compared to 1.00 ±1.36) and CS (1.00 ±1.60 compared to 0.87 ±1.13).

Because longer response times might have artifically inflated the magnitude of bias in the SWDS group, correlations were carried out between bias scores and response times to neutral and drug words separately in each group. Bias scores did not correlate with response times to neutral (r=-0.011, p=0.970) or drug response times in CS (r=0.382, p=0.160). In SWDS bias scores did not correlate with response time to neutral words (r=0.254, p=0.380) but were positively correlated with response times to drug words (r=0.605, p=0.022). This suggests that the bias effect in SWDS was not attributable to slower response times in general and instead reflects interference when specifically exposed to drug-related material.

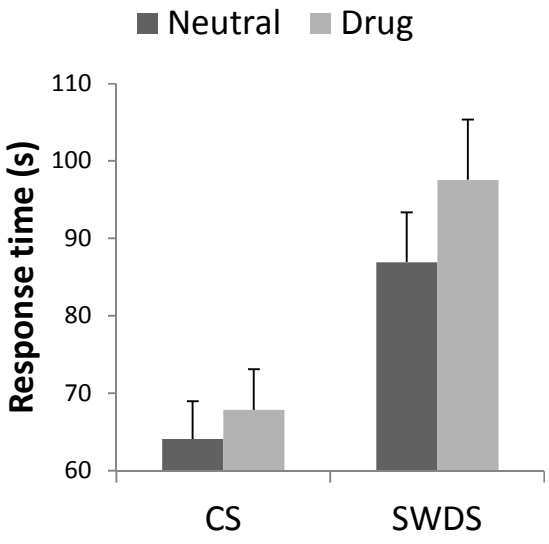


Figure 4.2: Attentional bias in smokers with a diagnosis of schizophrenia. Stroop interference between neutral and drug-related words was higher in SWDS than CS. Error bars show SEM.

Drug Cue Reward Prediction Error Task

Analysis of training data revealed a Cue x Block interaction ($F_{12,700}$=1.903, p = 0.033, η_p^2=0.64), a main effect of Block ($F_{5,700}$=5.848, p < 0.001, η_p^2=0.173), and a trend for a Cue x Block x Group interaction ($F_{12,700}$=1.649, p = 0.078, η_p^2=0.056). Exploration of this trend using Cue x Block RMANOVA models split by group revealed a Cue x Block interaction ($F_{8,350}$=2.473, p = 0.016) and main effect of Block ($F_{3,350}$=6.667, p < 0.001) in CS, but not in SWDS. The Type x Block interaction in controls reflected a reliable effect of Block for GH ($F_{3,350}$=6.373, p < 0.001) but not for other cues (all p's > 0.012). Thus, learning was especially progressive for GH trials in controls, which appeared to be driven by extremely low accuracy at block 1 compared to later blocks for this cue (see figure 4.3 vi).

Accuracy (Table 4.3)

Blocking: A trend for lower accuracy in SWDS compared to controls was found ($F_{1,28}$=3.977, p = 0.056, η_p^2=0.124). No other effects emerged.

Blocking of a drug cue: A main effect of Group reflected lower accuracy in SWDS compared to controls ($F_{1,28}$=7.692, p = 0.010, η_p^2=0.216). No interactions with cue or other effects emerged.

Overshadowing: No significant effects emerged.

Importance (Table 4.3)

Blocking: No significant effects or trends emerged.

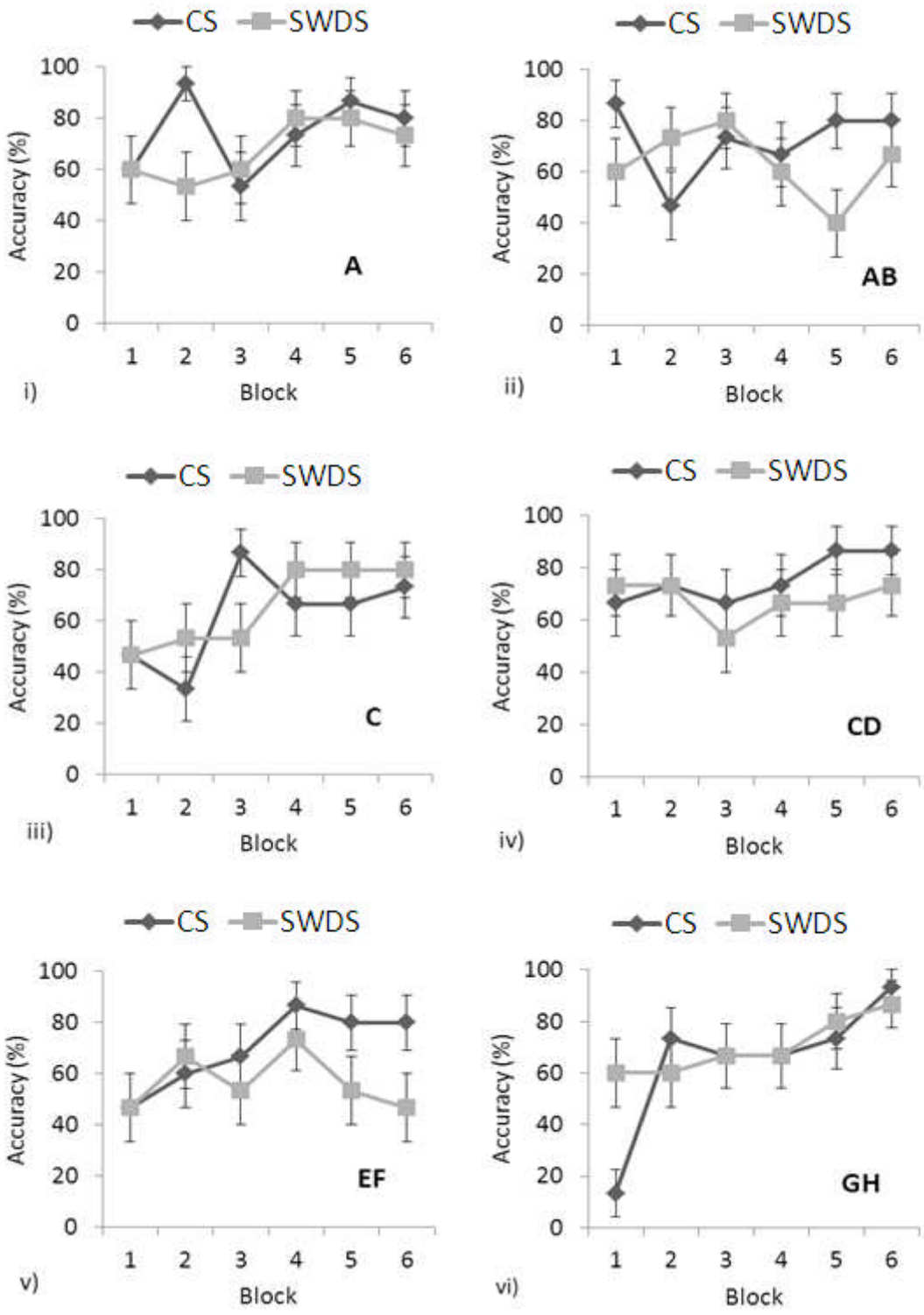


Figure 4.3: Training data from the DCRPET-short. Learning increased progressively across blocks in both groups. This was more pronounced for the GH cue pair in controls, due to low accuracy on the first block. Error bars show SEM.

Table 4.3: Accuracy and importance scores from the DCRPET-short.

	Controls	Sz
Control Cue accuracy	90.00 ±28.03	56.67 ±41.69
B accuracy	66.67 ±98.80	66.67 ±48.80
D accuracy	66.67 ±48.80	46.67±51.64
G accuracy	73.33 ±45.77	73.33 ±45.77
H accuracy	86.67 ±35.19	73.33 ±45.77
Control Cue importance	54.00±28.61	47.00±16.12
B importance	46.00±37.76	56.67±27.95
D importance	66.00±33.55	60.00±31.40
G importance	38.00±32.78	66.00±26.67
H importance	56.67±36.97	69.33±25.76

Blocking of a drug cue: A main effect of Cue emerged ($F_{1,28}$=4.498, p = 0.043, η_p^2=0.138), reflecting higher importance ratings to the drug cue in both groups. No other significant effects emerged.

Overshadowing: A main effect of Cue was found ($F_{1,28}$=5.320, p = 0.029, η_p^2=0.138), reflecting higher importance ratings to the drug cue in both groups. In addition, a trend for higher importance ratings in SWS compared to CS was found ($F_{1,28}$=3.958, p = 0.057, η_p^2=0.124).

Accuracy x Importance (Figure 4.4)

Blocking: a trend for a Cue x Group interaction was found ($F_{1,28}$=3.618, p = 0.065, η_p^2=0.116). This reflected higher scores in CS compared to SWDS for the Control Cue (p =0.005) but not the blocked cue B (p=0.529).

Blocking of a drug cue: A main effect of Group was found ($F_{1,28}$=5.795, p = 0.023, η_p^2=0.171), reflecting lower scores SWDS compared to CS. The absence of a main effect of cue (F<1) indicates that both groups showed a lack of the blocking effect to drug cues.

Overshadowing: No significant effects emerged.

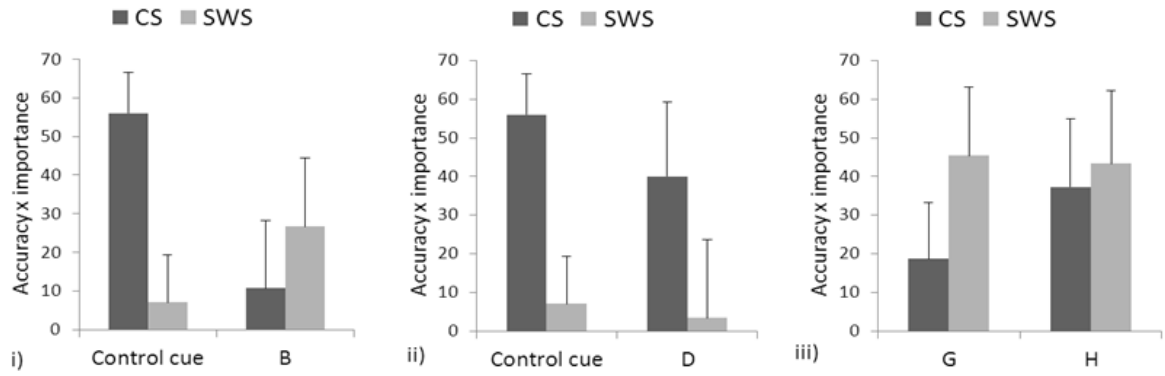


Figure 4.4: Accuracy x importance scores from the DCRPET-short. Blocking was attenuated in SWDS compared to CS, but both groups showed an absence of blocking to a drug cue and neither group showed overshadowing by a drug cue. Error bars show SEM.

4.3.6 Correlations

Correlations between attentional bias (response time to smoking words – response time to neutral words) and degree of blocking (accuracy x importance) scores for the Control Cue minus choice x accuracy scores for blocked cue B) were carried out with Subjective Attentional Bias, nicotine dependence, cigarettes per day, carbon monoxide, salivary cotinine, increase in VAS scores from post exposure to post session, clozapine dose and

symptoms (SAPS and SANS global subscale scores in SWS; O-LIFE subscales in CS) separately in each group, with an α level adjusted to 0.01. In SWDS, response time interference on the Stroop task correlated with positive symptoms (SAPS global subscale scores r=0.741, *p*=0.002, Figure 4.5) and showed trend level correlations with daily clozapine dose (r=0.615, *p*=0.002) and subjective experiences of attentional bias (r=0.553, *p*=0.040). No significant correlations were found with blocking scores, apart from a trend for a negative relationship with subjective experiences of attentional bias (r=-0.519, *p*=0.047). In controls response time interference on the Stroop task correlated with salivary cotinine (r=0.701, *p* =0.008, Figure 4.6) and showed a trend level correlation with increases in anticipated pleasure from smoking from post-cue exposure to the end of the testing session (r=0.542, *p* =0.045). Finally, a significant negative relationship was found between blocking and the 'Unusual Experiences' subscale of the O-LIFE (r=-0.660, *p* =0.007, Figure 4.7).

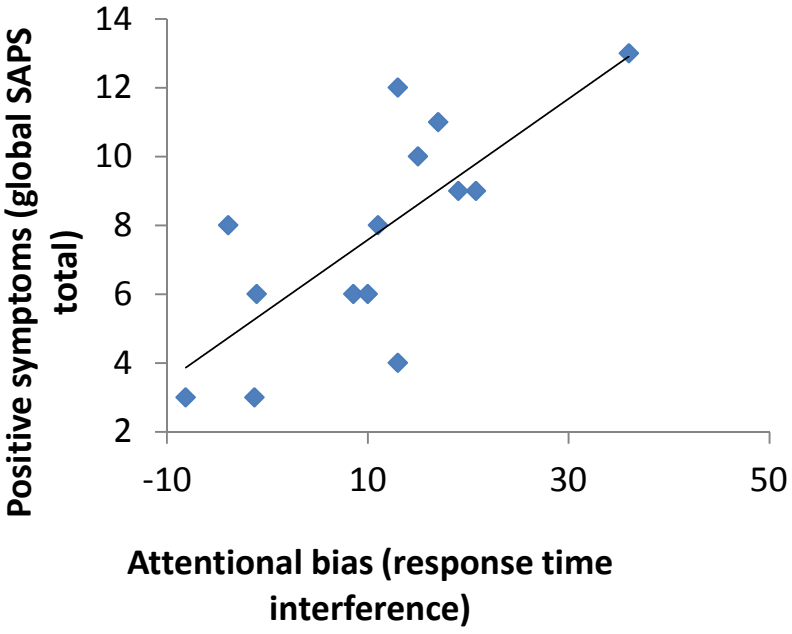


Figure 4.5: Correlation between attentional bias and positive psychotic symptoms in smokers with a diagnosis of schizophrenia (r=0.741). A strong relationship was still present (r=0.645) with omission of the data point at the upper end of both distributions.

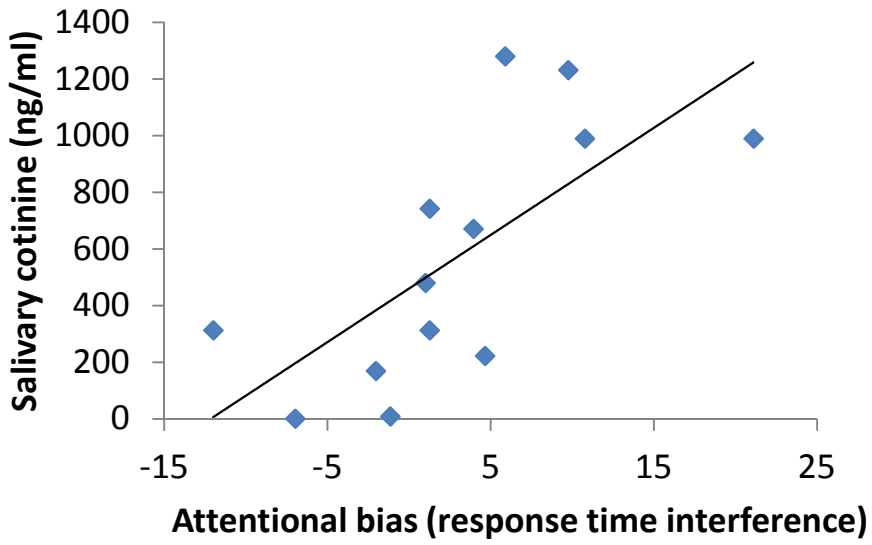


Figure 4.6: Attentional bias and salivary cotinine. These variables were positively correlated in control smokers (r=0.701)

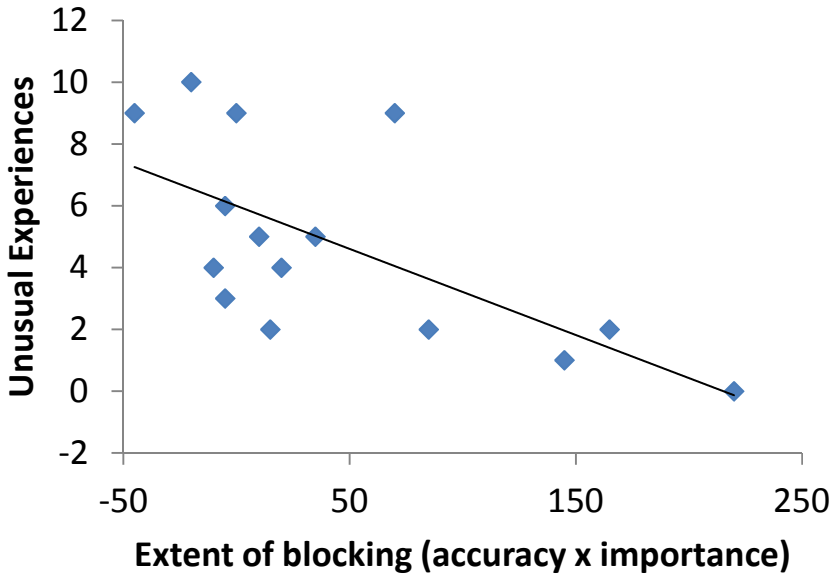


Figure 4.7: Blocking and 'unusual experiences' were negatively correlated in control smokers (r= -0.660).

4.4 Discussion

The main findings of this study were as follows: smokers with schizophrenia showed heightened attentional bias towards smoking-related words on a modified Stroop task compared to control smokers. Additionally, smokers with schizophrenia showed reduced blocking compared to control smokers, whilst both groups showed an absence of blocking towards smoking cues.

These findings provide the first evidence that people with schizophrenia attribute drug-related cues with heightened salience. Although smokers with schizophrenia displayed slower response time in general on this task, the difference observed between conditions here suggests that it was specific to smoking-related word content. Moreover, the extent to which these individuals showed heightened salience attribution towards drug related stimuli correlated positively with the severity of their positive psychotic symptoms. These findings are thus supportive of a common neurobiological abnormality that might cause drug-associated stimuli to be particularly salient to people with psychotic symptoms (Chambers et al., 2001; O'Daly et al., 2005; Tsapakis et al., 2003). These findings offer one potential explanation for high rates of tobacco smoking in people diagnosed with schizophrenia (de Leon & Diaz, 2005).

The findings obtained differ from previous evidence showing that a diagnosis of schizophrenia was associated with an absence of attentional bias towards cocaine-related words in a Stroop task (Copersino et al., 2004). These findings may have been attributable to lower craving in the schizophrenia group, or differences in cocaine use, which were not reported in the study. Other explanations for these contrasting results include differences between the populations tested, such as the context of drug use and interpretation of drug-

related word content, as well as the different pharmacology of the two drugs. However, if sensitisation of the dopamine system is responsible for high levels of salience attribution to drug cues in people with psychosis (O'Daly et al., 2005; Tsapakis et al., 2003), it would be predicted that cocaine might be particularly associated high levels of incentive salience attribution towards drug cues (e.g. Robinson and Becker, 1986).

In addition to heightened salience attribution on the Stroop task, smokers with schizophrenia also showed a reduction in blocking compared to control smokers in this study, in agreement with previous findings (Bender et al., 2001; Jones et al., 1992, 1997; Moran et al., 2003; 2008; Oades et al., 1996). This offers some validation of the sensitivity of the DCRPET task to selective learning deficits shown in schizophrenia. Furthermore a negative correlation was found between scores on a subclinical index of positive symptoms and blocking scores, albeit in controls rather than smokers with schizophrenia. A link between positive symptoms and blocking has been reported by some studies (e.g. Jones et al., 1992, 1997; Moran et al., 2003) whilst others have found performance to be linked to negative symptoms (Moran et al., 2008) or both (Bender et al., 2001, Oades et al., 1996). Our task was most similar to that employed by Haselgrove and Evans (2010) who used cues (food) and a fictitious outcome (food poisoning). The authors found a relationship between a loss of blocking and subclinical negative symptoms in the general population. However, they did not employ a reward-based learning procedure and the task design was substantially different from the one used here.

Performance on the DCRPET in terms of smoking images did not reveal any interactions between groups. Participants generally showed a lack of blocking to drug-related cues in this study according to accuracy and accuracy x importance ratings alone. Both groups also showed overshadowing of a neutral cue by a drug cue, although this was only found for

importance ratings. These findings support the hypothesis that drug-associated cues can interact with associative learning processes in drug using populations, but run contrary to the hypothesis that this should be enhanced in people with disrupted associative learning (i.e. people with a diagnosis of schizophrenia and a relative reduction in blocking). Instead these findings suggest that the relationship between salience attribution in addiction and psychosis might differ in ketamine users and people with schizophrenia. However the differential control groups and task variation preclude such a direct comparison at this stage.

Another consideration with regard to the DCRPET task is that smokers with a diagnosis of schizophrenia did not show the same progressive increase in accuracy across the training stages as controls. This indicates that the results from the test stage should be treated with some caution as they might be attributable to poor learning of task contingencies. On the other hand, accuracy was not lower overall in this group on the training stages. Furthermore these effects would be expected to result in poor accuracy at test overall and should not artificially reproduce within-task comparisons (e.g. such as blocking and overshadowing).

In agreement with previous studies (Ahnallen &Tidey, 2012; Fonder et al., 2005; Tidey et al., 2008) cue reactivity did not differ across smokers with schizophrenia and control smokers. This appears to support the selectivity of smoking-cue related disturbances in schizophrenia to salience attribution as opposed to explicitly rated subjective craving or urges. However, we treat this interpretation with caution due to the non-significant effect of cue exposure on VAS scores in both groups. We chose to use a video-based cue reactivity paradigm in order to control for levels of engagement in the paradigm that might influence *in vivo* cue reactivity. Future research might benefit from different or longer smoking-related videos, or to compute cue reactivity as the summation of different exposure techniques (e.g. *in vivo*,

imaginal and video-based; Kamboj et al., 2012). Another consideration is that administering this procedure at the start of the testing battery might have rendered it ineffective because smokers were adequately satiated and were therefore insensitive to the manipulation.

Analysis of VAS ratings between the end of the cue reactivity session and the end of the testing battery showed that smokers with schizophrenia showed a larger increase in anticipated pleasure from smoking (but not 'wanting') during the course of the experiment. This might bear some similarity to a study which found that smokers with a diagnosis of schizophrenia showed a greater increase in tobacco craving than 'healthy' smokers across a parallel time period (Lo et al., 2011). However inspection of the data suggests that the relative increase in scores in this study resulted in a lower discrepancy between the groups rather than an elevation of anticipated pleasure in this group.

In terms of limitations, the interactions between Group and Type in the modified Stroop task and between Group and Cue in analysis of blocking were at trend level of significance; furthermore the effect sizes of these interactions were of small magnitude. Whilst a reduction in blocking is a well-documented finding in schizophrenia the assessment of attentional bias was novel and should be treated with caution until replicated. Initially it was hoped that a larger sample of smokers with schizophrenia could have been recruited and which could have offered a partial solution to this concern. On the other hand, an important strength of this study was the similarity across groups on smoking-related variables, according to both biologically verified indices of recent cigarette consumption and self-reported smoking behaviour, dependence, motivation to quit, and the characteristics of previous quit attempts. The groups also did not differ in terms of gender, age, estimated IQ and subjective experiences of attentional bias.

Despite these similarities, it is worth acknowledging the groups will have differed substantially in the amount of medical contact they were receiving and this may have meant that individuals with a diagnosis of schizophrenia had more encouragement to give up smoking. Although all volunteers were informed that the study was not in any way trying to influence their smoking behaviour, this issue may be difficult to control for in studies of this kind. Finally, our patients were taking atypical medication (clozapine) and the extent to which these findings extend to patients with schizophrenia who are taking different medications is a question for future research. Whilst it is noteworthy that clozapine has been associated with lower rates of smoking (Chatterton, Sanderson, Van Leent, & Plant, 1998; George, Sernyak, Ziedonis, & Woods, 1995; McEvoy, Freudenreich, McGee, & VanderZwaag, 1995), results from a study with a larger sample did not support this conclusion (de Leon, Diaz, Josiassen, Cooper, & Simpson, 2005). Moreover, a reduction in smoking in these individuals would not be expected to artificially inflate levels of attentional bias seen in schizophrenia.

In conclusion, this study found that attentional bias as indexed using the modified Stroop task was heightened in smokers with a diagnosis of schizophrenia. These individuals also showed a reduction in blocking to reward predicting cues compared to controls, but both groups failed to show a blocking effect to smoking-related images in the task. These findings provide preliminary evidence that aberrant salience attribution towards both irrelevant stimuli and drug-related cues may be enhanced in people with a diagnosis of schizophrenia.

Chapter 5: The role of dopamine in salience attribution in smokers

5.1 Introduction

The attribution of incentive salience to drug-associated stimuli is thought to occur due to the release of dopamine, acting to change the way they are perceived by substance users and biasing attention towards them (Robinson & Berridge 1993; Franken 2003). In support of this hypothesis, a single 2mg dose of the D_2 antagonist haloperidol reduced drug-related attentional bias in heroin-dependent individuals (Franken et al, 2004) as well as BOLD activation in brain regions associated with attentional bias in smokers (Luijten et al., 2012). Additionally, manipulating dopaminergic function through acute tyrosine/phenylalanine depletion (ATPD) can dampen attentional bias in smokers (Hitsman et al, 2008, females in Munafò et al, 2007).

Interestingly, none of these studies observed any changes in subjective craving or urges alongside effects on attentional bias, as might have been expected according to theoretical models (Franken 2003; Robinson & Berridge, 1993) and empirical evidence (Field et al., 2009b). Dopamine-induced attentional bias may precede subjective craving (Franken, 2003), and thus might be detected experimentally in the absence of altered craving. On the other hand, one study found that ATPD reduced attentional bias in females but increased cigarette craving amongst males (Munafò et al, 2007). Although these contrasting effects emerged in different groups, this raises the possibility that dopamine might produce opposite effects on craving and attentional bias within the same individuals, which would be problematic for theoretical models (Franken et al, 2003, Robinson & Berridge, 1993).

One way to test address this hypothesis would be administer a drug that would be expected to produce changes on attentional bias and craving and to if these effects correspond with one another. In terms of smokers, dopamine agonists used for the treatment of Parkinson's Disease are able to reduce *ad libitum* smoking and tobacco craving dose dependently (Caskey, Jarvik, & Wirshing, 1999; Caskey et al., 2002; Jarvik et al., 2000) and are associated with lower rates of smoking after extended use (Murphy et al., 2002). To the author's knowledge, the effects of dopamine agonist treatment on attentional bias have not yet been tested in smokers. However a single dose of the dopamine D_2/D_3 agonist pramipexole produced effects in stimulant users that were differed according to the nature of their drug use, exacerbating a pronounced substance-related bias in highly compulsive users but eliminating it in those with less compulsive style of use (Ersche et al., 2010). If pramipexole is able to influence tobacco craving and attentional bias in parallel, this might suggest that dopamine plays a common role in both processes.

Another concern with studies that have examined the role of dopamine in attentional bias (Ersche et al., 2010; Franken et al., 2004; Hitsman et al., 2008; Luijten et al., 2012; Munafò et al., 2007) is the extent to which these effects were specific to drug-related stimuli (Anselme, 2009). Cross-sectional evidence for a substance-related bias in a group of drug users does not rule out the possibility that they experience a range of other stimuli as highly salient as well (Robbins & Ehrman, 2004); similarly dopaminergic effects in previous studies might have produced generalised effects on salience attribution rather than specific effects towards the drug. This may be an important consideration because drug users may show a loss of salience attribution towards non-drug rewards (Goldstein & Volkow, 2011). Targeting both drug and non-drug reward appears to be effective in psychological treatments for addiction (Curran and Drummond, 2005; Petry, 2000). However the extent to which

pharmacological approaches can address this problem is not well understood. Based on the results reported in chapter 2, it might be expected that a reduction in bias towards smoking-related images could reduce overshadowing of non-drug reward.

This study assessed the effects of a single 0.5mg dose of pramipexole in smokers. It was hypothesised that pramipexole would reduce subjective craving, urges to smoke and drug-related memory retrieval following the effects of dopamine agonist treatment in smokers (Caskey et al., 1999, 2002; Jarvik et al., 2000; Murphy et al., 2002). Based on theoretical predictions (Franken, 2003) and previous evidence for a link between craving and attentional bias (Field et al., 2009b) it was hypothesised that pramipexole would also reduce substance related bias. In order to assess the specificity of this effect it was compared against levels of bias to non-drug reward stimuli. Finally, we examined whether pramipexole might reduce overshadowing of non-drug reward.

5.2 Methods

5.2.1 Design and participants

A randomized double-blind placebo controlled crossover design was used to assses the effects of 0.5mg pramipexole in 16 non treatment-seeking smokers (8 male) recruited from the community. Inclusion criteria were age 18-40, smoking ≥ 10 cigarettes per day for ≥ 1 year, smoking a first cigarette ≤ 1 hour after waking, normal or corrected to normal vision, and fluent spoken English. Exclusion criteria were current use of any smoking cessation aid, a learning, mental health or substance abuse problem, tumours of the pituitary or adrenal gland, reduced liver or kidney function, pregnancy or breast feeding. All participants provided written, witnessed, informed consent. This study was approved by the UCL Graduate School Ethics Committee (appendix 9 and 10) and conducted in accordance with the Declaration of Helsinki.

5.2.2 Assessments

Visual probe task (Figure 5.1)

The allocation of attention towards smoking related and monetary images was indexed using eye tracking synchronized to a computer-based task. Participants were seated with their head in a chin/forehead rest 70cm away from a 19-inch monitor used to present the stimuli. Trials began with central fixation that was verified using the eye tracking device. Next, two images were presented side by side for either 250ms or 2000ms. Both images were 109mm wide and 84mm high when displayed onscreen, with a distance of 58mm between their closest edges. At stimulus offset, a blank screen was displayed with a probe (an arrow pointing upwards or downwards) presented in the same location as one of the previously displayed images. Participants were required to press a key corresponding to its orientation (either ‘up’ or

'down') as quickly and accurately as possible. Images were presented in pairs consisting of a target image (e.g. a woman smoking a cigarette) and a non–target image matched for visual composition (e.g. a woman applying lipstick). Similar pairs were used for money trials (e.g. UK bank notes; train tickets). Two task versions were created using different images to control for stimulus novelty across testing sessions. The task consisted of 8 neutral practice trials and 192 experimental trials employing 10 pairs of monetary images (expanded from Morgan et al., 2008), 10 pairs of smoking images and 4 pairs of neutral filler images (from Mogg et al. 2003). Each pair of images was presented 4 times for 250ms and 4 times for 2000ms. Target images appeared equally often on the left and the right and were replaced by the probe on half of the trials. Orientation of the probe was balanced across trials.

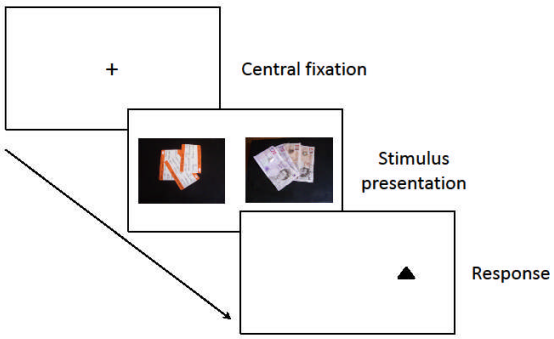


Figure 5.1: Design of the visual probe task. Following central fixation, two stimuli were displayed side by side on screen for either 250ms or 2000ms. Experimental trials used smoking-related or monetary picture pairs, consisting of a target (shown here on the right; money) and matching non-target image (shown on the left; train tickets). Eye tracking was used to determine the extent to which participants' first fixation occurred towards target images, and the duration of fixation on both images across the trial. Reaction times to a probe displayed at stimulus offset was used as a behavioural measure of attentional bias.

Picture rating task

After the dot probe task, participants rated smoking and monetary images for their pleasantness on a 7 item scale from -3 (very unpleasant) to +3 (very pleasant).

Phonological, semantic and drug fluency

Participants were asked to name as many unique exemplars as possible beginning with the same letter (M; phonological), from the same category (fruit; semantic) and related to smoking (drug fluency) in that order, based on a previous study (Goldstein, Woicik, Lukasik, Maloney, & Volkow, 2007)

Mood and Physical Symptoms Scale (MPSS)(West & Hajek, 2004)

This 7 item scale includes 'Depression', 'Irritability', 'Restlessness', 'Hunger' and 'Poor Concentration' which were rated 'at this time' from 0 (not at all) to 4 (extremely). Time Spent with Urges ('How much of the time have you felt the urge to smoke in the past 2 hours?') was rated from 0 (not at all) to 5 (all the time) and Strength of Urges to Smoke ('How strong have these urges been?') was rated from 0 (no urges) to 5 (extremely strong).

Tobacco Craving Questionnaire-Short Form (TCQ-SF; Heishman et al. 2008)

Each of the 12 items on this scale were rated 'right now' from 1 (strongly disagree) to 7 (strongly agree). Higher scores reflect stronger tobacco craving. It has 4 subscales (Emotionality, Expectancy, Compulsivity and Purposefulness).

Fagerström Test of Nicotine Dependence (FTND; Heatherton et al. 1991)

This scale consists of six items rated between 0 and 3, with scores ranging from 0 (low dependence) to 10 (high dependence).

5.2.3 Procedure

Following screening, participants attended two three-hour laboratory sessions separated by a washout period lasting between 5 and 9 days. Participants were asked to fast for an hour before attendence, to refrain from caffeine consumption on the day of testing and to avoid driving or using machinery for the remainder of day. After smoking a cigarette, a carbon monoxide (CO) reading (Bedfont Micro Smokerlyzer, UK) and baseline assessments (Mood and Physical Symptoms Scale, Tobacco Craving Questionnaire) were taken. This was followed by drug administration, which was either 0.5mg pramipexole (peak plasma levels at 1-3 hours) (Wright, Sisson, Ichhpurani, & Peters, 1997) or matched placebo. The peripheral D_2 antagonist domperidone (30mg) was co-admistered on both days in order to reduce unwanted side effects of dopamine agonist treatment such as nausea and vomitting (Parkes, 1986). Smoking was not permitted for the remainder of each test day. After drug administration, participants were given trait questionnaires (mood and smoking behavior; 0-15 minutes post drug) and were encouraged to read magazines or books provided (15-90 minutes post drug) before testing began (90 minutes post drug). The tasks were conducted in the following order: DCRPET (90 minutes), visual probe (125 minutes), Mood and Physical Symptoms Scale and Tobacco Craving Questionnaire (150 minutes), picture rating task (155 minutes) phonogical, semantic and drug fluency (160 minutes).

5.2.4 Preparation of eye movement and manual RT data for the visual probe task

Eye movements were recorded at a 1 KHz sampling rate, using a desktop mounted EyeLink 1000 eye tracking device (SR Research, Ontario, Canada). Prior to recording, participants' eye movements were calibrated by fixation on a 3×3 point grid. Drift correction was performed between each trial to ensure participants were attending to the centre of the screen before stimulus picture onset. Based on previous research (Bradley, Garner, Hudson, & Mogg, 2007) analysis of eye movement data was restricted to (i) 2000ms trials only (ii) trials in which at least one fixation was made to the target or non-target image between 100ms after stimulus onset and stimulus offset (this criterion excluded 8.1% of trials). Initial orientation was calculated as the proportion of trials in which the first fixation was directed towards the target image, with 0.5 indicating no bias, and scores above/below 0.5 reflecting increased/decreased bias respectively. Dwell time was calculated as the mean duration (ms) of fixation time to each image (target and non-target) across 2000ms trials. For behavioural data, stimuli for both 250 and 2000msec were included and following Bradley et al. (2007), manual RTs were excluded if they were <200ms, >1000ms, ± 3 SD's from each participant's mean for each Type and Target, or if an incorrect response was made (12.4% of total data). Bias scores were calculated by subtracting reaction times on congruent trials (where a probe replaced a target image) from incongruent trials (where a probe replaced a non-target image), with positive/negative scores indicating bias towards/away from target images respectively.

5.2.5 Statistical Analysis

All analyses were carried out using Statistical Package for Social Sciences (SPSS version 19). Paired sample t-tests and RMANOVA models were used to assess effects of Treatment (pramipexole versus placebo). All analysis of the visual probe data included an extra within-subject factor of Type (Smoking, Money), with additional factors of Target (Target, Non-target) for dwell time and picture rating, and Trial (Congruent, Incongruent) for RT data. Fluency tasks were analysed using planned orthogonal contrasts comparing (i) non-drug (phonological and semantic) fluency with drug-related fluency, (ii) phonological and semantic fluency. For the DCRPET task training data, control cue scores (e, f) were collapsed and compared with blocked cues in separate RMAONVA models assessing (i) blocking, (ii) blocking of a drug cue. Overshadowing was analysed by comparing scores to the neutral cue g with the drug cue **H**. As in previous chapters, analysis was carried out on 1) accuracy, 2) importance, 3) accuracy x importance scores. Time (Pre, Post) was a within-subject factor for analysing the Mood and Physical Symptoms Scale and the Tobacco Craving Questionnaire. One sample t tests were used to assess whether bias in initial orientation occurred to smoking or monetary stimuli, using a test value of 0.5 (no bias). Post hoc t-tests were two-tailed unless stated and were conducted using a Bonferroni-corrected α level.

5.3 Results

Participants

Participants were 24.81 (±4.92) years old, had smoked for 8.25 (±5.21) years and were currently smoking 13.25 (±4.64) cigarettes per day, scoring 4.81 (±1.17) on the FTND. Expired carbon monoxide levels did not differ before treatment with placebo (15.63 ±6.75 PPM) and pramipexole (15.75 ±4.63 PPM).

Visual probe task

For direction of first fixation (Figure 5.2) a trend for a Treatment x Type interaction ($F_{1,15}$=3.897, p=0.067, η_p^2=0.206) emerged as well as a main effect of Type ($F_{1,15}$=10.009, p=0.006, η_p^2=0.400) indicating a greater bias towards the target image for smoking-neutral picture pairs compared to money-neutral picture pairs. Exploration of the interaction showed that on placebo, individuals showed significantly greater bias in initial orientation towards smoking targets than money targets (p = 0.003), but after pramipexole no difference in bias was evident between these two types of image (p = 0.520). Significant bias scores (i.e. different from 0.5) were shown towards smoking targets on placebo (p<0.001) and to a lesser extent after pramipexole (p=0.022); no significant bias was shown to money images on placebo (p=0.475) or pramipexole (p=0.249).

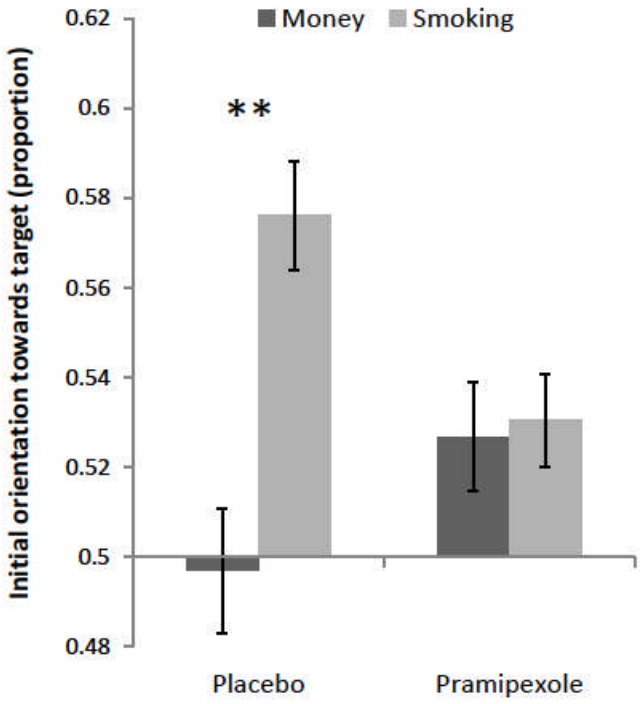


Figure 5.2: Initial orientation on the visual probe task. Pramipexole abolished a marked bias towards smoking-related compared to monetary images seen on placebo. Error bars show SEM.

Analysis of dwell time (Figure 5.3) revealed a trend for a Type x Target interaction ($F_{1,15}$=4.282, p=0.056, η_p^2=0.222) as well as main effects of Type ($F_{1,15}$=51.181, p<0.001, η_p^2=0.773) and Target ($F_{1,15}$=11.530, p=0.004, η_p^2=0.435), reflecting a greater amount of dwell time towards towards stimuli on smoking trials compared to monetary trials and towards target images compared to non-target images. Exploration of the interaction revealed significantly greater dwell time for target compared to non-target images on smoking trials (p<0.001) but not on monetary trials (p=0.102). Analysis of manual RT bias scores (Table 1) did not reveal any significant effects of Day, Type or Duration.

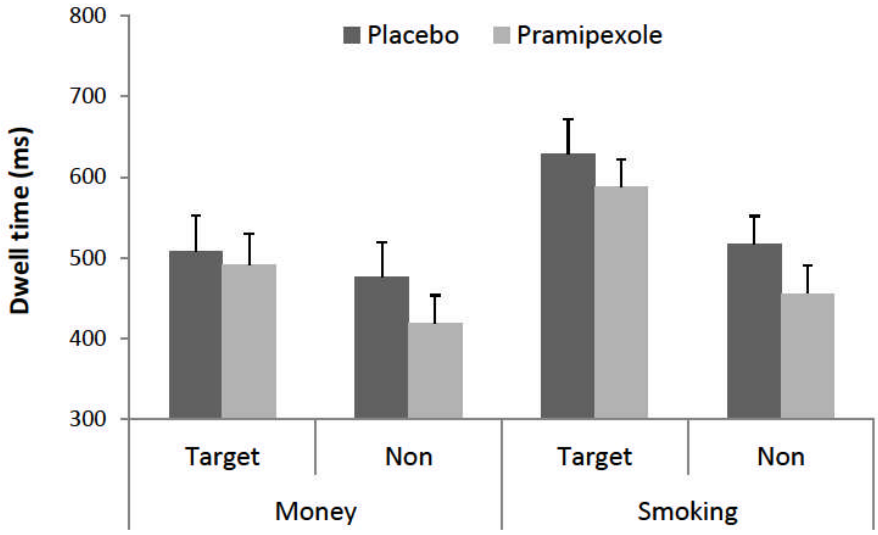


Figure 5.3: Dwell time to monetary and smoking picture pairs on the visual probe task. Smokers showed longer dwell time towards smoking targets compared to non-targets, but equivalent dwell time towards both types of monetary image. Error bars show SEM.

Picture rating task (Table 5.1)

A significant Type x Target interaction emerged ($F_{1,15}$=8.517, p=0.011, η_p^2=0.362), as well as a main effect of Target ($F_{1,15}$=39.009, p<0.001, η_p^2=0.722) and a trend for a main effect of Type ($F_{1,15}$=4.183, p=0.059, η_p^2=0.218). The Type x Target interaction indicated that equal pleasantness ratings were given towards smoking and monetary non-target images (p=0.314), but higher pleasantness ratings were made towards monetary relative to smoking target images (p=0.011).

Table 5.1: Behavioural data from the visual probe and picture rating tasks. No effects or interactions emerged for bias scores on the visual probe task. In the picture rating task, target images (particularly money) were rated as more pleasant than non-target images.

			Placebo	Pramipexole
Visual probe	Money	250ms	1.57 (19.54)	6.61 (22.52)
RT bias		2000ms	-0.33 (24.46)	9.00 (27.98)
	Smoking	250ms	-1.01 (23.20)	2.75 (26.66)
		2000ms	3.46 (22.14)	-3.20 (28.24)
Picture rating	Money	Non target	0.11 (0.72)	0.11 (0.60)
		Target	1.75 (0.85)	1.66 (0.82)
	Smoking	Non target	0.21 (0.38)	0.33 (0.35)
		Target	1.26 (1.06)	0.68 (1.36)

DCRPET-short

Training data (Figure 5.4)

Significant main effects emerged for Cue ($F_{5,375}$=6.518, p<0.001, η_p^2=0.303) and Block ($F_{5,350}$=19.733, p<0.001, η_p^2=0.568) reflecting higher accuracy for pretrained cue pairs (AB and CD) and across successive blocks (see Figure 5.4). A trend for a Cue x Treatment interaction also emerged ($F_{5,350}$=2.188, p=0.065, η_p^2=0.135), but paired t tests compairing the effects of treatment on each cue did not reach significance after Bonferroni correction (all *p's* > 0.027). Inspection of figure 5.4 shows that learning increased progressively for novel cues (a, c, ef, g**H** but learning transferred across stages for ab and c**D** trials).

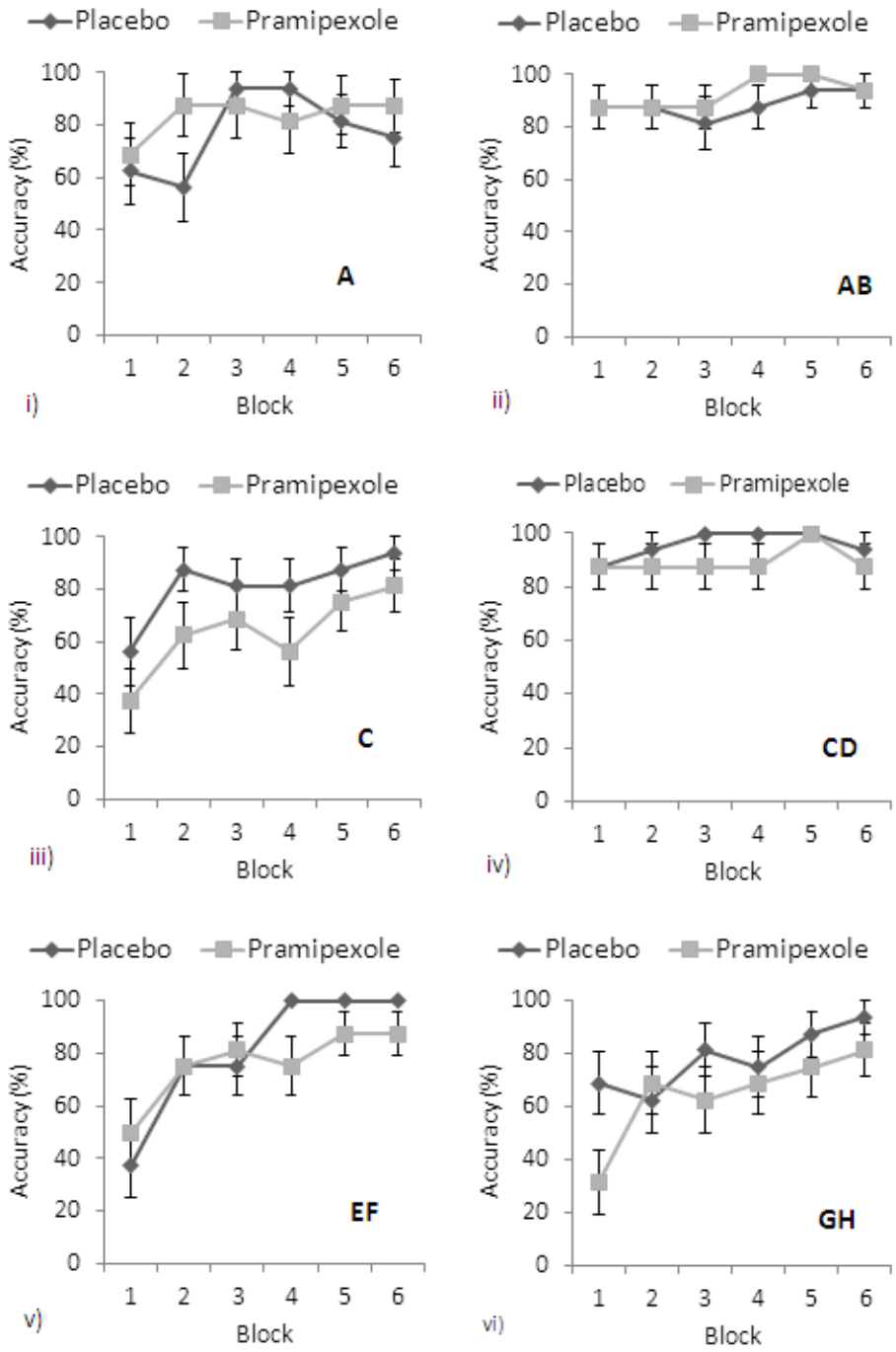


Figure 5.4: Training data from the DCRPET-short. Error Bars show SEM.

Test data (Table 5.2)

Blocking: No effects or interactions emerged for analysis of accuracy, importance, or accuracy x importance.

Blocking of a drug cue: Again, no significant effects or interactions emerged

Overshadowing: No significant effects or interactions were found.

Table 5.2: Test data from the DCRPET-short.

	Placebo	Pramipexole
Control Cue accuracy	87.50 ±34.16	68.75 ±47.87
B accuracy	81.25 ±40.31	68.75 ±47.87
D accuracy	93.75 ±25.00	46.67±51.64
G accuracy	81.25 ±40.31	68.75 ±47.87
H accuracy	87.50 ±34.16	68.75 ±47.87
Control Cue importance	50.94±21.46	51.56±23.92
B importance	48.75±23.35	41.25±27.05
D importance	55.00±29.66	53.13±26.51
G importance	48.13±21.98	43.13±26.51
H importance	60.63±25.42	54.38±29.66
Control Cue accuracy x importance	51.56±36.04	39.69±49.55
B accuracy x importance	31.25±56.44	23.75±54.14
D accuracy x importance	60.00±39.33	34.38±60.77
G accuracy x importance	41.88±47.08	29.38±52.85
H accuracy x importance	56.88±50.16	28.13±66.76

Fluency tasks (Figure 5.5)

A significant interaction was found between Treatment and the contrast comparing non-drug fluency tasks with drug fluency ($F_{1,15}$=5.363, p=0.035, η_p^2=0.263). Phonological and semantic fluency scores did not differ from each other or interact with Treatment. The only other effect to emerge was a trend for lower drug fluency compared to non-drug fluency on both testing days ($F_{1,15}$=4.051, p=0.062, η_p^2=0.213). Exploration of the interaction showed that performance on the phonological and semantic fluency tasks did not differ across the two testing days (p=0.692) but fewer smoking-related words were generated after pramipexole compared with placebo (p=0.016).

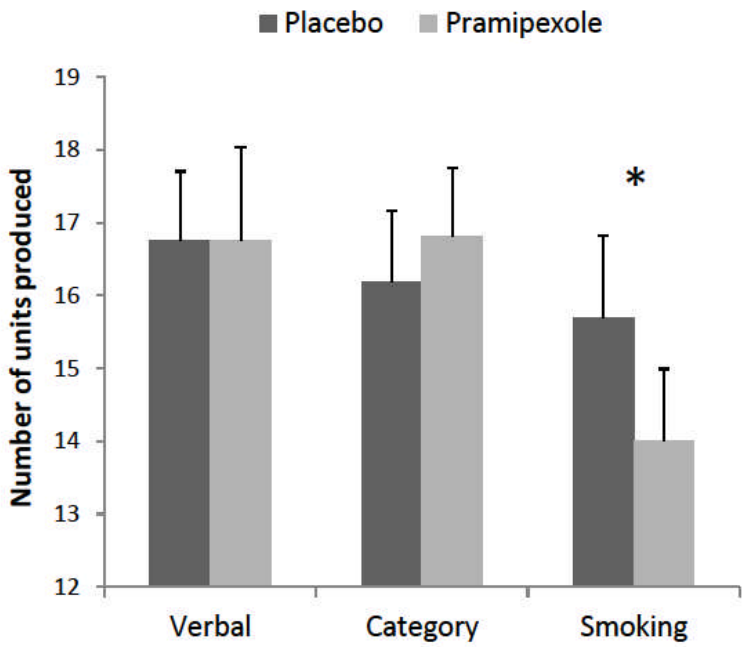


Figure 5.5: Fluency tasks. Verbal and category fluency did not differ across treatment days but significantly fewer smoking-related words were generated for the drug fluency task after pramipexole compared to placebo. Error bars show SEM.

Mood, physical symptoms and tobacco craving (Table 5.3)

Analysis of the MPSS revealed significant effects of Time for 'Irritable', 'Restless', 'Hungry' and 'Poor concentration', reflecting increased severity of symptoms post- compared to pre-drug. Analysis of 'Strength of Urges to Smoke (SUTS)' revealed a significant Treatment x Time interaction; SUTS decreased from pre to post pramipexole treatment (p=0.017; one-tailed as predicted) but tended to increase with Time on the placebo day (p=0.035).

For the Tobacco Craving Questionnaire, significant effects of Time emerged for 'Emotionality', 'Expectancy', 'Purposefulness' and total scores, reflecting elevated craving scores post- compared to pre- drug. For Compulsivity, main effects of Time and Day were found. Although a significant Treatment x Time interaction did not emerge for the Compulsivity subscale, reduced scores on the pramipexole day were more pronounced post drug (p=0.030) compared to pre drug (p=0.155).

Table 5.3: Mood and physical symptoms, smoking urges and tobacco craving at baseline and 150 minutes after treatment.

	Placebo		**Pramipexole**		**Time x Treatment** $F_{(1,15)}$	**Time** $F_{(1,15)}$	**Treatment** $F_{(1,15)}$
	Pre	**Post**	**Pre**	**Post**			
MPSS Depressed	0.19 (0.40)	0.06 (0.25)	0.31 (0.60)	0.13 (0.34)	0.319	4.310	0.808
MPSS Irritable	0.06 (0.25)	0.25 (0.58)	0.19 (0.54)	0.44 (0.63)	0.072	4.623*	1.518
MPSS Restless	0.38 (0.50)	1.06 (0.68)	0.50 (0.73)	1.19 (1.17)	0.000	12.020**	0.484
MPSS Hungry	0.57 (0.63)	1.81 (0.83)	0.57 (0.63)	1.81 (0.91)	0.000	31.250***	0.00
MPSS Poor concentration	0.44 (0.63)	1.13 (0.81)	0.44 (0.51)	1.38 (0.81)	0.652	18.778***	0.484
MPSS Time Spent with Urges	2.06 (0.85)	1.94 (1.29)	2.06 (0.68)	1.69 (0.70)	0.319	2.500	0.385
MPSS Strength of Urges to Smoke	1.94 (0.85)	2.50 (1.32)	2.44 (0.73)	1.88 (0.72)	7.275*	0.00	0.048
TCQ Emotionality	8.66 (3.94)	10.72 (5.87)	7.60 (3.93)	10.06 (5.63)	0.078	5.249*	0.718
TCQ Expectancy	14.03 (4.28)	18.06 (3.33)	13.28 (3.97)	15.53 (4.54)	1.575	17.833***	1.903
TCQ Compulsivity	8.25 (4.86)	11.94 (6.05)	6.41 (3.04)	8.91 (4.50)	0.951	18.490***	4.985*
TCQ Purposefulness	12.28 (4.97)	14.66 (4.83)	11.94 (3.23)	13.66 (3.99)	1.390	7.080*	0.501
TCQ Total	43.22 (14.05)	55.38 (17.61)	39.22 (10.22)	48.16 (15.34)	0.921	13.995**	2.268

p <0.05; p <0.01; ***p <0.001*

Correlations

Pearson correlational analyses were carried out between treatment effects (change scores) on the following variables: initial orientation to smoking images, initial orientation to monetary images, drug fluency, and the changes in strength of urges to smoke across the testing session. No significant correlations emerged.

5.4 Discussion

The main findings of this study were as follows: pramipexole abolished a marked bias in the allocation of attention towards smoking relative to monetary cues but did not influence maintained attention towards either smoking-related or monetary images. Pramipexole also decreased individuals' strength of urges to smoke tobacco and smoking-related word production, without affecting performance on standard assessments of phonological and semantic fluency, but did not influence overshadowing of non-drug reward.

These findings show for the first time that treatment with a dopamine D_2/D_3 agonist drug can reduce the ability of smoking-related images to attract initial orientation relative to images of a non-drug reward. On placebo smokers showed a clear bias in initial orientation and were 9.6% more likely to attend towards images of smoking than monetary stimuli. However after treatment with pramipexole this difference was markedly reduced (1.7%). These results show a specific reduction in drug-related bias relative to other appetitive stimuli, which has not been shown in previous studies supporting a role of dopamine in substance-related attentional bias (Ersche et al., 2010; Franken et al., 2004; Hitsman et al, 2008; Luijten et al., 2012; Munafò et al., 2007). These results may be clinically relevant because individuals who show a low attentional response to pleasant stimuli and a high reactivity to smoking-related images prior to a quit attempt are more likely to relapse (Versace et al., 2011). A discrepancy between the attention-grabbing properties of drug-related and natural reward stimuli was also found to predict frequency of drug use at follow up in opiate users (Lubman et al., 2009).

In contrast to its effects on initial orientation, pramipexole did not impact on maintained attention towards smoking-related or monetary images. The lack of changes in maintained attention after drug treatment may provide some explanation for the absence of treatment

effects on the DCRPET, since previous studies have reported that changes in maintained attention correlate with changes associative learning (Beesley & Le Pelley, 2011; Kruschke et al., 2006; Wills et al., 2007). However, analysis of this task did not reveal any overshadowing of drug cues in general. These results run contrary to the hypothesis that pramipexole might reduce drug-cue induced overshadowing. However, it may be the case that overshadowing by drug cues only arises after extended periods of abstinence (e.g. 12+ hours; as shown in chapter 2) and not after brief abstinence (2 hours in the current study).

In parallel to its effects on the visual probe task, pramipexole also decreased individuals' strength of urges to smoke. Dopamine release in response to drug-related cues is thought to underpin their ability to attract selective attention, increase craving and cause drug-seeking behavior (Franken 2003; Robinson & Berridge 1993). Dopaminergic effects on attentional bias have been previously reported (Ersche et al., 2010; Franken et al., 2004; Hitsman et al., 2008; Luitjen et al., 2012; Munafò et al., 2007). However to the author's knowledge, this is the first evidence supporting a change in subjective urges or craving alongside dopaminergic effects on attentional bias. This suggests that dopamine plays a common role in influencing craving and attentional bias, as predicted (Franken, 2003; Robinson & Berridge, 1993).

Because of its retrospective nature this 'strength of urges to smoke' item is thought to be especially sensitive to peak craving experiences such as cue exposure (Ferguson, Shiffman, & Bruno, 2011) and is highly predictive of successful smoking cessation 6 months later (Fidler, Shahab, & West, 2011). In our sample the strength of urges to smoke item was rated over a 2 hour time period corresponding to the time of attentional bias assessment and might have been directly associated with reductions in smoking-related attentional bias during the visual probe task. This could partially explain the contrasting effects seen for 'in the moment'

tobacco craving, which only revealed lower scores on the 'Compulsivity' subscale on the pramipexole day that did not interact with time of assessment. On the other hand, reduced urges to smoke and tobacco craving have previously been reported following dopamine agonist treatment in the absence of experimental cue exposure (Caskey et al., 1999; 2002; Jarvik et al., 2000) and treatment effects on urges to smoke did not correlate with those observed for attentional bias. The use of a novel experimental design (e.g. manipulating the level of cue exposure across different groups after pramipexole treatment) could offer one way to investigate a causal relationship between dopaminergic effects on attentional bias and craving or urges to smoke.

Pramipexole also reduced the production of smoking-related words on the drug fluency task. Performance was equivalent on both days for standard phonological and semantic fluency, suggesting that this was a drug-specific retrieval effect. Drug fluency is theoretically related to attentional bias (Goldstein et al., 2007), and correlates with drug-cue elicited BOLD activation in DA innervated midbrain regions among people with a cocaine use disorder (Goldstein et al., 2009b). Dopaminergic effects on attentional bias are theoretically related to drug-related memory processes (Franken, 2003) and our results are supportive of this hypothesis. Drug fluency is a recent concept and its ability to predict clinical outcomes in substance users is yet to be established. However, the speed at which this task can be administered would allow for it to be widely implemented in clinical settings if this was shown to be the case.

Money is an abstract reinforcer that applies to everyday life and therefore offers one way to index non-drug reward processes in drug addiction (Goldstein & Volkow, 2011). However, attention was not significantly 'biased' towards images of money according to initial

orientation or maintained attention. Our findings differ from previous work showing that both monetary and drug images were attention-grabbing in frequent ketamine users but not infrequent users, ex users or controls (Morgan et al., 2008). These contrasting findings might be attributable to differences in the way money is used to purchase and sometimes consume controlled drugs such as ketamine. However, monetary reward images were explicitly rated as more 'pleasant' than smoking images on both days. Taken together these results suggest that the monetary images we employed offered a suitable index of non-drug reward, being 'liked' more than drug cues but not pathologically 'wanted' according to their effects on incentive salience attribution (Robinson & Berridge, 1993).

A mechanistic explanation for our findings remain speculative, however pramipexole is thought to bind preferentially to presynaptic autoreceptors at low doses (Maj, Rogoz, Skuza, & Kołodziejczyk, 1997) thereby acting to inhibit phasic dopamine release in response to behaviourally relevant stimuli such as drug cues (Phillips, Stuber, Heien, Wightman, & Carelli, 2003). This might have accounted for the reduction in bias towards drug images relative to monetary images, which would be consistent with a role of phasic dopamine in cue-based motivational salience and learning (Bromberg-Martin et al., 2010; Zweifel et al., 2009) and the effects of pramipexole on a reward responsivity paradigm (Pizzagalli et al., 2008) It has been suggested that the threshold of dopamine release that is necessary to elicit spontaneous orientation towards a salient stimulus can become more liberal for drug-related cues than non-drug rewards (Anselme, 2009) and if so, a reduction in the release of dopamine might be expected to reduce bias towards smoking-related images relative to monetary images. Furthermore, non-linear (e.g. inverted-U) dose response effects of dopamine have been reported for working memory and cognitive control (Cools & D'Esposito, 2011) and are thought to mediate the effects of motivation on cognition (Aarts, van Holstein, & Cools,

2011). Another possibility is that pramipexole 'overdosed' the level of dopamine necessary to orientate towards smoking-related but not monetary images, producing a relative reduction in smoking-related bias. Following Ersche et al. (2010) we administered a single relatively low (0.5mg) dose of prampexole in this study with the peripheral dopamine antagonist domperidone (30mg) to prevent unwanted side effects. Future studies could investigate these possiblities by administering a range of doses and/or selecting individuals who might be predicted to experience specific effects of drug treatment due to baseline dopaminergic function.

This study suffered from some limitations. Firstly, it is clear that 'smoking' and 'monetary' images can only provide a crude index of reward processing that may be dependent on the nature of specific images and individual differences across volunteers. However, the interactive effects of treatment and picture type in this crossover design cannot be attributed to these cross-sectional factors and provide strong evidence for a role of dopamine in altering incentive salience attribution to different types of reward. Furthermore, whilst our sample size was similar to previous studies of this kind (Franken et al., 2004; Hitsman et al., 2008) and larger than other studies addressing subgroups of drug users (Ersche et al., 2010; Munafò et al., 2007) one of the three interactions we found with treatment did not reach conventional levels of significance. A larger sample would might therefore increase power to detect significant effects in future studies.

These results are the first to show that manipulating dopaminergic function can reduce the salience of drug-related cues compared to other rewards. Taken together with simultaneous reductions in smoking urges and drug-related memory retrieval, these findings highlight an important role for D_2/D_3 receptor function in tobacco dependence and its treatment.

Chapter 6: General discussion

This thesis set out to address the following questions:

1) Can exposure to drug-related cues influence the attribution of salience to non-drug stimuli, and what is the role of dopamine in this process?
2) Is there a relationship between salience attribution processes linked to addiction and those linked to psychosis?

In this chapter I will discuss how the results obtained in this thesis have provided some answers to these questions and what implications these findings have in terms of theory and clinical practice. Methodological limitations of the empirical work of this thesis will be discussed and finally directions for future research will be suggested.

6.1 Summary of findings

The research described in this thesis examined the effects of stimuli with different associative history (drug-related, non-drug related) in situations where they varied in task relevance (predictive or irrelevant with respect to associative learning). In doing so, this research allowed for the exploration of how these two factors interact, that is, whether previous associative history of a stimulus can determine the extent to which it acts as a 'relevant' or 'irrelevant' stimulus in experimental contexts. As such, it allowed for the potential integration of salience attribution processes involved in substance use and psychosis. As part of this thesis, a novel task was developed with this integrative intention in mind.

In Chapter 2 I found that drug-related images were able to overshadow neutral images that were equally predictive of reward according to composite accuracy/importance ratings on this task. This effect was found in abstaining smokers only, alongside an attentional bias towards smoking-related images on a dot probe task, and enhanced craving scores, reflecting higher anticipated pleasure from smoking. The absence of overshadowing effects and attentional bias in satiated smokers would suggest that these effects might be exacerbated during periods of nicotine deprivation and/or craving, such as when an individual is engaging in a cessation attempt.

Overshadowing of non-drug reward stimuli was replicated in chapter 3 but was found across both groups tested (regular ketamine users and polydrug using controls). However, drug-associated cues interacted with blocking in ketamine users but not controls, as evidenced by a resistance to being blocked by neutral cues. Furthermore, ketamine users showed a reduction in blocking generally and elevated self-rated delusional beliefs and schizotypy. These findings appear to suggest that the ketamine using group were showing aberrant salience attribution processes that are related to both substance use (enhanced learning about drug-

related compared to neutral stimuli) and psychosis (elevated learning about stimuli that were irrelevant predictors in the task). The disruption of blocking by drug cues in ketamine users but not in other groups tested in chapters 2 and 3 might suggest that aberrant salience attribution processes relevant to addiction and psychosis co-vary with each other, which would support the prediction that people suffering from positive psychotic symptoms might attribute drug-related cues with heightened salience.

In Chapter 4 I tested these predictions. In contrast to the findings regarding ketamine users in chapter 3, smokers with a diagnosis of schizophrenia did not show differential effects relating to drug associated stimuli in the DCRPET when compared to controls. However, they did show an absence of blocking, in agreement with findings in ketamine users from chapter 2 and also previous evidence for a reduction in blocking in people with schizophrenia. Moreover, they showed some evidence of elevated attentional bias when compared to controls, which correlated positively with the severity of positive psychotic symptoms in the patient group and with salivary cotinine in controls. When combined with the absence of blocking in the patient group, these findings tentatively indicate that people who are diagnosed with schizophrenia may attribute heightened salience to irrelevant stimuli and drug-related cues alike.

In Chapter 5 I aimed to probe the role of dopamine in the attribution of salience towards drug-associated stimuli in smokers. Results showed that the dopamine D_2/D_3 agonist pramipexole was able to reduce bias in initial orientation towards smoking images compared to images of money. Furthermore, pramipexole reduced urges to smoke and drug-related word retrieval but did not alter overshadowing of non-drug rewards.

In summary, the research in this thesis shows that stimuli associated with drug use can impair substance users' ability to form new relationships with salient outcomes in associative learning and provides some preliminary evidence for an association between salience attribution processes in addiction and psychosis. Furthermore, the research conducted highlights a role of dopamine in smoking-related urges and the relative salience of drug-related compared to non-drug reward.

6.2 All that glitters is not gold (or ketamine): associative learning processes in addiction

The attribution of salience towards drug-related stimuli is thought to be underpinned by their ability to elicit dopamine release, increasing drug craving and causing drug use to occur (Franken, 2003; Robinson & Berridge, 1993). The work carried out in this thesis provides a novel contribution towards understanding of how processing of drug-related cues can be influenced by dopamine and may also influence learning processes beyond drug-seeking itself.

The results I found in Chapter 5 expand on current understanding of the role of dopamine in salience attribution with relevance to addiction. They showed for the first time that manipulating central dopaminergic function can produce a relative dampening of bias towards smoking-related images in parallel to a reduction in strength of urges to smoke and smoking-related word retrieval. These findings - and those in chapter 2 showing an elevation of smoking-related attentional bias and tobacco craving during tobacco abstinence – concur in showing that acute pharmacological changes are able to modulate craving and attentional bias in parallel. These findings add to previous research showing that these variables correlate with each other (Field et al., 2009b) and support the idea that the effects of prior associative learning with regard to drug-associated stimuli can be modulated by transient changes in physiological drive or changes in dopaminergic function (Robinson & Berridge, 1993). These findings support the hypothesis that salience attribution is an incentive-motivational process that coincides with craving and urges to use the drug (Franken, 2003).

Attentional biases towards drug cues may not always act to influence drug-seeking. To the author's knowledge, the results from this study provide the first evidence that exposure to drug-related cues can impair an individual's ability to learn about non-drug rewarding outcomes. In addition to its role in motivation and action, selective attention is also thought

to play a crucial role in learning. Clearly, some degree of attention (overt or covert) will need to be paid towards drug-related stimuli in order for their identity to be recognised in future situations predictive of drug use. However, some associative learning theories have afforded a key role for selective attention beyond the detection of a stimulus. As such, the amount of learning that occurs between a given stimulus and an associated outcome will be directly related to the amount of attention that paid to that cue relative to other stimuli that also happen to be present at the time (Mackintosh, 1975; Pearce & Hall, 1980).

If selective attention plays an important role in learning, biases in attention should have very marked effects on these processes. The results obtained in this thesis support this hypothesis by showing that stimuli that had been previously associated with drug use were able to overshadow neutral stimuli in terms of accurate reward prediction (chapter 3), importance for earning money (chapter 4), and composite scores reflecting correctly assigned importance (chapters 2 and 3). Moreover, drug-related stimuli were not blocked by neutral stimuli in ketamine users in terms of prediction alone (ketamine users in chapter 3) and composite accuracy and importance scores (ketamine users in chapter 3; both groups of smokers in chapter 4). Importantly all of these cases show that learning was enhanced with respect to the drug cue rather than the neutral cue; in no case was a reduction in learning seen towards drug-related stimuli relative to neutral stimuli.

If it is assumed that drug cues are allocated with more selective attention than neutral stimuli in general, then it follows that they might have produced a false impression of reward prediction or uncertainty which would act to increase their associability in new learning. This would be consistent with the idea that selective attention to conditioned stimuli has more than one role (Hogarth, Dickinson, & Duka, 2010). For example, the initial identification of a stimulus may be particularly responsible for action such as drug seeking, whilst biases in

maintained attention may instead reflect the extent to which a cue predicts a positive outcome, or how reliably it predicts an outcome.

The results obtained here support this proposition by showing that drug-related stimuli do appear to play a role in both incentive and learning processes. However, the precise relationship between drug-related cues and associative learning cannot be established based on the results obtained. A role of attention in learning, as predicted by some theories (Mackintosh, 1975; Pearce & Hall, 1980) is indirectly supported by the enhancement of attentional bias on the dot probe task alongside overshadowing in chapter 2. However, an alternative explanation is that these cues were not attended to differently and were associated with learning via alternative mechanisms. For example, the ability of drug cues to elicit phasic dopamine release in animals (Phillips et al., 2003) might suggest that they provide a 'teaching signal' even if they are irrelevant predictors of reward (Redish, 2004). In animals, the adaptation of phasic dopamine release and speeding of saccade latencies to reward predicting cues emerge in parallel (Takikawa, Kawagoe, & Hikosaka, 2004) and current data suggest that phasic dopamine is important for learning directly and for orientation towards motivationally salient stimuli (Bromberg-Martin et al., 2010).

Attentional bias towards drug cues was hypothesised to increase drug-related cognition, such as a drug-related memory bias, and in addition to deplete limited resources in selective attention (Franken, 2003). The work carried out here suggests that in combination, these factors might contribute to learning biases due to cue competition between drug and non-drug stimuli. It seems probable that drug-related cues might impact on other learning processes in a variety of domains. This is supported by recent research which found a second-order conditioning effect after pairing neutral cues with established drug cues in smokers. Following conditioning the neutral cues were able to elicit larger P2 and P3 amplitudes resembling those shown by drug-related stimuli (Littel & Franken, 2012) Taken together

with the research presented here, this would suggest that drug-related stimuli can not only become associated with new learning more readily than other stimuli, but also cause other stimuli to become 'secondary drug cues', creating an extended web of associative dominated by drug-related material and overshadowing other learning functions (Pothos & Cox, 2002)

The results obtained in this thesis provide support for the hypothesis that hyposensitivity to reward may be potentiated by exposure to drug-related stimuli (Volkow et al., 2010). Overshadowing and resistance to blocking may provide some further explanation as to why people who are drug dependent often find non-drug rewards less salient than the general population (Goldstein & Volkow, 2011). This suggests that attempts to reduce the salience of drug cues specifically might also enhance the salience of non-drug reward cues in specific contexts that have been previously associated with use. Because we did not investigate whether the use of highly rewarded stimuli might be able to prevent overshadowing of non-drug reward, it remains an open question whether enhancing responsivity to non-drug reward might dampen overshadowing effects. However, encouraging people to engage in non-drug reinforcing behaviours is effective for treating drug addiction in clinical settings (Curran & Drummond, 2005; Petry, 2000).

Cue exposure therapy relies on the process of extinction, or new learning that occurs between a drug-predictive cue and the lack of drug-related outcome (Bouton, 2004). The aim is that this new form of learning with regard to the drug-related cue will override the associative strength of the previous drug taking response. Evidence for the efficacy of cue-exposure in clinical settings is relatively weak (Conklin & Tiffany, 2002) and animal work suggests that drug-associated cues appear to be more resistant to extinction than cues predicting non-drug reward (Wanat, Willuhn, Clark, & Phillips, 2009). The findings obtained in this thesis offer an additional explanation for why drug-associated stimuli are less prone to extinction. If drug associated cues are highly associable with new outcomes, perhaps by virtue of their ability to

attract selective attention and/or elicit dopamine release, they will constantly be updated in new relationships through reconsolidation.

The balance between reconsolidation and extinction processes has attracted considerable interest in terms of treating drug addiction (Torregrossa & Taylor, 2012). This area of research is based on the idea that when a memory trace is reactivated it enters a temporary labile state, either resulting in strengthening/updating through reconsolidation, or instead undergoing extinction learning. For example exposure to a drug-related video 10 minutes before extinction training reduced cue-induced craving at follow up (4, 34 and 184 days later) in abstinent heroin users, but this effect was not found when the delay between reactivation and extinction was 6 hours, in agreement with the time sensitive nature of this effect (Xue et al., 2012). Since reconsolidation may be triggered by changes to the original memory trace, overshadowing and resistance to blocking with regards to new learning might serve to constantly tip the balance in favour of reconsolidation, resulting in updating and strengthening of the original memory, rather than extinction. Identifying individual differences in reconsolidation of drug memories might be useful in assigning pharmacological treatments aiming to interfere with this process (Das, Freeman & Kamboj, in press).

As previously stated, we cannot be sure about the precise cause of the effects of drug cues on associative learning in the work carried out in this thesis. However, if biases in attention are responsible, training substance users to attend away from drug-related stimuli should be effective in preventing their capacity to elicit overshadowing. Interestingly, attentional bias training appears to employ the opposite approach to that used in cue exposure therapy – rather than engaging with a drug cue in extinction, volunteers are required train their attention away from them. So far, studies using such training paradigms have generally been effective in reducing attentional bias towards those same stimuli which were used in training and some

have found that these effects can extent to new stimuli and tasks (Attwood, O'Sullivan, Leonards, Mackintosh, & Munafò, 2008; Field & Eastwood, 2005; Salehi Fadardi, 2009; Schoenmakers et al., 2010) which might indicate that they could reduce overshadowing of non-drug reward.

Although pramipexole did not affect performance on the DCRPET task, its effects on smoking-related urges and bias in initial orientation would suggest that it might make a useful adjunct for attentional bias training programs. In smokers these results have been mixed, with one study finding a post training reduction in bias towards the images used in training but towards not towards novel images or tasks, such as a modified Stroop task, urges to smoke or choice to smoke (Field, Duka, Tyler, & Schoenmakers, 2009) and another study finding no effect of training at all (McHugh, Murray, Hearon, Calkins, & Otto, 2010). The strongest results in tobacco smokers have come from a study showing that participants who were trained to attend away from these images also showed a reduction in cue-elicited tobacco craving (Attwood et al., 2008) although this result was found in males only. Some explanation for these weak findings might be found in the inclusion of light (mean < 10 per day) smokers (Field et al. 2009a) an absence of bias at baseline (McHugh et al., 2010), and the use of non-treatment seeking samples up until now. However, the results of pramipexole treatment on attentional bias and urges to smoke (chapter 5) might suggest that it could make a possible adjunctive treatment in order to bolster attentional bias training effects in tobacco smokers.

More generally, these findings add to previous evidence for the efficacy of dopamine agonists in reducing tobacco craving and smoking (Caskey et al., 1999, 2002; Jarvik et al., 2000). These drugs have not been tested in clinical trials for smoking cessation. However, people who used bromocriptine to aid conception were found to be half as likely to be smoking during pregnancy when compared to those who had used a different/no medication (Murphy

et al., 2002). Controlled clinical trials regarding the efficacy of drugs such as bromocriptine and pramipexole for smoking cessation present a beneficial step towards improving rates of cessation in countries where tobacco smoking is endemic but first-line pharmacotherapies may be too expensive, such as India (Sarkar & Reddy, 2012).

6.3 A common role for salience attribution in substance use and psychosis?

This thesis set out to make a preliminary step at addressing what was an enormous field of enquiry - the relationship between salience attribution in psychosis and salience attribution in substance use. This question was addressed by two studies (chapters 3 and 4). In chapter 3 I examined the effects of drug cues on associative learning in chronic ketamine users with elevated delusional beliefs and schizotypy compared to polydrug controls. The findings from this study offered the opportunity to provide a tentative model of substance use in psychotic disorders, which was tested in chapter 4 by comparing smokers with a diagnosis of schizophrenia to a group of otherwise healthy smokers.

Aberrant salience attribution is thought to contribute towards positive psychotic symptoms (Kapur, 2003) and can be indexed using tasks that assess the effects of previous contingencies on current experience and learning (Fletcher & Frith, 2008; Gray et al., 1991). The DCRPET was adapted in order to index aberrant salience attribution by incorporating associative blocking contingencies into the task design. The results obtained supported my hypothesis that blocking should be reduced in ketamine users compared to polydrug controls and in smokers with a diagnosis of schizophrenia compared to control smokers (although this was at trend level). Furthermore, blocking was evident in all groups tested in chapter 2. Taken together these results support an association between a reduction in associative blocking and the presence of psychotic symptoms. This was further suggested by a significant negative correlation between levels of blocking and positive schizotypy in a control group of smokers (chapter 4).

These findings thus add support to chronic exposure to ketamine as a human model of aberrant salience attribution. Previous results have indicated that ketamine users show (i) enhanced superstitious conditioning to cues that were paired with different values of reward

at random (Freeman et al., 2009), (ii) elevated delusional beliefs (Morgan et al., 2009; Uhlhaas, Millard, Muetzelfeldt, Curran, & Morgan, 2007) and (iii) basic symptoms on the schizophrenia proneness instrument that resembled people who subsequently developed psychosis illness (Morgan et al., 2012). An absence of blocking in this population models an observation that has been widely observed in people with a diagnosis of schizophrenia (Bender et al., 2001; Jones et al., 1992, 1997; Moran et al., 2003; 2008; Oades et al., 1996) and my findings in patients (chapter 4) further support this observation.

Although lower levels of blocking were correlated with positive schizotypy in chapter 4, this effect was associated with the presence of negative symptoms in other samples (Haselgrove & Evans, 2009; Moran et al., 2008). Relatedly, although ketamine users in chapter 3 may appear to provide a good model of aberrant salience they clearly do not recreate a 'clean' model of positive psychotic symptoms alone. In addition to showing elevated scores on Peters' Delusion Inventory and the Cognitive/Perceptual subscale of the Schizotypal Personality Questionnaire (SPQ) ketamine users reported in chapter 3 also scored higher on Interpersonal and Disorganised indices of the SPQ, and more than half them met cut-off criteria for depression (8 minimal, 2 mild, 7 moderate, 1 severe) whilst the majority of those in the control group did not (12 minimal, 3 mild, 1 severe). Added to this, blocking did not correlate with any of these symptoms in ketamine users, which leaves the source of variance relating to this effect as an open question. Clinically the differentiation of antipsychotic-induced dysphoria, depression and negative symptoms remains challenging in people with a diagnosis of schizophrenia (Barnes & McPhillips, 1995) and an advantage of a ketamine model of aberrant salience attribution is the absence of antipsychotic medication use in this population.

The neurobiology underpinning the emergence of schizophrenia may enhance individuals' use of addictive substances by recreating a neurobiological abnormality that would normally occur after repeated drug exposure (Chambers et al., 2001). Alternatively, repeated drug use may sensitise dopaminergic systems and give rise to both schizophrenia and drug abuse (Tsapakis et al., 2003). In both of these cases, salience attribution towards substance-related cues might be heightened in people with schizophrenia. However, evidence supporting this idea has been lacking up until now.

When investigating the performance of ketamine users compared to controls in chapter 3 I found that the use of drug cues as blocking or blocked cues interacted with group membership. Specifically, ketamine users showed a reduction in blocking to drug cues, suggesting that these salient images influenced reward-based learning, even though they were redundant at this stage in the task. This effect was absent in polydrug controls, who showed some evidence of salience attribution to drug cues (overshadowing) but no deficits in blocking or drug cue effects on blocking. This suggests that a tendency to attribute salience towards irrelevant cues and drug cues may coincide with each other in schizophrenia as hypothesised (Chambers et al., 2001; Tsapakis et al., 2003). On the other hand, an alternative explanation for these findings might be that the ketamine users were simply attending to drug cues more than polydrug controls because of their dependence on ketamine. The results of chapter 2 appear to argue against this possibility because drug cues did not affect blocking in any of the groups, and the abstaining smokers who exhibited significant attentional bias towards drug-related stimuli showed changes in overshadowing but not blocking. However, this issue could be addressed in future research by using an alternative design, recruiting two groups with similar levels of ketamine dependence but differing in psychotic-like symptoms, in order to examine whether a lack of blocking is associated with more pronounced effects of

drug-related stimuli in associative learning, or if these effects might instead be related to levels of dependence alone.

The possibility that drug cue effects on the DCRPET are related to levels of dependence but not psychotic symptoms is supported by observations in chapter 4 showing drug cues were resistant to blocking according to composite accuracy/importance scores, and overshadowing based on importance scores in both groups tested. The similarity of these effects between the groups, in parallel to their equivalent smoking history, would suggest that the effect of drug cues on the DCRPET are not related to the presence of psychotic illness. Indeed, the only differences that emerged on the DCRPET task between these groups was in the analysis concerning non-drug cues, evidenced by a reduction in blocking in the smokers with a diagnosis of schizophrenia when compared to the control group. As such, drug cue effects on the DCRPET here would suggest that salience attribution processes related to addiction do not share any relationship with those related to psychosis.

In contrast, findings of elevated attentional bias on the Stroop task in smokers diagnosed with schizophrenia provide some preliminary evidence for a link between salience attribution in addiction and psychotic illness. Moreover, evidence for a lack of blocking in this group demonstrates that aberrant salience attribution as previously reported in schizophrenia and drug addiction are both heightened in this group when compared to a control sample with similar smoking behaviour. The positive correlation between the magnitude of this Stroop interference to drug-related words and positive psychotic symptoms might indicate that people with more severe psychosis might have higher attentional bias and possibly seek drugs more readily as a result. However, the interaction between group and condition was at trend level and these findings should clearly be treated with caution until replicated.

It is worth acknowledging that whilst this thesis aimed to investigate salience attribution alone, cognitive impairment is a core feature of schizophrenia and may also be heterogeneous across samples (Joyce & Roiser, 2007). Moreover, ketamine users often show impairments in episodic, working and semantic memory (Curran & Morgan, 2006) and these may be pronounced in frequent users (Morgan et al., 2009). Although tasks such as blocking and latent inhibition index aberrant performance in terms of specific elevations of learning, deficits in associative learning generally may influence performance on these tasks (Jones et al., 1997) and specific differences between and within samples tested should therefore be considered when interpreting differences in performance. Furthermore, overall naming time on the Stroop task (chapter 4) was slower in the patient group compared to controls and elevated Stroop interference is a common feature of people diagnosed with schizophrenia (Westerhausen, Kompus, & Hugdahl, 2011). A recent study analysing Stroop interference did not reveal any interactions or main effects when comparing never, former and current smokers with and without a diagnosis of schizophrenia, however the group sizes were small and the study may have lacked power to detect significant effects (Wing, Bacher, Sacco, & George, 2011). Furthermore, interpretation of Stroop performance in substance users is not straightforward and it may be determined by multiple factors such as inhibitory control, selective attention and cognitive strategies. That said, the fact it is determined by multiple factors may explain why it appears to have superior predictive ability over other measures in clinical outcomes (Field & Christiansen, 2012)

Another qualification of higher attentional bias in smokers with a diagnosis of schizophrenia is that this effect might have been driven by lack of bias shown in the control group. The relatively low bias (trend level) in this control group is consistent with a lower bias towards smoking cues in heavy smokers compared to light smokers (Hogarth et al., 2003) and less dependent smokers compared to high dependent smokers in the general population (Mogg et

al. 2005). These findings were interpreted by the authors of both studies as evidence that incentive salience drives smoking in lighter or less dependent smokers, whilst heavier or more dependent smokers are driven by habit (Di Chiara, 2000). Salivary cotinine correlated positively with attentional bias in controls here which would appear to argue against this interpretation, and longitudinal investigation within the same individuals might be necessary to convincingly demonstrate a shift from incentive to habit driven behaviour. However, these findings do raise the possibility that smokers with a diagnosis of schizophrenia are less prone to develop 'habit based' smoking.

This possibility is supported by a study showing that 'healthy' individuals were more likely to smoke without awareness or intention than those with a diagnosis of schizophrenia (Galazyn, Steinberg, Gandhi, Piper, & Williams, 2010). Interestingly the group with schizophrenia had higher nicotine dependence scores than controls in that study, which would argue against the idea that automatically driven behaviour is necessarily core feature of drug dependence (Tiffany, 1990). It might be the case that people with schizophrenia learn and respond to smoking-related cues using more controlled strategies than people from the general population. This would be in agreement with the idea that a loss of blocking or latent inhibition reflects inappropriate use of controlled processing when certain stimuli should be processed as irrelevant, and preventing them from influencing behaviour or action (Gray, Buhusi, & Schmajuk, 1997). In this way, people with schizophrenia might be expected to show a greater level of conscious and controlled processing of both irrelevant and drug-related stimuli in general. This is partially supported by a trend level correlation between Stroop interference and subjective experiences of attentional bias (at trend level) whereas this was not found in controls.

In a larger sample (n=40) of people from the general population aged 21.13 ±3.86 and smoking 13.05±7.40 cigarettes per day I found that subjective experiences of attentional bias

did not correlate with Stroop interference (r=0.190, p=0.240) but was strongly correlated with explicit pleasantness ratings to smoking-related images (r=0.634, p<0.001) (Freeman, unpublished observations). This adds to previous evidence that subjective experiences of attentional bias do not correlate show a strong correlation with attentional bias in the general population (Waters, A., personal communication). It is possible that people with a diagnosis of schizophrenia might show a closer relationship between their awareness of attending to drug-related stimuli and actual levels of attentional bias due to inappropriate use of controlled processing strategies although further research would be needed to clarify this.

The suggestion that salience attribution towards drug-related stimuli should be heightened in schizophrenia has been explained in different ways. Specifically, Chambers et al. (2001) argued that a neurodevelopmental abnormality which manifests itself as 'schizophrenia' will also lead to the vulnerability to use drugs of abuse, even if that individual has not consumed any drugs in their lifetime. In contrast Tsapakis et al. (2003) suggested that a sensitisation process following exposure to certain drugs of abuse might cause schizophrenia or precipitate its emergence in vulnerable individuals. The results gathered in this thesis did not provide data that can adequately distinguish between these two hypotheses. In terms of cannabis, in which there are have been a number of well-controlled longitudinal populations based studies it has been difficult to definitively establish a causal relationship between cannabis use and schizophrenia (Moore et al., 2007).

One advantage of the Chambers hypothesis is that can account for enhanced use of all substances in people with psychotic illness, and can explain cases of schizophrenia and substance abuse with minimal prior drug use. However, putting aside the question of causality, there does appear to be marked differences in the psychotomimetic symptoms associated with chronic exposure to various drugs of abuse. Morgan et al. (2012) found that daily users of ketamine (and to a lesser extent, cannabis users) showed elevated

schizophrenia-proneness as measured by clinical assessment. Recently a newer drug, mephedrone has been linked to psychotic symptoms and schizotypy (Bajaj, Mullen, & Wylie, 2010; Freeman et al., 2012). However other drugs (e.g. tobacco) appear less related to psychotic symptoms. Many (e.g. as many as 90%) people with a diagnosis of schizophrenia report having started smoking before the onset of illness (Kelly & McCreadie, 1999). However, tobacco smoking does not appear to be related to age of onset of psychosis (Myles et al., 2012) and nor does alcohol, in contrast to cannabis and unspecified substance use which are both associated with earlier onset of illness (Large et al., 2011). This provides some support for the idea that certain drugs may contribute to development of psychotic symptoms more than others, as suggested by Tsapakis et al. (2003).

Clinically, it is noted that whilst typical antipsychotics tend to increase substance abuse in schizophrenia, atypical antipsychotics have been associated with a reduction in drug use amongst patients (Green, Drake, Brunette, & Noordsy, 2007). Smokers in chapter 4 were all taking the atypical antipsychotic clozapine, which has been linked to a reduction in cigarette smoking in a number of studies (see chapter 4). Interestingly a trend level correlation did emerge between clozapine dose and attentional bias, although this effect might have been an artefact of the stronger relationship between attentional bias and the severity of positive psychotic symptoms. The role of clozapine on salience attribution in addiction and psychosis presents an important area of future research given that it may be most effective drug in clinical use for treating comorbid schizophrenia and substance use. Clozapine has a wide range of binding targets including dopaminergic, cholinergic, and serotonergic receptors (Naheed & Green, 2001). Furthermore, olanzapine is another atypical antipsychotic and was shown to reduce smoking-cue induced craving in smokers from the general population after 5 days of treatment when compared to placebo (Hutchison et al., 2004).

It may seem paradoxical that atypical drugs, with a lower affinity for blocking dopamine D_2 receptors may be advantageous for treating substance use. If dopamine release increases attentional bias towards drug-associated cues and motivates drug use, the most potent dopamine antagonist drugs might be expected to effective in reducing substance use. Haloperidol can reduce attentional bias in heroin users (Franken et al., 2004) and brain activation associated with attentional bias in smokers (Luijten et al., 2012). However, haloperidol has been reported to increase levels of smoking and subjective cigarette craving in experimental studies (Caskey et al., 1999, 2002; Dawe et al., 1995) and can increase *ad libitum* smoking in people diagnosed with schizophrenia compared to when they were not medicated, as indexed by increased expired carbon monoxide levels (McEvoy et al., 1995).

On explanation for these findings is that typical antipsychotics such as haloperidol reduce cue-elicited dopamine release and craving, but at the same time are able to increase drug use due to independent effects on baseline tonic craving (Childress & O'Brien, 2000; Franken, Booij, & van den Brink, 2005; Hitsman et al., 2008; Pilla et al., 1999). In this way, phasic cue induced craving might influence addictive behaviour via incentive salience, whilst the effects of dopamine receptor occupancy by antipsychotic medication might lead to self-medication for the dysphoric symptoms they are associated with (Green, Zimmet, Straus, & Schildkraut, 1999). According to this theory, drug use is an attempt to regain 'normal levels of reward' experienced by healthy individuals (Green et al., 1999). If this is the case, effective treatments for dual diagnosis would ideally show (i) efficacy in treating psychosis (ii) a reduction/no increase in cue-induced craving and (iii) the lowest blockade of dopamine D_2 receptors possible in order to achieve an antipsychotic effect.

Future research should examine whether 'neuroleptic induced dysphoria' alters the salience of drugs relative to other rewards, which might be expected given that treatment with a dopamine D_2/D_3 agonist can selectively shift the balance between initial orientation towards

stimuli related to drug and non-drug reward (chapter 5). The effects of dopamine antagonists on motivation were central to the development of the incentive salience theory of addiction. However, research in animals has shown that blockade of dopamine D_2 receptors can inhibit behaviour in situations that engender high levels of effort (Denk et al., 2005). This could indicate that elevated rates of smoking or other drug use after treatment with dopamine D_2 receptor antagonists might be attributable to a relative reduction in the salience of non-drug rewards, due to the high effort or costs necessary to obtain them. In contrast, drug use may be a low cost, low payoff alternative to other forms of reward that carry high levels uncertainty and effort in other aspects of life. In this way, typical antipsychotics might not lead to enhanced drug use as an attempt to alleviate symptoms of dysphoria (i.e. self-medication) and instead could produce a relative increase in the salience of drug-related stimuli relative to other rewards.

6.4 Salient regrets

The research conducted in this thesis was inevitably subject to methodological limitations, many of which have been discussed in each relevant chapter. However, in reflecting on these studies as a whole, some extra considerations merit comment.

The Drug Cue Reward Prediction Error task formed a large part of the focus of this thesis and was not without its problems. The task was adapted during the course of the thesis in response to the findings obtained and an attempt to address the questions of future studies. However in retrospect, interpretation of the task might have been clearer across the studies collectively if it had been left unchanged. For example, the addition of extra training trials in chapter 3 may have been useful for ensuring that both ketamine users and controls reached sufficient accuracy before the test stage. However, this may have resulted in a tendency towards ceiling at the test stage, and prevented direct comparison with the results from chapter 2 in smokers.

Moreover, based on findings that drug cues were resistant to blocking, but not able to increase levels of blocking themselves (chapter 3) the task was simplified to incorporate 'blocking of a drug cue' and 'overshadowing' into a simpler design for chapters 4 and 5. Whilst this shorter version of the task did appear to be effective in replicating previous findings of blocking in schizophrenia it also found less evidence of overshadowing than blocking (in contrast to chapters 2 and 3) raising doubt as to whether overshadowing is a different process from blocking as proposed in the animal literature (Cassaday & Moran, 2010) or whether they overlap and are expressed in accordance with the precise nature of the task design across stages, outcomes, and cue manipulation.

In future, tasks such as the DCRPET may benefit from using completely factorial designs that are balanced for the use of drug and non-drug cues across stages and outcomes. These would

have the benefit of ruling out stimulus novelty effects, which was not possible in the studies carried out in this thesis. In these circumstances it may be necessary to use between subject saliency designs as used previously in the schizophrenia literature (Jones et al, 1992). However this introduces additional between subjects variance and may not be less able to address the relationship between variance in performance and specific symptoms.

Finally, using accuracy to positively or negatively score importance ratings may be problematic in terms of interpreting test score data as it appears to confound two different measures. Whilst the interpretation of these scores is not as straightforward as accuracy scores alone, the findings obtained across the studies carried out appear to show that these scores were best able to capture processes that they were designed to test in 'healthy' individuals tested (i.e. the presence of blocking according to behavioural methods). In that way, use of these is satisfactory in terms of construct validity.

6.5 If it's not about blocking, don't come knocking

The research conducted as part of this thesis has raised several questions for future research. Given that the work arising from this thesis tentatively suggests that a common salience attribution system might play a role in substance use and schizophrenia, an initial priority would be to replicate findings of increased attentional bias in patients with schizophrenia, using different patient groups (e.g. un-medicated first episode patients; people taking medication other than clozapine, ultra high risk), different drugs of abuse (e.g. cannabis, alcohol) and using different paradigms, such as the visual probe task. If, as has been shown in a range of different substance using populations, the degree of attentional bias can predict their chances in achieving successful cessation, it would be worth pursuing this line of research further in clinical settings.

The effects of drug cues on associative learning in this thesis were examined but only provide a brief indication of the way in which learning biases might operate in normal circumstances. It will be important to investigate whether these effects are associated with other clinically relevant processes either in laboratory assessment or in terms of drug use or and other behaviours in naturalistic settings. The balance between reconsolidation and extinction processes following memory reactivation offers one potential line area of enquiry.

Future research might wish to address the impact of drugs that are known to have effects on salience attribution processes relevant to substance and psychosis. Furthermore, given that pramipexole can reduce attentional bias towards smoking cues relative to monetary cues alongside urges to smoke (Chapter 5) and it can be effective for positive and negative symptoms in schizophrenia as an adjunctive treatment (Kasper et al., 1997; Kelleher et al., 2011) pramipexole could make another potential for the treatment of co-morbid substance use and schizophrenia. Pramipexole is noted for its ability to improve motivation and alleviate

depression in Parkinson's disease (Leentjens et al., 2009) however the extent to which similar effects might occur in schizophrenia is not clear. Furthermore, the potential for impulse control disorders to emerge would be an important clinical concern (Weintraub et al., 2006)

Evidence suggests that cannabidiol along with the presence of Δ^9-THC as indexed in hair is associated with lower positive schizotypal symptoms in cannabis users compared with Δ^9-THC without cannabidiol (Morgan & Curran, 2008). Further cannabidiol may acutely protect against acute psychotic-like symptoms following intravenous Δ^9-THC administration in healthy volunteers (Englund et al., 2012). Recently a month's treatment with cannabidiol was shown to have similar efficacy in treating positive and negative symptoms in schizophrenia when compared to amisulpride but with fewer reported side effects (Leweke et al., 2012).

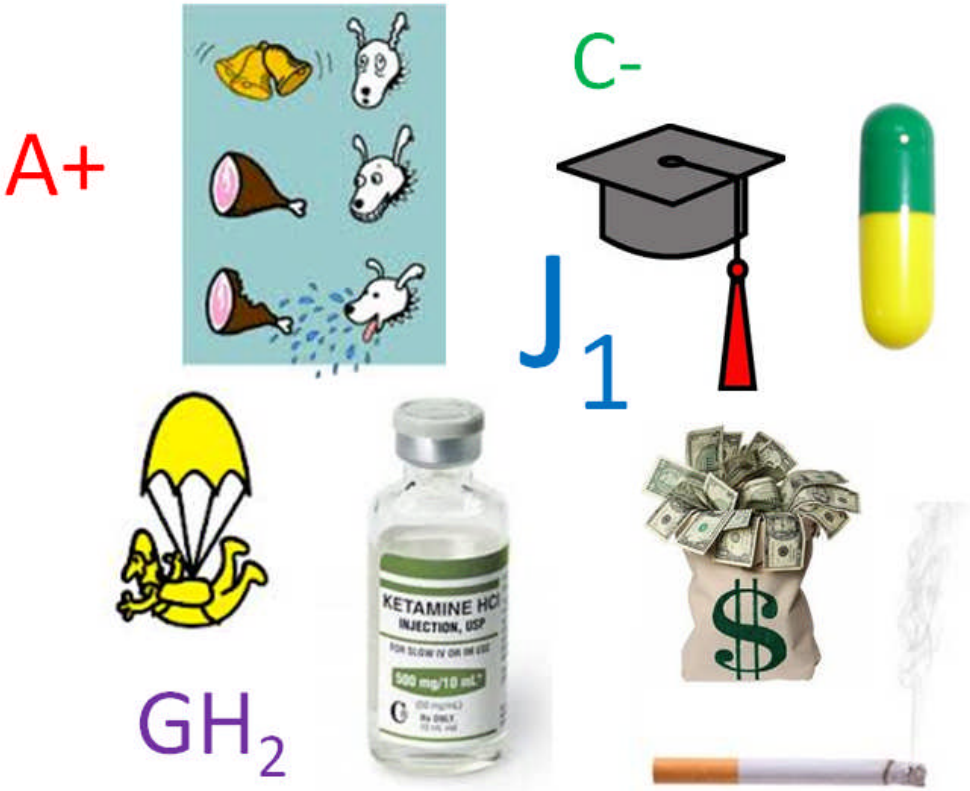
In terms of salience attribution, cannabidiol attenuates BOLD signal in the right prefrontal cortex during and oddball detection task, whereas Δ^9-THC produced opposite effects (Bhattacharyya et al., 2012). Moreover, cannabidiol can reverse an attentional bias for cannabis and food images induced acutely by Δ^9-THC in cannabis users (Morgan et al., 2010). These findings might suggest that cannabidiol could be an effective treatment for comorbid substance abuse and psychosis. This would be one way in which to investigate whether drugs that do not act via blockade of D_2 receptors are better suited to this indication.

Finally future research should aim to examine processes such as latent inhibition and blocking in patients with schizophrenia using functional neuroimaging. There has been a renewed interest in applying fMRI to blocking paradigms in healthy humans (Corlett & Fletcher, 2012; Eippert, Gamer, & Büchel, 2012; Moran, Rouse, Cross, Corcoran, & Schürmann, 2012; Tobler, O'Doherty, Dolan, & Schultz, 2006). However in general, interest in applying these methods has lagged behind investigation of aberrant salience attribution in schizophrenia using newer tasks (e.g. Walter et al., 2009). The wealth of research into these

processes in basic and clinical investigation of animals and humans should be utilised in order to inform future work.

Postscript: overshadowing by doctoral research

The past three years have been characterised by many of the themes that defined the work described in this thesis. Doctoral research requires strong motivation, plenty of learning and a certain degree of acceptance that other aspects of one's life may be overshadowed. I am lucky that I find this subject area fascinating and am happy to have devoted this time to investigating it. Two of my closest friends have also been undertaking doctoral research in other disciplines at University College London and their attitudes towards the experience have been less positive than mine. At the same time I've also had some hard times myself and as I write this now, I'm looking forward to what some associative learning theorists call 'release from overshadowing'



References

Aarts, E., van Holstein, M., & Cools, R. (2011). Striatal dopamine and the interface between motivation and cognition. *Frontiers in Psychology, 2*. doi: 10.3389/fpsyg.2011.00163.

AhnAllen, C. G., & Tidey, J. W. (2011). Personalized smoking environment cue reactivity in smokers with schizophrenia and controls: a pilot study. *Psychiatry Res, 188*(2), 286-288.

Al-Adawi, S., & Powell, J. (1997). The influence of smoking on reward responsiveness and cognitive functions: A natural experiment. *Addiction, 92*(12), 1773-1782.

Andreasen, N. C. (1984a). Scale for the assessment of negative symptoms. *Iowa City: University of Iowa*.

Andreasen, N. C. (1984b). *Scale for the Assessment of Positive Symptons:(SAPS)*: University of Iowa.

Anselme, P. (2009). The effect of exposure to drugs on the processing of natural rewards. *Neurosci Biobehav Rev, 33*(3), 314-335. doi: 10.1016/j.neubiorev.2008.10.002.

Attwood, A. S., O'Sullivan, H., Leonards, U., Mackintosh, B., & Munafò, M. R. (2008). Attentional bias training and cue reactivity in cigarette smokers. *Addiction, 103*(11), 1875-1882.

Awad, A. G. (2012). Is it time to consider comorbid substance abuse as a new indication for antipsychotic drug development? *Journal of Psychopharmacology, 26*(7), 953-957.

Baddeley, A., Emslie, H., & Nimmo-Smith, I. (1992). The spot-the-word test. *Bury St Edmunds, Thames Valley Test Company*.

Bajaj, N., Mullen, D., & Wylie, S. (2010). Dependence and psychosis with 4-methylmethcathinone (mephedrone) use. *BMJ Case Reports, 2010*.

Barkus, E., Morrison, P. D., Vuletic, D., Dickson, J. C., Ell, P. J., Pilowsky, L. S., et al. (2011). Does intravenous Δ9-tetrahydrocannabinol increase dopamine release? A SPET study. *Journal of Psychopharmacology, 25*(11), 1462-1468.

Barnes, T., & McPhillips, M. (1995). How to distinguish between the neuroleptic-induced deficit syndrome, depression and disease-related negative symptoms in schizophrenia. *International clinical psychopharmacology*.

Baruch, I., Hemsley, D. R., & Gray, J. A. (1988). Differential performance of acute and chronic schizophrenics in a latent inhibition task. *Journal of Nervous and Mental Disease*.

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). Manual for the Beck depression inventory-II. *San Antonio, TX: Psychological Corporation, 1*, 82.

Beesley, T., & Le Pelley, M. (2011). The influence of blocking on overt attention and associability in human learning. *Journal of Experimental Psychology: Animal Behavior Processes, 37*(1), 114.

Bender, S., Müller, B., Oades, R. D., & Sartory, G. (2001). Conditioned blocking and schizophrenia: A replication and study of the role of symptoms, age, onset-age of psychosis and illness-duration. *Schizophrenia research, 49*(1), 157-170.

Berridge, K. C. (2007). The debate over dopamine's role in reward: the case for incentive salience. *Psychopharmacology, 191*(3), 391-431.

Berridge, K. C. (2012). From prediction error to incentive salience: mesolimbic computation of reward motivation. *European Journal of Neuroscience*, *35*(7), 1124-1143.

Berridge, K. C., & Robinson, T. E. (1998). What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Research Reviews*, *28*(3), 309-369.

Bhattacharyya, S., Crippa, J. A., Allen, P., Martin-Santos, R., Borgwardt, S., Fusar-Poli, P., et al. Seal, M. L. (2012). Induction of psychosis by {delta} 9-tetrahydrocannabinol reflects modulation of prefrontal and striatal function during attentional salience processing. *Archives of general psychiatry*, *69*(1), 27.

Bloomfield, M., Morgan, C., Egerton, A., Kapur, S., Curran, H., & Howes, O. (2012). Dopaminergic function in cannabis users: an 18[F]-DOPA positron emission tomography study of dopamine synthesis capacity. *European Neuropsychopharmacology*, *22*, S404.

Bossong, M. G., van Berckel, B. N. M., Boellaard, R., Zuurman, L., Schuit, R. C., Windhorst, A. D., et al. (2008). Δ9-Tetrahydrocannabinol induces dopamine release in the human striatum. *Neuropsychopharmacology*, *34*(3), 759-766.

Bouton, M. E. (2004). Context and behavioral processes in extinction. *Learning & Memory*, *11*(5), 485-494.

Bradley, B., Field, M., Mogg, K., & De Houwer, J. (2004). Attentional and evaluative biases for smoking cues in nicotine dependence: component processes of biases in visual orienting. *Behavioural pharmacology*, *15*(1), 29-36.

Bradley, B. P., Garner, M., Hudson, L., & Mogg, K. (2007). Influence of negative affect on selective attention to smoking-related cues and urge to smoke in cigarette smokers. *Behavioural pharmacology, 18*(4), 255-263.

Bradley, B. P., Mogg, K., Wright, T., & Field, M. (2003). Attentional bias in drug dependence: vigilance for cigarette-related cues in smokers. *Psychology of Addictive Behaviors, 17*(1), 66.

Broadbent, D. E. (1958). Perception and communication.

Bromberg-Martin, E. S., Matsumoto, M., & Hikosaka, O. (2010). Dopamine in motivational control: rewarding, aversive, and alerting. *Neuron, 68*(5), 815.

Carpenter, K. M., Martinez, D., Vadhan, N. P., Barnes-Holmes, D., & Nunes, E. V. (2012). Measures of Attentional Bias and Relational Responding Are Associated with Behavioral Treatment Outcome for Cocaine Dependence. *The American journal of drug and alcohol abuse, 38*(2), 146-154.

Carpenter, K. M., Schreiber, E., Church, S., & McDowell, D. (2006). Drug Stroop performance: relationships with primary substance of use and treatment outcome in a drug-dependent outpatient sample. *Addictive behaviors, 31*(1), 174-181.

Caskey, N. H., Jarvik, M. E., & Wirshing, W. C. (1999). The effects of dopaminergic D_2 stimulation and blockade on smoking behavior. *Experimental and Clinical Psychopharmacology; Experimental and Clinical Psychopharmacology, 7*(1), 72.

Caskey, N. H., Jarvik, M. E., Wirshing, W. C., Madsen, D. C., Iwamoto-Schaap, P. N., Eisenberger, N. I., .et al. (2002). Modulating tobacco smoking rates by dopaminergic stimulation and blockade. *Nicotine & tobacco research, 4*(3), 259-266.

Caskey, N. H., Jarvik, M. E., Wirshing, W. C., Madsen, D. C., Iwamoto-Schaap, P. N., Eisenberger, N. I., et al. (2002). Modulating tobacco smoking rates by dopaminergic stimulation and blockade.*Nicotine Tob Res, 4*(3), 259-266. doi: 10.1080/14622200210153830

Cassaday, H. J., & Moran, P. M. (2010). Latent inhibition and other salience modulation effects: same neural substrates. *Latent Inhibition: Cognition, Neuroscience and Applications to Schizophrenia, 1st edn. Cambridge University Press: Cambridge*, 342-371.

Chambers, R. A., Krystal, J. H., & Self, D. W. (2001). A neurobiological basis for substance abuse comorbidity in schizophrenia. *Biol Psychiatry, 50*(2), 71-83.

Chapman, J. (1966). The early symptoms of schizophrenia. *The British journal of psychiatry, 112*(484), 225-251.

Chatterton, R., Sanderson, L., Van Leent, S., & Plant, K. (1998). Does clozapine affect smoking rates? *The Australian and New Zealand journal of psychiatry, 32*(6), 890.

Childress, A. R. A. R., & O'Brien, C. P. C. P. (2000). Dopamine receptor partial agonists could address the duality of cocaine craving. *Trends in pharmacological sciences, 21*(1), 6-9.

Conklin, C. A., Robin, N., Perkins, K. A., Salkeld, R. P., & McClernon, F. J. (2008). Proximal versus distal cues to smoke: the effects of environments on smokers' cue-reactivity. *Experimental and Clinical Psychopharmacology, 16*(3), 207.

Conklin, C. A., & Tiffany, S. T. (2002). Applying extinction research and theory to cue-exposure addiction treatments. *Addiction, 97*(2), 155-167.

Cools, R., & D'Esposito, M. (2011). Inverted-U–Shaped Dopamine Actions on Human Working Memory and Cognitive Control. *Biol Psychiatry, 69(12),* e113-e125. doi: 10.1016/j.biopsych.2011.03.028

Copersino, M. L., Serper, M. R., Vadhan, N., Goldberg, B. R., Richarme, D., Chou, J. C. Y. et al. (2004). Cocaine craving and attentional bias in cocaine-dependent schizophrenic patients. *Psychiatry Res. 128(3), 209-218.*

Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews Neuroscience 3(3), 201-215.*

Corlett, P., & Fletcher, P. (2012). The Neurobiology Of Schizotypy: Fronto-Striatal Prediction Error Signal Correlates With Delusion-Like Beliefs In Healthy People. *Neuropsychologia. doi: 10.1016/j.neuropsychologia.2012.09.045.*

Corlett, P., Murray, G., Honey, G., Aitken, M., Shanks, D., Robbins, T., et al. (2007). Disrupted prediction-error signal in psychosis: evidence for an associative account of delusions. *Brain, 130*(9), 2387-2400.

Corlett, P. R., Honey, G. D., Aitken, M. R. F., Dickinson, A., Shanks, D. R., Absalom, A. R., et al. (2006). Frontal responses during learning predict vulnerability to the psychotogenic effects of ketamine: linking cognition, brain activity, and psychosis. *Archives of general psychiatry, 63*(6), 611.

Corlett, P. R., Honey, G. D., Krystal, J. H., & Fletcher, P. C. (2010). Glutamatergic model psychoses: prediction error, learning, and inference. *Neuropsychopharmacology, 36*(1), 294-315.

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*(3), 237-243.

Crider, A., Solomon, P. R., & McMahon, M. A. (1982). Disruption of selective attention in the rat following chronic *d*-amphetamine administration: Relationship to schizophrenic attention disorder. *Biol Psychiatry. 17(3)* 351-361.

Crookes, A., & Moran, P. (2003). An investigation into age and gender differences in human Kamin blocking, using a computerized task. *Developmental neuropsychology, 24*(1), 461-477.

Curran, H. V., & Morgan, C. (2002). Cognitive, dissociative and psychotogenic effects of ketamine in recreational users on the night of drug use and 3 days later. *Addiction, 95*(4), 575-590.

Curran, V., & Drummond, C. (2005). Psychological treatments of substance misuse and dependence. *Foresight Brain Science, Addiction and Drugs Project (www. Foresight. gov. uk).*

Das, R. K., Freeman, T. P., & Kamboj, S. K. (in press). effects of N-Methyl D-Aspartate and B-Adrenergic Receptor Antagonists on the Reconsolidation of Reward Memory: A Meta-Analysis. *Neuroscience & Biobehavioral Reviews.*

Dawkins, L., Acaster, S., & Powell, J. H. (2007). The effects of smoking and abstinence on experience of happiness and sadness in response to positively valenced, negatively valenced, and neutral film clips. *Addictive behaviors, 32*(2), 425-431.

Dawkins, L., Powell, J. H., West, R., Powell, J., & Pickering, A. (2006). A double-blind placebo controlled experimental study of nicotine: I--effects on incentive motivation. *Psychopharmacology (Berl), 189*(3), 355-367. doi: 10.1007/s00213-006-0588-8.

de Leon, J., Diaz, F. J., Josiassen, R. C., Cooper, T. B., & Simpson, G. M. (2005). Does clozapine decrease smoking? *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 29*(5), 757-762.

Denk, F., Walton, M., Jennings, K., Sharp, T., Rushworth, M., & Bannerman, D. (2005). Differential involvement of serotonin and dopamine systems in cost-benefit decisions about delay or effort. *Psychopharmacology, 179*(3), 587-596.

Denton, S. E., & Kruschke, J. K. (2006). Attention and salience in associative blocking. *Learning & Behavior, 34*(3), 285-304.

Di Chiara, G. (2000). Role of dopamine in the behavioural actions of nicotine related to addiction. *Eur J Pharmacol, 393*(1-3), 295-314.

Dixon, L. (1999). Dual diagnosis of substance abuse in schizophrenia: prevalence and impact on outcomes. *Schizophrenia research, 35,* S93-S100.

Dixon, L., Haas, G., Weiden, P. J., Sweeney, J., & Frances, A. J. (1991). Drug abuse in schizophrenic patients: clinical correlates and reasons for use. *Am J Psychiatry, 148*(2), 224-230.

Ehrman, R. N., Robbins, S. J., Bromwell, M. A., Lankford, M. E., Monterosso, J. R., & O'Brien, C. P. (2002). Comparing attentional bias to smoking cues in current smokers, former smokers, and non-smokers using a dot-probe task. *Drug and Alcohol Dependence 67(2),* 185-191.

Eippert, F., Gamer, M., & Büchel, C. (2012). Neurobiological Mechanisms Underlying the Blocking Effect in Aversive Learning. *The Journal of Neuroscience, 32*(38), 13164-13176.

Englund, A., Morrison, P. D., Nottage, J., Hague, D., Kane, F., Bonaccorso, S., et al. (2012). Cannabidiol inhibits THC-elicited paranoid symptoms and hippocampal-dependent memory impairment. *Journal of Psychopharmacology*. doi: 10.1177/0269881112460109

Ersche, K. D., Bullmore, E. T., Craig, K. J., Shabbir, S. S., Abbott, S., Muller, U., et al. (2010). Influence of compulsivity of drug abuse on dopaminergic modulation of attentional bias in stimulant dependence. *Archives of general psychiatry, 67*(6), 632.

Feldman, J. M. (1975). Blocking as a function of added cue intensity. *Learning & Behavior, 3*(2), 98-102.

Ferguson, S. G., Shiffman, S., & Bruno, R. (2011). Commentary on Fidler et al.(2011): Identifying quitters who are at increased risk of relapse–where to from here? *Addiction, 106*(3), 639-640.

Fidler, J. A., Shahab, L., & West, R. (2011). Strength of urges to smoke as a measure of severity of cigarette dependence: comparison with the Fagerström Test for Nicotine Dependence and its components. *Addiction, 106*(3), 631-638.

Field, M., & Christiansen, P. (2012). Commentary on,'Internal reliability of measures of substance-related cognitive bias'. *Drug and Alcohol Dependence*.

Field, M., & Cox, W. M. (2008). Attentional bias in addictive behaviors: A review of its development, causes, and consequences. *Drug and Alcohol Dependence, 97*(1–2), 1-20. doi: 10.1016/j.drugalcdep.2008.03.030

Field, M., Duka, T., Tyler, E., & Schoenmakers, T. (2009a). Attentional bias modification in tobacco smokers. *Nicotine & tobacco research, 11*(7), 812-822.

Field, M., & Eastwood, B. (2005). Experimental manipulation of attentional bias increases the motivation to drink alcohol. *Psychopharmacology, 183*(3), 350-357.

Field, M., Mogg, K., & Bradley, B. P. (2004). Eye movements to smoking-related cues: effects of nicotine deprivation. *Psychopharmacology (Berl), 173*(1-2), 116-123. doi: 10.1007/s00213-003-1689-2

Field, M., Munafo, M. R., & Franken, I. H. (2009b). A meta-analytic investigation of the relationship between attentional bias and subjective craving in substance abuse. *Psychol Bull, 135*(4), 589-607. doi: 10.1037/a0015843

Field, M., Santarcangelo, M., Sumnall, H., Goudie, A., & Cole, J. (2006). Delay discounting and the behavioural economics of cigarette purchases in smokers: the effects of nicotine deprivation. *Psychopharmacology, 186*(2), 255-263.

Fletcher, P. C., & Frith, C. D. (2008). Perceiving is believing: a Bayesian approach to explaining the positive symptoms of schizophrenia. *Nature Reviews Neuroscience, 10*(1), 48-58.

Fonder, M. A., Sacco, K. A., Termine, A., Boland, B. S., Seyal, A. A., Dudas, M. M., . . . George, T. P. (2005). Smoking cue reactivity in schizophrenia: Effects of a nicotinic receptor antagonist. *Biol Psychiatry, 57*(7), 802-808.

Franken, I. H. A. (2003). Drug craving and addiction: integrating psychological and neuropsychopharmacological approaches. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 27*(4), 563-579. doi: 10.1016/s0278-5846(03)00081-2

Franken, I. H. A., Booij, J., & van den Brink, W. (2005). The role of dopamine in human addiction: from reward to motivated attention. *Eur J Pharmacol, 526*(1), 199-206.

Franken, I. H. A., Hendriks, V. M., Stam, C. J., & Van den Brink, W. (2004). A role for dopamine in the processing of drug cues in heroin dependent patients. *European Neuropsychopharmacology, 14*(6), 503-508.

Franken, I. H. A., Rosso, M., & van Honk, J. (2003). Selective memory for alcohol cues in alcoholics and its relation to craving. *Cognitive therapy and research, 27*(4), 481-488.

Freedman, B., & Chapman, L. J. (1973). Early subjective experiences in schizophrenic episodes. *Journal of abnormal psychology, 82*(1), 46.

Freeman, T. P., Morgan, C. J. A., Klaassen, E., Das, R. K., Stefanovic, A., Brandner, B., & Curran, H. V. (2009). Superstitious conditioning as a model of delusion formation following chronic but not acute ketamine in humans. *Psychopharmacology, 206*(4), 563-573.

Freeman, T. P., Morgan, C. J. A., Vaughn-Jones, J., Hussain, N., Karimi, K., & Curran, H. V. (2012). Cognitive and subjective effects of mephedrone and factors influencing use of a ‘new legal high’. *Addiction 107*(4), 792-800.

Galazyn, M., Steinberg, M. L., Gandhi, K. K., Piper, M., & Williams, J. M. (2010). Reasons for smoking among individuals with schizophrenia. *Schizophrenia research, 122*(1-3), 268.

Galdos, M., Simons, C., Fernandez-Rivas, A., Wichers, M., Peralta, C., Lataster, T., et al. (2011). Affectively salient meaning in random noise: A task sensitive to psychosis liability. *Schizophrenia bulletin, 37*(6), 1179-1186.

Garland, E. L., Franken, I. H. A., & Howard, M. O. (2012). Cue-elicited heart rate variability and attentional bias predict alcohol relapse following treatment. *Psychopharmacology*, 1-10.

George, T. P., Sernyak, M. J., Ziedonis, D. M., & Woods, S. W. (1995). Effects of clozapine on smoking in chronic schizophrenic outpatients. *Journal of Clinical Psychiatry*.

Goldstein, R., Woicik, P., Lukasik, T., Maloney, T., & Volkow, N. (2007). Drug fluency: a potential marker for cocaine use disorders. *Drug and Alcohol Dependence, 89*(1), 97-101.

Goldstein, R. Z., Alia-Klein, N., Tomasi, D., Carrillo, J. H., Maloney, T., Woicik, P. A., et al. (2009a). Anterior cingulate cortex hypoactivations to an emotionally salient task in cocaine addiction. *Proceedings of the National Academy of Sciences, 106*(23), 9453-9458.

Goldstein, R. Z., Tomasi, D., Alia-Klein, N., Carrillo, J. H., Maloney, T., Woicik, P. A., et al. (2009b). Dopaminergic response to drug words in cocaine addiction. *The Journal of Neuroscience, 29*(18), 6001-6006.

Goldstein, R. Z., & Volkow, N. D. (2002). Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. *The American journal of psychiatry, 159*(10), 1642.

Goldstein, R. Z., & Volkow, N. D. (2011). Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. *Nat Rev Neurosci, 12*(11), 652-669. doi: 10.1038/nrn3119

Goldstein, R. Z., Woicik, P. A., Maloney, T., Tomasi, D., Alia-Klein, N., Shan, J., et al. (2010). Oral methylphenidate normalizes cingulate activity in cocaine addiction during a salient cognitive task. *Proceedings of the National Academy of Sciences, 107*(38), 16667-16672.

Granon, S., Passetti, F., Thomas, K. L., Dalley, J. W., Everitt, B. J., & Robbins, T. W. (2000). Enhanced and impaired attentional performance after infusion of D1 dopaminergic receptor agents into rat prefrontal cortex. *The Journal of Neuroscience, 20*(3), 1208-1215.

Gray, J., Feldon, J., Rawlins, J., Hemsley, D., & Smith, A. (1991). The neuropsychology of schizophrenia. *Behavioral and Brain Sciences, 14*(01), 1-20.

Gray, J. A. (1998). Integrating schizophrenia. *Schizophrenia bulletin, 24*(2), 249-266.

Gray, J. A., Buhusi, C. V., & Schmajuk, N. (1997). The transition from automatic to controlled processing. *Neural Networks, 10*(7), 1257-1268.

Gray, N., Pickering, A., Gray, J., Jones, S. H., Abrahams, S., & Hemsley, D. (1997). Kamin blocking is not disrupted by amphetamine in human subjects. *Journal of Psychopharmacology, 11*(4), 301-311.

Gray, N., Pickering, A., Hemsley, D., Dawling, S., & Gray, J. (1992). Abolition of latent inhibition by a single 5 mg dose ofd-amphetamine in man. *Psychopharmacology, 107*(2), 425-430.

Gray, N., Pilowsky, L., Gray, J., & Kerwin, R. (1995). Latent inhibition in drug naive schizophrenics: relationship to duration of illness and dopamine D2 binding using SPET. *Schizophrenia research, 17*(1), 95-107.

Green, A., Drake, R., Brunette, M., & Noordsy, D. (2007). Schizophrenia and co-occurring substance use disorder. *American Journal of Psychiatry, 164*(3), 402-408.

Green, A. I., Zimmet, S. V., Straus, R. D., & Schildkraut, J. J. (1999). Clozapine for comorbid substance use disorder and schizophrenia: Do patients with schizophrenia have a reward-deficiency syndrome that can be ameliorated by clozapine? *Harvard review of psychiatry, 6*(6), 287-296.

Gross, T. M., Jarvik, M. E., & Rosenblatt, M. R. (1993). Nicotine abstinence produces content-specific Stroop interference. *Psychopharmacology, 110*(3), 333-336.

Hall, G., Mackintosh, N., Goodall, G., & Martello, M. D. (1977). Loss of control by a less valid or by a less salient stimulus compounded with a better predictor of reinforcement. *Learning and Motivation, 8*(2), 145-158.

Haselgrove, M., & Evans, L. H. (2010). Variations in selective and nonselective prediction error with the negative dimension of schizotypy. *The Quarterly Journal of Experimental Psychology, 63*(6), 1127-1149.

Heatherton, T. F., Kozlowski, L. T., Frecker, R. C., & Fagerstrom, K.-O. (1991). The Fagerström Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. *British Journal of Addiction, 86*(9), 1119-1127. doi: 10.1111/j.1360-0443.1991.tb01879.x

Heckler, A. F., Kaminski, J. A., & Sloutsky, V. M. (2006). *Differential cue salience, blocking, and learned inattention.* Paper presented at the Proceedings of the XXVIII Annual Conference of the Cognitive Science Society.

Heishman, S. J., Singleton, E. G., & Moolchan, E. T. (2003). Tobacco Craving Questionnaire: reliability and validity of a new multifactorial instrument. *Nicotine & tobacco research, 5*(5), 645-654.

Heishman, S. J., Singleton, E. G., & Pickworth, W. B. (2008). Reliability and validity of a Short Form of the Tobacco Craving Questionnaire. *Nicotine Tob Res, 10*(4), 643-651. doi: 10.1080/14622200801908174

Hennekens, C. H., Hennekens, A. R., Hollar, D., & Casey, D. E. (2005). Schizophrenia and increased risks of cardiovascular disease. *Am Heart J, 150*(6), 1115.

Hester, R., & Garavan, H. (2009). Neural mechanisms underlying drug-related cue distraction in active cocaine users. *Pharmacology, Biochemistry and Behavior, 93*(3), 270-277.

Hester, R., Lee, N., Pennay, A., Nielsen, S., & Ferris, J. (2010). The effects of modafinil treatment on neuropsychological and attentional bias performance during 7-day inpatient withdrawal from methamphetamine dependence. *Experimental and Clinical Psychopharmacology, 18*(6), 489.

Hicks, J. A., Friedman, R. S., Gable, P. A., & Davis, W. E. (2012). Interactive effects of approach motivational intensity and alcohol cues on the scope of perceptual attention. *Addiction 107*(6), 1074-80.

Hitsman, B., MacKillop, J., Lingford-Hughes, A., Williams, T. M., Ahmad, F., Adams, S., et al. (2008). Effects of acute tyrosine/phenylalanine depletion on the selective

processing of smoking-related cues and the relative value of cigarettes in smokers. *Psychopharmacology, 196*(4), 611-621.

Hogarth, L., Dickinson, A., & Duka, T. (2009). Detection versus sustained attention to drug cues have dissociable roles in mediating drug seeking behavior. *Experimental and Clinical Psychopharmacology, 17*(1), 21.

Hogarth, L., Dickinson, A., & Duka, T. (2010). Selective attention to conditioned stimuli in human discrimination learning: untangling the effects of outcome prediction, valence, arousal, and uncertainty. *Attention and associative learning: From brain to behaviour*, 71-97.

Hogarth, L., Dickinson, A., Janowski, M., Nikitina, A., & Duka, T. (2008). The role of attentional bias in mediating human drug-seeking behaviour. *Psychopharmacology, 201*(1), 29-41.

Hogarth, L. C., Mogg, K., Bradley, B., Duka, T., & Dickinson, A. (2003). Attentional orienting towards smoking-related stimuli. *Behavioural pharmacology, 14*(2), 153-160.

Holt, D. J., Titone, D., Long, L. S., Goff, D. C., Cather, C., Rauch, S. L., et al. (2006). The misattribution of salience in delusional patients with schizophrenia. *Schizophrenia research, 83*(2-3), 247-256.

Housden, C. R., O'Sullivan, S. S., Joyce, E. M., Lees, A. J., & Roiser, J. P. (2010). Intact reward learning but elevated delay discounting in Parkinson's disease patients with impulsive-compulsive spectrum behaviors. *Neuropsychopharmacology, 35*(11), 2155-2164.

Howes, O. D., Kambeitz, J., Kim, E., Stahl, D., Slifstein, M., Abi-Dargham, A., & Kapur, S. (2012). The nature of dopamine dysfunction in schizophrenia and what this means for treatment: meta-analysis of imaging studies. *Archives of General Psychiatry 69*(8), 776-86.

Hutchison, K. E., Rutter, M. C., Niaura, R., Swift, R. M., Pickworth, W. B., & Sobik, L. (2004). Olanzapine attenuates cue-elicited craving for tobacco. *Psychopharmacology, 175*(4), 407-413.

Janes, A. C., Pizzagalli, D. A., & Richardt, S. (2010). Brain reactivity to smoking cues prior to smoking cessation predicts ability to maintain tobacco abstinence. *Biol Psychiatry, 67*(8), 722.

Jarvik, M. E., Caskey, N. H., Wirshing, W. C., Madsen, D. C., Iwamoto-Schaap, P. N., & Elins, J. L. (2000). Bromocriptine reduces cigarette smoking. *Addiction, 95*(8), 1173-1183.

Jensen, J., Willeit, M., Zipursky, R. B., Savina, I., Smith, A. J., Menon, M., et al. (2007). The formation of abnormal associations in schizophrenia: neural and behavioral evidence. *Neuropsychopharmacology, 33*(3), 473-479.

Jones, S. H., Gray, J. A., & Hemsley, D. R. (1992). Loss of the Kamin blocking effect in acute but not chronic schizophrenics. *Biol Psychiatry, 32*(9), 739-755.

Jones, S. H., Hemsley, D., Ball, S., & Serra, A. (1997). Disruption of the Kamin blocking effect in schizophrenia and in normal subjects following amphetamine. *Behav Brain Res, 88*(1), 103-114.

Joseph, M., Young, A., & Gray, J. (1996). Are neurochemistry and reinforcement enough—can the abuse potential of drugs be explained by common actions on a dopamine reward system in the brain? *Human Psychopharmacology: Clinical and Experimental, 11*(S1), S55-S63.

Joyce, E. M., & Roiser, J. P. (2007). Cognitive heterogeneity in schizophrenia. *Current Opinion in Psychiatry, 20*(3), 268.

Kamin, L. J. (1969). Selective association and conditioning. *Fundamental issues in associative learning*, 42-64.

Kapur, S. (2003). Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. *American Journal of Psychiatry, 160*(1), 13-23.

Kasper, S., Barnas, C., Heiden, A., Volz, H., Laakmann, G., Zeit, H., & Pfolz, H. (1997). Pramipexole as adjunct to haloperidol in schizophrenia: safety and efficacy. *European Neuropsychopharmacology, 7*(1), 65-70.

Kelleher, J. P., Centorrino, F., Huxley, N. A., Bates, J. A., Drake, J. K., Egli, S., & Baldessarini, R. J. (2011). Pilot randomized, controlled trial of pramipexole to augment antipsychotic treatment. *European Neuropsychopharmacology*.

Kelly, C., & McCreadie, R. G. (1999). Smoking habits, current symptoms, and premorbid characteristics of schizophrenic patients in Nithsdale, Scotland. *American Journal of Psychiatry, 156*(11), 1751-1757.

Kelly, D. L., McMahon, R. P., Wehring, H. J., Liu, F., Mackowick, K. M., Boggs, D. L., et al. (2011). Cigarette smoking and mortality risk in people with schizophrenia. *Schizophrenia bulletin, 37*(4), 832-838.

Khantzian, E. J. (1997). The self-medication hypothesis of substance use disorders: a reconsideration and recent applications. *Harvard review of psychiatry, 4*(5), 231-244.

Kim, S. Y., Lee, H., Kim, H. J., Bang, E., Lee, S. H., Lee, D. W., et al. (2011). In vivo and ex vivo evidence for ketamine-induced hyperglutamatergic activity in the cerebral cortex of the rat: Potential relevance to schizophrenia. *NMR in Biomedicine, 24*(10), 1235-1242.

King, R., Barchas, J. D., & Huberman, B. (1984). Chaotic behavior in dopamine neurodynamics. *Proceedings of the National Academy of Sciences, 81*(4), 1244-1247.

Koch, C., & Tsuchiya, N. (2007). Attention and consciousness: two distinct brain processes. *Trends in cognitive sciences, 11*(1), 16-22.

Kotz, D., Brown, J., & West, R. (2012). Predictive validity of the Motivation To Stop Scale (MTSS): A single-item measure of motivation to stop smoking. *Drug and Alcohol Dependence*. http://dx.doi.org/10.1016/j.drugalcdep.2012.07.012

Kruschke, J. K., Kappenman, E. S., & Hetrick, W. P. (2005). Eye gaze and individual differences consistent with learned attention in associative blocking and highlighting. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 31*(5), 830.

Krystal, J. H., D'Souza, D. C., Gallinat, J. Ü., Driesen, N., Abi-Dargham, A., Petrakis, I., et al. (2006). The vulnerability to alcohol and substance abuse in individuals diagnosed with schizophrenia. *Neurotoxicity research, 10*(3), 235-252.

Kumari, V., Cotter, P. A., Mulligan, O. F., Checkley, S. A., Gray, N. S., Hemsley, D. R., . et al. (1999). Effects of d-amphetamine and haloperidol on latent inhibition in healthy male volunteers. *Journal of Psychopharmacology, 13*(4), 398-405.

Kumari, V., & Postma, P. (2005). Nicotine use in schizophrenia: the self medication hypotheses. *Neuroscience & Biobehavioral Reviews, 29*(6), 1021-1034.

Lahti, A. C., Weiler, M. A., Tamara, M., Parwani, A., & Tamminga, C. A. (2001). Effects of ketamine in normal and schizophrenic volunteers. *Neuropsychopharmacology, 25*(4), 455-467.

Large, M., Sharma, S., Compton, M. T., Slade, T., & Nielssen, O. (2011). Cannabis use and earlier onset of psychosis: a systematic meta-analysis. *Archives of general psychiatry, 68*(6), 555.

Leentjens, A. F. G., Koester, J., Fruh, B., Shephard, D. T. S., Barone, P., & Houben, J. J. G. (2009). The effect of pramipexole on mood and motivational symptoms in Parkinson's disease: a meta-analysis of placebo-controlled studies. *Clinical therapeutics, 31*(1), 89-98.

Leweke, F., Piomelli, D., Pahlisch, F., Muhl, D., Gerth, C., Hoyer, C., et al. (2012). Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. *Translational Psychiatry, 2*(3), e94. 10.1038/tp.2012.15

Littel, M., Euser, A. S., Munafò, M. R., & Franken, I. H. A. (2012). Electrophysiological indices of biased cognitive processing of substance-related cues: A meta-analysis. *Neuroscience & Biobehavioral Reviews 36*(8), 1803-1816.

Littel, M., & Franken, I. H. A. (2012). Electrophysiological correlates of associative learning in smokers: a higher-order conditioning experiment. *BMC neuroscience, 13*(1), 8.

Lo, S., Heishman, S. J., Raley, H., Wright, K., Wehring, H. J., Moolchan, E. T., et al. (2011). Tobacco craving in smokers with and without schizophrenia. *Schizophrenia research, 127*(1), 241-245.

Lubman, D. I., Yucel, M., Kettle, J. W. L., Scaffidi, A., MacKenzie, T., Simmons, J. G., & Allen, N. B. (2009). Responsiveness to drug cues and natural rewards in opiate addiction: associations with later heroin use. *Archives of general psychiatry, 66*(2), 205.

Lubow, R. E. a., & Moore, A. U. (1959). Latent inhibition: The effect of nonreinforced pre-exposure to the conditional stimulus. *Journal of Comparative and Physiological Psychology,, Vol 52*(4), 415-419.

Luijten, M., Veltman, D. J., Hester, R., Smits, M., Pepplinkhuizen, L., & Franken, I. H. A. (2012). Brain Activation Associated with Attentional Bias in Smokers is Modulated by a Dopamine Antagonist. *Neuropsychopharmacology 37*(13), 2772-9.

Mackintosh, N., & Reese, B. (1979). One-trial overshadowing. *The Quarterly Journal of Experimental Psychology, 31*(3), 519-526.

Mackintosh, N. J. (1975). A theory of attention: Variations in the associability of stimuli with reinforcement. *Psychological review, 82*(4), 276.

Mackintosh, N. J. (1976). Overshadowing and stimulus intensity. *Learning & Behavior, 4*(2), 186-192.

Maj, J., Rogoz, Z., Skuza, G., & Kołodziejczyk, K. (1997). The behavioural effects of pramipexole, a novel dopamine receptor agonist. *Eur J Pharmacol, 324*(1), 31.

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*(9), 1306-1312.

Mason, O., Linney, Y., & Claridge, G. (2005). Short scales for measuring schizotypy. *Schizophrenia research, 78*(2), 293-296.

Matute, H., Arcediano, F., & Miller, R. R. (1996). Test question modulates cue competition between causes and between effects. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 22*(1), 182.

McEvoy, J., Freudenreich, O., McGee, M., & VanderZwaag, C. (1995). Clozapine decreases smoking in patients with chronic schizophrenia. *Biol Psychiatry*.

McHugh, R. K., Murray, H. W., Hearon, B. A., Calkins, A. W., & Otto, M. W. (2010). Attentional bias and craving in smokers: the impact of a single attentional training session. *Nicotine & tobacco research, 12*(12), 1261-1264.

Mitchell, S. H. (2004). Effects of short-term nicotine deprivation on decision-making: delay, uncertainty and effort discounting. *Nicotine & tobacco research, 6*(5), 819-828.

Mizrahi, R., Kiang, M., Mamo, D. C., Arenovich, T., Bagby, R. M., Zipursky, R. B., & Kapur, S. (2006). The selective effect of antipsychotics on the different dimensions of the experience of psychosis in schizophrenia spectrum disorders. *Schizophrenia research, 88*(1), 111-118.

Mogg, K., Bradley, B. P., Field, M., & De Houwer, J. (2003). Eye movements to smoking-related pictures in smokers: relationship between attentional biases and implicit and explicit measures of stimulus valence. *Addiction, 98*(6), 825-836.

Mogg, K., Field, M., & Bradley, B. P. (2005). Attentional and approach biases for smoking cues in smokers: an investigation of competing theoretical views of addiction. *Psychopharmacology (Berl), 180*(2), 333-341. doi: 10.1007/s00213-005-2158-x

Mogg, K., Field, M., & Bradley, B. P. (2005). Attentional and approach biases for smoking cues in smokers: an investigation of competing theoretical views of addiction. *Psychopharmacology, 180*(2), 333-341.

Mogg, K., Garner, M., & Bradley, B. P. (2007). Anxiety and orienting of gaze to angry and fearful faces. *Biological psychology, 76*(3), 163.

Moore, T. H. M., Zammit, S., Lingford-Hughes, A., Barnes, T. R. E., Jones, P. B., Burke, M., & Lewis, G. (2007). Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *The Lancet, 370*(9584), 319-328.

Moran, P., Al-Uzri, M., Watson, J., & Reveley, M. (2003). Reduced Kamin blocking in non paranoid schizophrenia: associations with schizotypy. *Journal of psychiatric research, 37*(2), 155-163.

Moran, P., Owen, L., Crookes, A., Al-Uzri, M., & Reveley, M. (2008). Abnormal prediction error is associated with negative and depressive symptoms in schizophrenia. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 32*(1), 116-123.

Moran, P. M., Rouse, J. L., Cross, B., Corcoran, R., & Schürmann, M. (2012). Kamin Blocking Is Associated with Reduced Medial-Frontal Gyrus Activation: Implications for Prediction Error Abnormality in Schizophrenia. *PLoS ONE, 7*(8), e43905.

Morgan, C., Duffin, S., Hunt, S., Monaghan, L., Mason, O., & Curran, H. (2012). Neurocognitive Function and Schizophrenia-Proneness in Individuals Dependent on Ketamine, on High Potency Cannabis (‘Skunk') or on Cocaine. *Pharmacopsychiatry 45*(7), 269-74.

Morgan, C., Rees, H., & Curran, H. (2008). Attentional bias to incentive stimuli in frequent ketamine users. *Psychol Med, 38*(09), 1331-1340.

Morgan, C. J. A., & Curran, H. V. (2006). Acute and chronic effects of ketamine upon human memory: a review. *Psychopharmacology, 188*(4), 408-424.

Morgan, C. J. A., & Curran, H. V. (2008). Effects of cannabidiol on schizophrenia-like symptoms in people who use cannabis. *The British journal of psychiatry, 192*(4), 306-307.

Morgan, C. J., Freeman, T. P., Schafer, G. L., & Curran, H. V. (2010). Cannabidiol attenuates the appetitive effects of Δ9-tetrahydrocannabinol in humans smoking their chosen cannabis. *Neuropsychopharmacology, 35*(9), 1879-1885.

Morgan, C. J. A., Muetzelfeldt, L., & Curran, H. V. (2009). Consequences of chronic ketamine self-administration upon neurocognitive function and psychological wellbeing: a 1-year longitudinal study. *Addiction, 105*(1), 121-133.

Mueser, K. T., Yarnold, P. R., Levinson, D. F., Singh, H., Bellack, A. S., Kee, K., et al.(1990). Prevalence of substance abuse in schizophrenia: demographic and clinical correlates. *Schizophrenia bulletin, 16*(1), 31.

Muetzelfeldt, L., Kamboj, S. K., Rees, H., Taylor, J., Morgan, C. J., & Curran, H. V. (2008). Journey through the K-hole: phenomenological aspects of ketamine use. *Drug Alcohol Depend, 95*(3), 219-229. doi: 10.1016/j.drugalcdep.2008.01.024

Munafò, M. R., Mannie, Z. N., Cowen, P. J., Harmer, C. J., & McTavish, S. B. (2007). Effects of acute tyrosine depletion on subjective craving and selective processing of smoking-related cues in abstinent cigarette smokers. *Journal of Psychopharmacology, 21*(8), 805-814.

Murphy, M. F., Hey, K., Johnstone, E., Munafo, M., Walton, R., Willis, B., & Harrison, P. J. (2002). Bromocriptine use is associated with decreased smoking rates. *Addict Biol, 7*(3), 325-328. doi: 10.1080/13556210220139550

Murray, G., Corlett, P., Clark, L., Pessiglione, M., Blackwell, A., Honey, G., et al. (2007). Substantia nigra/ventral tegmental reward prediction error disruption in psychosis. *Molecular psychiatry, 13*(3), 267-276.

Myles, N., Newall, H., Compton, M. T., Curtis, J., Nielssen, O., & Large, M. (2012). The age at onset of psychosis and tobacco use: a systematic meta-analysis. *Social psychiatry and psychiatric epidemiology, 47*(8), 1243-1250.

Nagy, H., Levy-Gigi, E., Somlai, Z., Takáts, A., Bereczki, D., & Kéri, S. (2011). The Effect of Dopamine Agonists on Adaptive and Aberrant Salience in Parkinson's Disease. *Neuropsychopharmacology, 37*(4), 950-958.

Naheed, M., & Green, B. (2001). Focus on clozapine. *Current Medical Research and Opinion®, 17*(3), 223-229.

Nelson, H. E. (1991). National adult reading test (NART): Nfer-Nelson.

O'Daly, O. G., Guillin, O., Tsapakis, E. M., Martinez, D., Shergill, S. S., Murray, R. M., & Buckley, P. F. (2005). Schizophrenia and Substance Abuse Co-Morbidity. *Journal of dual diagnosis, 1*(2), 11-40.

O'Tuathaigh, C., & Moran, P. (2002). Evidence for dopamine D1 involvement in the stimulus selection test: overshadowing in the rat. *Psychopharmacology, 162*(3), 225-231.

Oades, R. D., Zimmermann, B., & Eggers, C. (1996). Conditioned blocking in patients with paranoid, non-paranoid psychosis or obsessive compulsive disorder: Associations with symptoms, personality and monoamine metabolism. *Journal of psychiatric research, 30*(5), 369-390.

Orosz, A. T., Feldon, J., Simon, A. E., Hilti, L. M., Gruber, K., Yee, B. K., & Cattapan-Ludewig, K. (2011). Learned irrelevance and associative learning is attenuated in individuals at risk for psychosis but not in asymptomatic first-degree relatives of schizophrenia patients: translational state markers of psychosis? *Schizophrenia bulletin, 37*(5), 973-981.

Panlilio, L. V., Thorndike, E. B., & Schindler, C. W. (2007). Blocking of conditioning to a cocaine-paired stimulus: Testing the hypothesis that cocaine perpetually produces a signal of larger-than-expected reward. *Pharmacology Biochemistry and Behavior, 86*(4), 774-777.

Parkes, J. D. (1986). Domperidone and Parkinson's Disease. *Clinical Neuropharmacology, 9*(6), 517-532.

Parkhurst, D., Law, K., & Niebur, E. (2002). Modeling the role of salience in the allocation of overt visual attention. *Vision research, 42*(1), 107-124.

Parsons, J. (2012). No quick fix for legal highs. *Addiction, 107*(11), 2053-2054.

Pearce, J. M., & Hall, G. (1980). A model for Pavlovian learning: variations in the effectiveness of conditioned but not of unconditioned stimuli. *Psychological review, 87*(6), 532.

Peters, E. R., Joseph, S. A., & Garety, P. A. (1999). Measurement of delusional ideation in the normal population: introducing the PDI (Peters et al. Delusions Inventory). *Schizophrenia bulletin, 25*(3), 553-576.

Petry, N. M. (2000). A comprehensive guide to the application of contingency management procedures in clinical settings. *Drug and Alcohol Dependence, 58*(1), 9-25.

Phillips, P. E. M., Stuber, G. D., Heien, M., Wightman, R. M., & Carelli, R. M. (2003). Subsecond dopamine release promotes cocaine seeking. *Nature, 422*(6932), 614-618.

Pilla, M., Perachon, S., Sautel, F., Garrido, F., Mann, A., Wermuth, C. G., et al. (1999). Selective inhibition of cocaine-seeking behaviour by a partial dopamine D3 receptor agonist. *Nature, 400*(6742), 371-375.

Pizzagalli, D. A., Evins, A. E., Schetter, E. C., Frank, M. J., Pajtas, P. E., Santesso, D. L., & Culhane, M. (2008). Single dose of a dopamine agonist impairs reinforcement learning in humans: behavioral evidence from a laboratory-based measure of reward responsiveness. *Psychopharmacology, 196*(2), 221-232.

Pomarol-Clotet, E., Honey, G., Murray, G., Corlett, P., Absalom, A., Lee, M., . . . Fletcher, P. (2006). Psychological effects of ketamine in healthy volunteers Phenomenological study. *The British journal of psychiatry, 189*(2), 173-179.

Potenza, M., & Chambers, R. (2001). Schizophrenia and pathological gambling. *The American journal of psychiatry, 158*(3), 497.

Pothos, E. M., & Cox, W. M. (2002). Cognitive bias for alcohol-related information in inferential processes. *Drug and Alcohol Dependence, 66*(3), 235-241.

Powell, J., Dawkins, L., & Davis, R. E. (2002). Smoking, reward responsiveness, and response inhibition: tests of an incentive motivational model. *Biol Psychiatry, 51*(2), 151-163.

Powell, J., Dawkins, L., West, R., Powell, J., & Pickering, A. (2010). Relapse to smoking during unaided cessation: clinical, cognitive and motivational predictors. *Psychopharmacology, 212*(4), 537-549.

Powell, J., Tait, S., & Lessiter, J. (2002). Cigarette smoking and attention to signals of reward and threat in the Stroop paradigm. *Addiction, 97*(9), 1163-1170.

Raine, A. (1991). The SPQ: a scale for the assessment of schizotypal personality based on DSM-III-R criteria. *Schizophrenia bulletin, 17*(4), 555.

Raine, A., Reynolds, C., Lencz, T., & Scerbo, A. (1994). Cognitive-perceptual, interpersonal, and disorganized features of schizotypal personality. *Schizophrenia bulletin, 20*(1), 191.

Raistrick, D., Bradshaw, J., Tober, G., Weiner, J., Allison, J., & Healey, C. (1994). Development of the Leeds Dependence Questionnaire (LDQ): a questionnaire to

measure alcohol and opiate dependence in the context of a treatment evaluation package. *Addiction (Abingdon, England), 89*(5), 563.

Rascle, C., Mazas, O., Vaiva, G., Tournant, M., Raybois, O., Goudemand, M., & Thomas, P. (2001). Clinical features of latent inhibition in schizophrenia. *Schizophrenia research, 51*(2), 149-161.

Ratcliff, R. (1993). Methods for dealing with reaction time outliers. *Psychol Bull, 114*(3), 510.

Redish, A. D. (2004). Addiction as a computational process gone awry. *Science Signalling, 306*(5703), 1944.

Rescorla, R. A., & Wagner, A. R. (1972). A theory of Pavlovian conditioning: Variations in the effectiveness of reinforcement and nonreinforcement. *Classical conditioning II: Current research and theory*, 64-99.

Robbins, S. J., & Ehrman, R. N. (2004). The role of attentional bias in substance abuse. *Behavioral and Cognitive Neuroscience Reviews, 3*(4), 243-260.

Robinson, T. E., & Becker, J. B. (1986). Enduring changes in brain and behavior produced by chronic amphetamine administration: a review and evaluation of animal models of amphetamine psychosis. *Brain Res, 396*(2), 157-198.

Robinson, T. E., & Berridge, K. C. (1993). The neural basis of drug craving: An incentive-sensitization theory of addiction. *Brain Research Reviews, 18*(3), 247-291.

Roiser, J., Stephan, K., Den Ouden, H., Barnes, T., Friston, K., & Joyce, E. (2009). Do patients with schizophrenia exhibit aberrant salience? *Psychol Med, 39*(2), 199-209.

Roiser, J. P., Howes, O. D., Chaddock, C. A., Joyce, E. M., & McGuire, P. (in press). Neural and behavioural correlates of aberrant salience attribution in individuals at-risk for psychosis. *Schizophrenia Bulletin*.

Fadardi, J., Cox, W. M. (2009). Reversing the sequence: Reducing alcohol consumption by overcoming alcohol attentional bias. *Drug and Alcohol Dependence*. *101,* 137-145.

Sarkar, B. K., & Reddy, K. S. (2012). Priorities for tobacco control research in India. *Addiction 107* (12), 2066-2068.

Sayette, M. A., & Hufford, M. R. (1994). Effects of cue exposure and deprivation on cognitive resources in smokers. *Journal of abnormal psychology*, *103*(4), 812.

Sayette, M. A., Monti, P. M., Rohsenow, D. J., Gulliver, S. B., Colby, S. M., Sirota, A. D., et al. (1994). The effects of cue exposure on reaction time in male alcoholics. *Journal of Studies on Alcohol and Drugs*, *55*(5), 629.

Schmidt, K., & Roiser, J. P. (2009). Assessing the construct validity of aberrant salience. *Frontiers in behavioral neuroscience, 3*, 58

Schoenmakers, T. M., de Bruin, M., Lux, I. F. M., Goertz, A. G., Van Kerkhof, D. H. A. T., & Wiers, R. W. (2010). Clinical effectiveness of attentional bias modification training in abstinent alcoholic patients. *Drug and Alcohol Dependence*, *109*(1), 30-36.

Schultz, W., Dayan, P., & Montague, P. R. (1997). A neural substrate of prediction and reward. *Science*, *275*(5306), 1593-1599.

Shaner, A. (1999). Delusions, superstitious conditioning and chaotic dopamine neurodynamics. *Medical hypotheses*, *52*(2), 119-123.

Skinner, B. F. (1948). 'Superstition'in the pigeon. *Journal of experimental psychology, 38*(2), 168.

Smelson, D. A., Losonczy, M. F., Kilker, C., Starosta, A., Kind, J., Williams, J., & Ziedonis, D. (2002). An analysis of cue reactivity among persons with and without schizophrenia who are addicted to cocaine. *Psychiatr Serv, 53*(12), 1612-1616.

Smith, A., Li, M., Becker, S., & Kapur, S. (2006). Dopamine, prediction error and associative learning: a model-based account. *Network: Computation in Neural Systems, 17*(1), 61-84.

Solomon, P. R. (1981). Disrupted latent inhibition in the rat with chronic amphetamine or haloperidol-induced supersensitivity: Relationship to schizophrenic attention disorder. *Biological Psychiatry; Biological Psychiatry*.

Stokes, P. R. A., Egerton, A., Watson, B., Reid, A., Breen, G., Lingford-Hughes, A., et al. (2010). Significant decreases in frontal and temporal [11C]-raclopride binding after THC challenge. *Neuroimage, 52*(4), 1521-1527.

Stokes, P. R. A., Mehta, M. A., Curran, H. V., Breen, G., & Grasby, P. M. (2009). Can recreational doses of THC produce significant dopamine release in the human striatum? *Neuroimage, 48*(1), 186-190.

Stone, J., Dietrich, C., Edden, R., Mehta, M., De Simoni, S., Reed, L., et al. (2012). Ketamine effects on brain GABA and glutamate levels with 1H-MRS: relationship to ketamine-induced psychopathology. *Molecular psychiatry 17* 664-665.

Swendsen, J., Ben-Zeev, D., & Granholm, E. (2011). Real-time electronic ambulatory monitoring of substance use and symptom expression in schizophrenia. *American Journal of Psychiatry, 168*(2), 202-209.

Swerdlow, N. R., Braff, D. L., Hartston, H., Perry, W., & Geyer, M. A. (1996). Latent inhibition in schizophrenia. *Schizophrenia research, 20*(1), 91-103.

Takikawa, Y., Kawagoe, R., & Hikosaka, O. (2004). A possible role of midbrain dopamine neurons in short-and long-term adaptation of saccades to position-reward mapping. *Journal of neurophysiology, 92*(4), 2520-2529.

Thornton, J., Dawe, S., Lee, C., Capstick, C., Corr, P., Cotter, P., et al. (1996). Effects of nicotine and amphetamine on latent inhibition in human subjects. *Psychopharmacology, 127*(1), 164-173.

Tidey, J. W., Rohsenow, D. J., Kaplan, G. B., Swift, R. M., & Adolfo, A. B. (2008). Effects of smoking abstinence, smoking cues and nicotine replacement in smokers with schizophrenia and controls. *Nicotine & tobacco research, 10*(6), 1047-1056.

Tiffany, S. T. (1990). A cognitive model of drug urges and drug-use behavior: role of automatic and nonautomatic processes. *Psychological review, 97*(2), 147.

Tobler, P. N., O'Doherty, J. P., Dolan, R. J., & Schultz, W. (2006). Human neural learning depends on reward prediction errors in the blocking paradigm. *Journal of neurophysiology, 95*(1), 301-310.

Torregrossa, M. M., & Taylor, J. R. (2012). Learning to forget: manipulating extinction and reconsolidation processes to treat addiction. *Psychopharmacology* 10.1007/s00213-012-2750-9

Tsapakis, E. M., Guillin, O., & Murray, R. M. (2003). Does dopamine sensitization underlie the association between schizophrenia and drug abuse? *Current Opinion in Psychiatry, 16*, S45-S52.

Uhlhaas, P. J., Millard, I., Muetzelfeldt, L., Curran, H. V., & Morgan, C. L. J. A. (2007). Perceptual organization in ketamine users: preliminary evidence of deficits on night of drug use but not 3 days later. *Journal of Psychopharmacology, 21*(3), 347-352.

Vaitl, D., Lipp, O., Bauer, U., Schüler, G., Stark, R., Zimmermann, M., & Kirsch, P. (2002). Latent inhibition and schizophrenia: Pavlovian conditioning of autonomic responses. *Schizophrenia research, 55*(1), 147-158.

Van Os, J. (2009). 'Salience syndrome'replaces 'schizophrenia'in DSM-V and ICD-11: psychiatry's evidence-based entry into the 21st century? *Acta Psychiatrica Scandinavica*, *120*(5), 363-372.

Versace, F., Lam, C. Y., Engelmann, J. M., Robinson, J. D., Minnix, J. A., Brown, V. L., & Cinciripini, P. M. (2011). Beyond cue reactivity: blunted brain responses to pleasant stimuli predict long-term smoking abstinence. *Addict Biol*.

Volkow, N. D., Wang, G. J., Fowler, J. S., Tomasi, D., Telang, F., & Baler, R. (2010). Addiction: decreased reward sensitivity and increased expectation sensitivity conspire to overwhelm the brain's control circuit. *Bioessays, 32*(9), 748-755.

Vollstädt-Klein, S., Loeber, S., Winter, S., Leménager, T., von der Goltz, C., Dinter, C., et al. (2011). Attention shift towards smoking cues relates to severity of dependence, smoking behavior and breath carbon monoxide. *European addiction research, 17*(4), 217-224.

Walter, H., Heckers, S., Kassubek, J., Erk, S., Frasch, K., & Abler, B. (2009). Further evidence for aberrant prefrontal salience coding in schizophrenia. *Frontiers in behavioral neuroscience, 3*, 62.

Wanat, M. J., Willuhn, I., Clark, J. J., & Phillips, P. E. M. (2009). Phasic dopamine release in appetitive behaviors and drug abuse. *Current drug abuse reviews, 2*(2), 195.

Waters, A. J., Shiffman, S., Sayette, M. A., Paty, J. A., Gwaltney, C. J., & Balabanis, M. H. (2003). Attentional bias predicts outcome in smoking cessation. *Health Psychology, 22*(4), 378.

Wechsler, D. (2001). *Wechsler Test of Adult Reading: WTAR*: Psychological Corporation.

Weintraub, D., Siderowf, A. D., Potenza, M. N., Goveas, J., Morales, K. H., Duda, J. E., et al. (2006). Association of dopamine agonist use with impulse control disorders in Parkinson disease. *Archives of neurology, 63*(7), 969.

West, R., & Hajek, P. (2004). Evaluation of the mood and physical symptoms scale (MPSS) to assess cigarette withdrawal. *Psychopharmacology, 177*(1), 195-199.

Westerhausen, R., Kompus, K., & Hugdahl, K. (2011). Impaired cognitive inhibition in schizophrenia: A meta-analysis of the Stroop interference effect. *Schizophrenia research, 133*(1), 172-181.

WHO. (1993). *The ICD-10 classification of mental and behavioural disorders: diagnostic criteria for research*: World Health Organization.

Wills, A., Lavric, A., Croft, G., & Hodgson, T. (2007). Predictive learning, prediction errors, and attention: Evidence from event-related potentials and eye tracking. *Journal of Cognitive Neuroscience, 19*(5), 843-854.

Wing, V. C., Bacher, I., Sacco, K. A., & George, T. P. (2011). Neuropsychological performance in patients with schizophrenia and controls as a function of cigarette smoking status. *Psychiatry Res, 188*(3), 320-326.

Wright, C. E., Sisson, T., Ichhpurani, A., & Peters, G. R. (1997). Steady-state pharmacokinetic properties of pramipexole in healthy volunteers. *The Journal of Clinical Pharmacology, 37*(6), 520-525.

Xue, Y. X., Luo, Y. X., Wu, P., Shi, H. S., Xue, L. F., Chen, C., et al. (2012). A memory retrieval-extinction procedure to prevent drug craving and relapse. *Science, 336*(6078), 241-245.

Yi, R., & Landes, R. D. (2012). Temporal and Probability Discounting by Cigarette Smokers Following Acute Smoking Abstinence. *Nicotine & tobacco research, 14*(5), 547-558.

Young, A., Joseph, M., & Gray, J. (1993). Latent inhibition of conditioned dopamine release in rat nucleus accumbens. *Neuroscience, 54*(1), 5-9.

Zweifel, L. S., Parker, J. G., Lobb, C. J., Rainwater, A., Wall, V. Z., Fadok, J. P., et al. (2009). Disruption of NMDAR-dependent burst firing by dopamine neurons provides selective assessment of phasic dopamine-dependent behavior. *Proceedings of the National Academy of Sciences, 106*(18), 7281-7288.

Appendix 1: Ethical approval letter (chapter 2) and chapter 4 (control group)

UCL DIVISION OF PSYCHOLOGY
AND LANGUAGE SCIENCES

UCL

Val Curran and Tom Freeman
Clinical Psychopharmacology Unit
University College London
Gower St
London WC1E 6BT

Dear Prof Curran & Mr Freeman

Notification of Ethical Approval:
Ethics Application Number: CEHP/2010/011: Causal Learning in Humans

I am pleased to confirm that your research proposal (including the amendments dated 13/08/12) has been approved by the UCL Psychology and Language Sciences Research Ethics Committee for the duration of the study (until May 2015).

Yours sincerely,

[redacted]

Prof. Essi Viding
Ethics Chair
UCL Psychology and Language Sciences

Appendix 2: Information sheet for chapter 2.

SUB-DEPARTMENT OF CLINICAL HEALTH PSYCHOLOGY
UCL PSYCHOLOGY AND LANGUAGE SCIENCES

VOLUNTEER INFORMATION SHEET

Title of project: Causal learning in humans

Investigators: Tom Freeman, Dr. Celia Morgan, Prof. H.Valerie Curran

Contact:
Tom Freeman, Clinical Psychopharmacology Unit, UCL, Gower Street, London WC1E 6BT.
Telephone: 02076798273.
Email: tom.freeman@ucl.ac.uk

INFORMATION LEAFLET FOR VOLUNTEERS

You are being 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 take time to read the following information carefully and discuss it with friends and relatives if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

WHAT IS THE PURPOSE OF THE STUDY AND WHAT WILL BE STUDIED?

We are interested in studying the processes involved in learning and memory. One factor that might influence learning and memory is cigarette smoking, and the abstinence of smoking. In this study, we will be investigating learning, memory, mood and well being in smokers and non smokers.

HOW WOULD I BE INVOLVED IF I AGREED TO TAKE PART?

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 decide to take part you are still free to withdraw at any time and without giving a reason.

If you agree to take part, the experimenter will take some brief demographic information from you and you will be asked to complete a number of computer tasks and short questionnaires. If you are a smoker, **you may be asked to refrain from smoking for at least 12 hours prior to the study. Smoking abstinence will be verified with a smokelyzer, and non compliance will result in exclusion from the study**. Altogether the testing session will last for approximately one hour and forty five minutes. You will then be paid for participation. You will be paid **AT LEAST £15** for your time, but have the opportunity to win **AN ADDITONAL £12.50** based on your performance on some of the tasks.

CONFIDENTIALITY

Any information collected about you will be held in accordance with the 1998 Data Protection Act. All the information that is collected about you during the course of the research will be kept strictly confidential. Your results will have your name and any other details about you removed first so that you cannot be recognized from them.

If you require further information please ask Tom Freeman

Thank you for reading this leaflet and we hope that you will be able to take part in the study.

You do not have to take part in the study if you do not want to. If you decide to take part, you may withdraw at any time without having to give a reason.

All proposals for research involving human subjects are reviewed by an ethics committee before they can proceed. This proposal was reviewed by the UCL Psychology and Language Sciences committee for ethics in non-invasive research on healthy adults.

Appendix 3: Ethical approval letter (chapter 3).

UCL RESEARCH ETHICS COMMITTEE
GRADUATE SCHOOL OFFICE

UCL

Professor Valerie Curran
UCL Research Department of Clinical, Educational
& Health Psychology
1-19 Torrington Place
London
WC1E 7HB

28 May 2010

Dear Professor Curran

Notification of Ethical Approval:
Ethics Application: 2504/001: How does use of recreational drugs influence causal learning?

I am pleased to confirm that your research proposal has been approved by the UCL Research Ethics Committee for the duration of the study (i.e. until May 2014).

Approval is subject to the following conditions:

1. You must seek Chair's approval for proposed amendments to the research for which this approval has been given. Ethical approval is specific to this project and must not be treated as applicable to research of a similar nature. Each research project is reviewed separately and if there are significant changes to the research protocol you should seek confirmation of continued ethical approval by completing the 'Amendment Approval Request Form'.

The form identified above can be accessed by logging on to the ethics website homepage: http://www.grad.ucl.ac.uk/ethics/ and clicking on the button marked 'Key Responsibilities of the Researcher Following Approval'.

2. It is your responsibility to report to the Committee any unanticipated problems or adverse events involving risks to participants or others. Both non-serious and serious adverse events must be reported.

Reporting Non-Serious Adverse Events
For non-serious adverse events you will need to inform Dr Angela Poulter, Ethics Committee Administrator (ethics@ucl.ac.uk), within ten days of an adverse incident occurring and provide a full written report that should include any amendments to the participant information sheet and study protocol. The Chair or Vice-Chair of the Ethics Committee will confirm that the incident is non-serious and report to the Committee at the next meeting. The final view of the Committee will be communicated to you.

Reporting Serious Adverse Events
The Ethics Committee should be notified of all serious adverse events via the Ethics Committee Administrator immediately the incident occurs. Where the adverse incident is unexpected and serious, the Chair or Vice-Chair will decide whether the study should be terminated pending the opinion of an independent expert. The adverse event will be considered at the next Committee meeting and a decision will be made on the need to change the information leaflet and/or study protocol.

On completion of the research you must submit a brief report (a maximum of two sides of A4) of your findings/concluding comments to the Committee, which includes in particular issues relating to the ethical implications of the research.

Yours sincerely

[redacted]

Sir John Birch
Chair of the UCL Research Ethics Committee

Cc. Mr Tom Freeman; Dr Celia Morgan, UCL Research Department of Clinical, Educational & Health Psychology

UCL Research Ethics Committee, c/o The Graduate School, North Cloisters, Wilkins Building
University College London Gower Street London WC1E 6BT
Tel: +44 (0)20 7679 7844 Fax: +44 (0)20 7679 7043
h.dougal@ucl.ac.uk
www.ucl.ac.uk/gradschool

Appendix 4: Information sheet (chapter 3).

SUB-DEPARTMENT OF CLINICAL HEALTH PSYCHOLOGY
UCL PSYCHOLOGY AND LANGUAGE SCIENCES

VOLUNTEER INFORMATION SHEET

Title of project: How does use of recreational drugs influence causal learning?

Investigators: Tom Freeman, Dr. Celia Morgan, Prof. H.Valerie Curran

Contact:
Tom Freeman, Clinical Psychopharmacology Unit, UCL, Gower Street, London WC1E 6BT. Telephone: 02076798273.
Email: tom.freeman@ucl.ac.uk

INFORMATION LEAFLET FOR VOLUNTEERS

You are being 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 take time to read the following information carefully and discuss it with friends and relatives if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

WHAT IS THE PURPOSE OF THE STUDY AND WHAT WILL BE STUDIED?

We are interested to find out if recreational drug use affects processes involved in causal learning and memory. In this study, we will be comparing groups of individuals who do and do not use the recreational drugs cannabis and/or ketamine. We aim to see if groups differ in mood, causal learning and memory.

SOME BACKGROUND TO THE RESEARCH

Use of recreational drugs has been shown in laboratory studies to have effects on brain areas important for memory and mental state. With many other drugs there are also long term effects; for instance people who drink lots of alcohol often find their memories are not as good as they were. This can often be affected by factors such as the length of time they have been drinking and the quantity that they drink. The present study aims to find out what the long-term effects of using cannabis and ketamine may be.

HOW WOULD I BE INVOLVED IF I AGREED TO TAKE PART?

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 decide to take part you are still free to withdraw at any time and without giving a reason.

If you agree to take part, the experimenter will take some brief demographic information from you and you will be asked to complete a number of computer tasks and short questionnaires. You will also be asked to provide information about your current and previous illicit drug use. Altogether this will last for approximately 90 minutes. You will then be paid for participation.

CONFIDENTIALITY

Any information collected about you will be held in accordance with the 1998 Data Protection Act. All the information that is collected about you during the course of the research will be kept strictly confidential. Your results will have your name and any other details about you removed first so that you cannot be recognized from them.

If you require further information please ask Tom Freeman

Thank you for reading this leaflet and we hope that you will be able to take part in the study.

You do not have to take part in the study if you do not want to. If you decide to take part, you may withdraw at any time without having to give a reason

Appendix 5: Ethical approval letter for chapter 4 (patient group).

NHS

National Research Ethics Service

NRES Committee London - Camden & Islington

REC Office
Maternity, Level 7
Northwick Park Hospital
Watford Road
Harrow
HA1 3UJ

Telephone: 020 8869 5446
Facsimile: 020 8869 5222

17 November 2011

Dr James Stone
Senior Clinical Lecturer in Psychological Medicine
Imperial College London
Burlington Danes Building
Hammersmith Hospital
Du Cane Road
W12 0NN

Dear Dr Stone

Study title: **The role of smoking heaviness on addictive behaviours and reward learning/motivation in chronic schizophrenia**

REC reference: **11/LO/1507**

Thank you for your letter received on 25 October 2011, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Advertisement	Poster Version 1	12 July 2011
Covering Letter	Letter from Mr Freeman	31 August 2011
Evidence of insurance or indemnity	Certificate of Currency	06 September 2010
GP/Consultant Information Sheets	GP Letter Version 1	12 July 2011
Investigator CV	CV for Dr James Michael Stone	
Letter from Sponsor	Letter to Dr Stone from Mr Wilson	19 July 2011
Other: CV for Professor Helen Curran		30 August 2011
Other: Letter to Professor Curran from Mr Craig		26 June 2009
Participant Consent Form	3	17 October 2011
Participant Information Sheet	3	17 October 2011
Protocol	1.00	12 July 2011
REC application	83753/247437/1/59	08 September 2011
Referees or other scientific critique report	Letter from Dr Kamboj	31 August 2011
Response to Request for Further Information	Letter from Mr Freeman	Received on 25 October 2011
Other: Email to Ms Braley from Dr Stone		17 November 2011

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

11/LO/1507	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

[redacted]

Ms Stephanie Ellis
Chair

Email: louise.braley@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Mr Dave Wilson, University College London*

Ms. Rubina Choudhry, West London Mental Health Trust

Appendix 6: Information sheet for chapter 4 (patient group).

West London Mental Health NHS Trust

We care to make the difference

UCL

TOBACCO SMOKING AND REWARD IN SCHIZOPHRENIA

Information Sheet for Participants

Version 3: 17/10/11

You are being 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 take time to read the following information carefully and discuss it with others if you wish. Please contact one of us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

What is the purpose of this study?

Smoking is the leading preventable cause of death worldwide. Compared to the general population, people with a diagnosis of schizophrenia are more likely to smoke and may find it harder to quit. For this reason, we are interested to find out more about why people who have a diagnosis of schizophrenia smoke. Please note that we are not trying to influence the amount you smoke in general in this study. If you decide you want to stop smoking or change the amount you smoke, please tell your clinician and/or clozapine nurse. Although there are no direct benefits of taking part in this study apart from being paid for your time, the results from this study may contribute to specific approaches to help people with schizophrenia quit smoking.

Why have I been invited?

You have been approached to volunteer for this study, as you are a smoker with a diagnosis of schizophrenia.

Do I have to take part?

If you wish to have another copy of this information sheet to give to a carer or family member, please ask the researcher. You can discuss this study with them or anybody else, but it is up to you to decide whether or not to take part. If you do decide to participate you will be asked to sign a consent form. You are free to withdraw from the study at any time and can do so without giving a reason. If you choose to withdraw, you will have the choice of removing any information collected from you or allowing it to be stored anonymously.

What will happen to me if I take part?

Should you wish to take part you will be invited to attend an interview on a pre-

arranged date. During this meeting the aim will be to obtain consent for your involvement, after which you will be asked to provide a breath sample to measure carbon monoxide and a saliva sample which will be analysed in a laboratory. Both of these samples give an indication of how much you smoke tobacco.

Next there will be a clinical interview to assess your symptoms (This should take no longer than 45 minutes).

This will be followed by a series of simple psychological tests using either a pen and paper or a laptop computer, which should take 45 to 60 minutes. The tasks are short and most people find them fun and easy to do. Some of these tasks involve viewing smoking related materials (e.g. a cigarette and lighter) or photos of smoking. This might make you crave a cigarette, but no more than during normal life such as when you see someone else smoke. You are welcome to take a short break at any point during the study. If you wish to take a break please ask the researcher.

To compensate you for your time, you will be paid £7.50 per hour for taking part. Some of the tasks you take part in can allow you to earn extra money based on how you respond. You can earn up to £5 extra on these tasks.

What do I have to do?

If you are interested in taking part, an appointment will be arranged at a convenient time for you. We recommend that you refrain from using illegal drugs or drinking alcohol on the day of the appointment. If you are taking regular medication we recommend that you continue doing so.

Will my taking part in this study be kept confidential?

As part of this study, some personal information will be collected, including contact details (phone number, email address) and information from your medical records by researchers who are not in your direct healthcare team. **All information collected about you during the course of the research will be kept strictly confidential**. Information will only be shared with your GP or other health professionals involved in your care if absolutely necessary for your health and well-being. All information about you will be anonymised and will be stored in accordance with Data Protection laws and only the main researchers will have access to your information for the purposes of this study. You will be allocated a unique number or code which we will use to record and recall your personal details should you need to be contacted in the future. You will not be identified by name in any report concerning this study.

What will happen to the results of the research study?

We plan to publish the results of this study so that other doctors and scientists can discover more about why people with schizophrenia smoke. We hope that these results will improve our ability to help people with schizophrenia quit smoking in the future. If you wish, we can provide you with a copy of the overall results of this study by phone or email. **Please inform a member of the research team if you would like to receive these results**.

Who is organising the research?

This study is being organised by Tom Freeman and Professor H Valerie Curran at University College London, Stephanie Minchin, and Dr James Stone at Imperial College London.

Who has reviewed the study?

The National Research Ethics Service for Camden and Islington in London (reference code 11/LO/1507) and the West London Mental Health Trust Clinical Projects Peer Review Group (reference code STOJW1102) have reviewed this study.

Contact for further information

We are very grateful to you for your help. If you would like to have any further information at all, please do not hesitate to contact Tom Freeman

Tom Freeman
Research Department of Clinical, Educational and Health Psychology
University College London
London WC1E 6BT

07973736096

tom.freeman@ucl.ac.uk

Appendix 7: Information sheet for chapter 4 (control group).

SUB-DEPARTMENT OF CLINICAL HEALTH PSYCHOLOGY
UCL PSYCHOLOGY AND LANGUAGE SCIENCES

VOLUNTEER INFORMATION SHEET

Title of project: Causal learning in humans

Investigators: Tom Freeman, Dr. Celia Morgan, Prof. H.Valerie Curran

Contact:
Tom Freeman, Clinical Psychopharmacology Unit, UCL, Gower Street, London WC1E 6BT. Telephone: 02076798273.
Email: tom.freeman@ucl.ac.uk

INFORMATION LEAFLET FOR VOLUNTEERS

You are being 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 take time to read the following information carefully and discuss it with friends and relatives if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

WHAT IS THE PURPOSE OF THE STUDY AND WHAT WILL BE STUDIED?

We are interested in studying the processes involved in learning and memory. One factor that might influence learning and memory is the potential cause of outcomes. In this study, we will be investigating the role of causation in learning, memory, mood and well being.

HOW WOULD I BE INVOLVED IF I AGREED TO TAKE PART?

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 decide to take part you are still free to withdraw at any time and without giving a reason.

If you agree to take part, the experimenter will take some brief demographic information from you and you will be asked to complete a number of computer tasks and short questionnaires. Altogether this will last for approximately 30 minutes. You will then be paid for participation.

You will also be asked to exhale through a smokerlyzer to measure the amount of carbon monoxide in your breath, and to provide a saliva sample in order to measure levels of cotinine. These are widely used non-invasive methods of assessing how much people smoke.

CONFIDENTIALITY

Any information collected about you will be held in accordance with the 1998 Data Protection Act. All the information that is collected about you during the course of the research will be kept strictly confidential. Your results will have your name and any other details about you removed first so that you cannot be recognized from them.

If you require further information please ask Tom Freeman

Thank you for reading this leaflet and we hope that you will be able to take part in the study.

You do not have to take part in the study if you do not want to. If you decide to take part, you may withdraw at any time without having to give a reason.

All proposals for research involving human subjects are reviewed by an ethics committee before they can proceed. This proposal was reviewed by the UCL Psychology and Language Sciences committee for ethics in non-invasive research on healthy adults.

Appendix 8: Subjective Attentional Bias Questionnaire (Waters A., personal communication).

For each of the following items, please circle a number that best describes you.

- **In general, how often have you found your attention drawn to cigarettes?**

0	1	2	3	4
Not at all	A little bit	A moderate amount	A lot	An extreme amount

- **In general, how attractive have you found the sight of cigarettes?**

0	1	2	3	4
Not at all attractive	A little attractive	Moderately attractive	Very attractive	Extremely attractive

- **In general, how sensitive have you been to the smell of smoke?**

0	1	2	3	4
Not at all sensitive	A little sensitive	Moderately sensitive	Very sensitive	Extremely sensitive

- **In general, how attractive have you found the smell of smoke?**

0	1	2	3	4
Not at all attractive	A little attractive	Moderately attractive	Very attractive	Extremely attractive

- **In general, how often have you found yourself noticing people smoking?**

0	1	2	3	4
Not at all	A little bit	A moderate amount	A lot	An extreme amount

- **In general, how often have you found yourself staring at cigarettes and cigarette smoke?**

0	1	2	3	4
Not at all	A little bit	A moderate amount	A lot	An extreme amount

- **In general, how often have thoughts or images of smoking popped into you mind?**

0	1	2	3	4
Not at all	A little bit	A moderate amount	A lot	An extreme amount

- **In general, how attractive have thoughts or images of smoking been?**

0	1	2	3	4
Not at all attractive	A little attractive	Moderately attractive	Very attractive	Extremely attractive

Appendix 9: Ethical approval letter (chapter 5).

UCL RESEARCH ETHICS COMMITTEE
GRADUATE SCHOOL OFFICE

Professor Valerie Curran
Clinical Psychopharmacology Unit
1-19 Torrington Place
UCL

9 June 2011

Dear Professor Curran

Notification of Ethical Approval
Ethics Application: 2504/004: The role of dopamine in cognitive and subjective effects of short term tobacco abstinence

I am pleased to confirm that in my capacity as Chair of the UCL Research Ethics Committee I have approved your project for the duration of the study (i.e. until May 2015).

However, approval is subject to the following conditions:

1. You must seek Chair's approval for proposed amendments to the research for which this approval has been given. Ethical approval is specific to this project and must not be treated as applicable to research of a similar nature. Each research project is reviewed separately and if there are significant changes to the research protocol you should seek confirmation of continued ethical approval by completing the 'Amendment Approval Request Form'.

The form identified above can be accessed by logging on to the ethics website homepage: http://www.grad.ucl.ac.uk/ethics/ and clicking on the button marked 'Key Responsibilities of the Researcher Following Approval'.

2. It is your responsibility to report to the Committee any unanticipated problems or adverse events involving risks to participants or others. Both non-serious and serious adverse events must be reported.

   Reporting Non-Serious Adverse Events
   For non-serious adverse events you will need to inform Helen Dougal, Ethics Committee Administrator (ethics@ucl.ac.uk), within ten days of an adverse incident occurring and provide a full written report that should include any amendments to the participant information sheet and study protocol. The Chair or Vice-Chair of the Ethics Committee will confirm that the incident is non-serious and report to the Committee at the next meeting. The final view of the Committee will be communicated to you.

   Reporting Serious Adverse Events
   The Ethics Committee should be notified of all serious adverse events via the Ethics Committee Administrator immediately the incident occurs. Where the adverse incident is unexpected and serious, the Chair or Vice-Chair will decide whether the study should be terminated pending the opinion of an independent expert. The adverse event will be considered at the next Committee meeting and a decision will be made on the need to change the information leaflet and/or study protocol.

On completion of the research you must submit a brief report (a maximum of two sides of A4) of your findings/concluding comments to the Committee, which includes in particular issues relating to the ethical implications of the research.

With best wishes for the research.

Yours sincerely

[redacted]

Sir John Birch
Chair of the UCL Research Ethics Committee

Cc: Tom Freeman, Clinical Psychopharmacology Unit, UCL

Amendment Approval Request Form

1	**ID Number:** 2504/004	**Name and Address of Principal Investigator:** Prof. H. Valerie Curran Clinical Psychopharmacology Unit, Department of Clinical, Education and Health Psychology, UCL, Gower Street, London WC1E 6BT
2	**Project Title: The role of dopamine in cognitive and subjective effects of short term tobacco abstinence**	
3	**Information about the amendment:** (a) Is the amendment purely administrative? ☐ Yes ☒ No ☐ N/A (b) Has the Participant Information Sheet/Consent Form been changed as a result of the amendment? If yes, please enclose a copy. ☒ Yes ☐ No ☐ N/A	
4	**Summarise the issues contained in the amendment:** We would like to use an eye tracker to monitor participants' eye movements on two tasks. This is a non-invasive procedure in which a camera records eye movements whilst participants view a computer screen	
5	**Please give any other information you feel may be necessary:**	
	Signature of Principal Investigator: [redacted]	**Date of Submission:** 22/07/11

FOR OFFICE USE ONLY:

Amendments to the proposed protocol have been approved by the Research Ethics Committee.

Chair's Signature: [redacted] e: 18/8/2011

Please return completed form to:

Secretary of the UCL Research Ethics Committee
Graduate School, North Cloisters, Wilkins Building
Gower Street, London WC1E 6BT

Appendix 10: Information sheet for chapter 5.

Information Sheet for Participants in Research Studies

You will be given a copy of this information sheet.

Title of Project: **The role of dopamine in cognitive and subjective effects of short term tobacco abstinence**

This study has been approved by the UCL Research Ethics Committee (Project ID Number):

Name	Tom Freeman
Work Address	Clinical Psychopharmacology Unit Research Department of CEH Psychology University College London 1-19 Torrington Place WC1E 7HB
Contact Details	tom.freeman@ucl.ac.uk

We would like to invite Smokers aged 18-40 to participate in this research project.

Details of Study: We would like to invite you to participate in this research project. You should only participate if you want to; choosing not to take part will not disadvantage you in any way. Before you decide whether you want to take part, it is important for you to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or you would like more information.

This study is being conducted by researchers from the Clinical Psychopharmacology Unit.

Why are we doing this study?

Smoking is the leading cause of preventable death worldwide. Many smokers want to stop but a year after they try, only 5% are successful. Many relapses occur in the first few days after a target quit date. Previous research suggests that activity of a brain chemical called dopamine plays an

important role in the symptoms experienced when smokers deprive themselves of cigarettes. We wish to test a specific idea about how dopamine regulates thoughts and symptoms following short term (1-2 hour) abstinence from cigarettes. To do this, the study uses a single dose of a widely prescribed medication which affects dopamine activity in the brain. By taking part you will contribute to the scientific knowledge of tobacco addiction, an area that is vital to public health. If you would like to receive a brief report of the findings of this study when it is completed, please ask the investigator. Please note that this is **not** a smoking cessation study and we will not be investigating changes in, or aiming to influence your general smoking behaviour.

What will I have to do?

If you agree to participate in this study you will be asked to come to the Clinical Psychopharmacology Unit at a convenient time for you for two sessions a week apart. We will then assess your recent smoking behaviour by asking you to breathe through a smoke-analyser. After going through a medical checklist you will be given 2 pills to swallow. One will be either pramipexole or placebo. On one testing day you will receive pramipexole and on the other day you will receive placebo. In order for the experiment to be 'blind', you will not know which drug you have taken. When pramipexole is administered at higher doses it can cause nausea or sickness to occur. Based on previous research in humans this is unlikely to occur. However as a precaution you will swallow an additional pill (domperidone) that prevents nausea and sickness. You will then wait for 1 ½ hours before testing resumes, during which time you will fill in some questionnaires about your smoking behaviour and mood. Finally you will rate your desire to smoke and mood, complete a number of pen and paper and computer tasks that most people find fun and easy to do. In two of these computer tasks your eye movements will recorded using an eye tracker. Some of these tasks will involve exposure to items that remind you of smoking, such as images of cigarettes. In addition, some of these tasks will enable you to win extra money (up to £5 extra per testing session) that you will be paid at the end of the experiment (on top of the £45 you will be paid for taking part). You will then be permitted to smoke a cigarette and rate your mood and craving once more. The whole experiment should take around 3 hours on each day (6 hours in total).

What are these drugs and are they safe?

Pramipexole is a widely used drug in Parkinson's disease. Clinically, this drug is given at a dose of 1-6 mg per day. When this drug is administered repeatedly at these doses, side effects can occur including nausea, dizziness, and lowered blood pressure. However, you will receive only a single dose of 0.5 mg in order to avoid the occurrence of side effects. If you have a known hypersensitivity to the drug, are breastfeeding, or have decreased kidney function you should **not** participate in this experiment.

Domperidone is a widely used non-prescription drug used to treat sickness, nausea and stomach upsets in healthy adults and children. The standard dose for treating sickness and nausea in adults is 40mg 3 to 4 times daily. You will be given a single, lower dose of 30mg in order to prevent any sickness or nausea caused by pramixpexole. Adverse effects from taking this drug are highly unlikely, but include lowered sex drive in men, diarrhoea, rash and abnormal body movements. If you have a known hypersensitivity to the drug, are lactose intolerance, breastfeeding, or have decreased kidney or liver function you should **not** participate in this experiment.

For safety reasons you should **not** drive or operate machinery on the day of testing once the study has been completed.

How will my data be stored?

All information which is collected about you during the course of the research will be kept strictly confidential and will be securely stored electronically, using a numbered code so that you cannot be identified. Only researchers directly involved in the study will have access to the data. All data will be stored in accordance with the Data Protection Act 1998. The data will be used only for informing the research question in this study and the results of the research will be disseminated in peer-reviewed scientific journals, but you will in no way be identifiable from such publications.

Note – if you have any further questions regarding this study please do not hesitate to contact any of the researchers above.

This study has been approved by the UCL ethics committee

It is up to you to decide whether or not to take part. If you choose not to participate it will involve no penalty or loss of benefits to which you are otherwise entitled. 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 are still free to withdraw at any time and without giving a reason.

All data will be collected and stored in accordance with the Data Protection Act 1998.

Please discuss the information above with others if you wish or ask us if there is anything that is not clear or if you would like more information.

It is up to you to decide whether to take part or not; choosing not to take part will not disadvantage you in any way. If you do decide to take part you are still free to withdraw at any time and without giving a reason.

All data will be collected and stored in accordance with the Data Protection Act 1998.