Processes of Addiction and Recreational Use of Cocaine

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Overview

Research into cocaine use and abuse has overwhelmingly concentrated on processes and theories of addiction. This thesis is concerned with those theories and how stable recreational use of cocaine might be understood in the light of what is known about addiction.

Part 1 of the thesis reviews what is known about the long-term effects of chronic cocaine abuse. Developments in theories of addiction are discussed with reference to empirical studies assessing cognitive abilities, and to neuroimaging studies demonstrating neurological changes associated with substance abuse. The lack of research into social patterns of cocaine use is high-lighted. The review concludes that research into the effects of recreational cocaine is needed both to provide information to social users, but also to provide further insights into addiction processes.

Part 2 is the report of an empirical study into the effects of recreational cocaine use on mood and cognitive abilities. A mixed repeated measures and within subjects design is used to compare a group of 19 social cocaine users and a group of 19 controls on a range of cognitive abilities. Both groups were tested on two occasions. On the first occasion, cocaine users were tested shortly after self-administration of cocaine. The study provides tentative support for the hypothesis that controlled recreational cocaine use may lead to subtle impairments in response inhibition, and to increased sensitisation towards cocaine.

Part 3 is a critical appraisal of the process of conducting this research project. It includes a more personal reflection on my journey of learning both about the research process and about addiction and drug use.

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Part 1

Literature Review

Processes of Addiction and Recreational Use of Cocaine

Abstract

This paper reviews recent gains in knowledge of addiction, with particular reference to cocaine. It starts by considering the history and prevalence both of recreational cocaine and chronic abuse. It goes on to describe what is known about acute cocaine action in the human brain, before reviewing developments in theories and models of processes in addiction. It concludes by discussing how current models do not yet account for ongoing, stable and controlled social use of cocaine, and suggests that tools used to measure inhibitory control and incentive sensitisation might be used to assess these attributes in recreational cocaine users in order to gain insights into controlled use as well as to further understandings of addiction processes.

Introduction

Cocaine use is increasingly widespread in modern society (British Crime Survey, 2003). Although there is much research about the effects of chronic dependent use, there is very little published literature on the effects of occasional, or recreational, use of cocaine. Use of cocaine is widespread in Britain and growing, particularly among young people. A prohibitionist society, while not effectively preventing use of illegal substances, is an environment in which myths and misinformation are fostered. Given the prevalence of recreational cocaine use, it is important for us to understand its effects, both for educational purposes and informed choice, and for the light it may shed on

non-dependent use of psychoactive drugs. This thesis, therefore, focuses on the effects of recreational use of cocaine on mood and cognitive processes.

History of cocaine use

Cocaine is a drug obtained from the leaves of the coca plant, which grows in mountainous areas of South America. Coca leaves have been chewed and smoked for thousands of years by native populations but it was only during the 1880s that cocaine was isolated from the plant. Its most common form is a white crystalline salt, cocaine hydrochloride (See Figure 1), which is often seen as a powder and is usually ingested by insufflation or 'snorting' whereby it is absorbed through the nasal lining.

When snorted, cocaine is quick to take effect, and within a few minutes the user can feel euphoric, alert, more energetic, and with enhanced perceptions, so that sights, sounds and touch feel particularly vivid. The high from a single dose usually lasts between 15 to 40 minutes. If crack cocaine is smoked the effect is more intense but shorter, perhaps lasting from between 5 to 10 minutes.

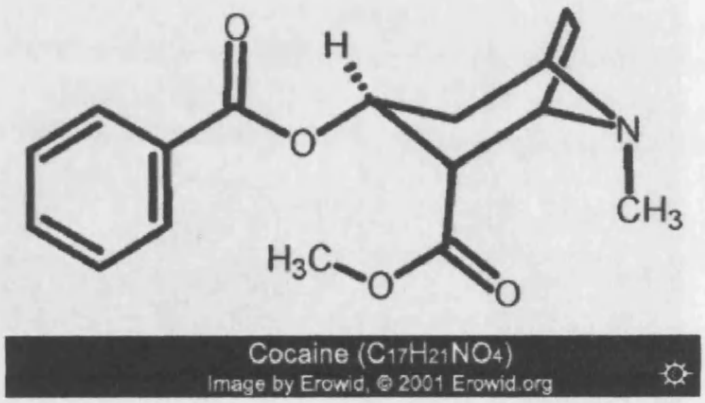

Figure 1. Chemical structure of cocaine.

During the late 19th and early 20th Century cocaine was used medicinally as an anaesthetic and a tonic. Some commercial products had cocaine added to them, for example the wine Vin Mariani which was praised by Pope Pius X and the Grand Rabbi of France for its 'life-giving properties'. Cocaine toothache drops were advertised not only for helping children with pain but for its ability to put children into a 'better mood' (Addiction Research Unit, University at Buffalo; see Figure 2).

1885 Advertisement for Cocaine Toothache Drops

Figure 2. Advertisment for cocaine drops for toothache.

By the early 20th Century concerns were being expressed about cocaine's potential to create dependency, particularly at the time of the Second World War. In 1916 an emergency law was enacted banning its possession and limiting its medical use.

Cocaine did not become widely used as a recreational drug until the 1970s. In the 1980s a new form of cocaine called 'freebase' or 'crack' was created by removing the chloride ion by 'washing' it with a solution of ammonia or bicarbonate of soda. This form is more easily vaporised and can therefore be smoked and absorbed more quickly via the lungs. It gives a more intense feeling of euphoria, which also lasts for a shorter time, and is more highly addictive.

Prevalence of cocaine use

Much of the information in this area comes from surveys commissioned and published by central government departments. The extent of drug use in the adult population is primarily measured by regular sweeps of the British Crime Survey (BCS; Condon &

Smith). The main findings from the BCS published in 2000 were that one third of those aged 16-59 had used an illegal drug, but in the younger age group of 16-29, half of the sample admitted to illegal drug use, 25% in the last year, with 16% in the last month. Cocaine use was reported by 5% of the sample overall, in the last year, a level similar to that of ecstasy use. However, among some geographical areas cocaine use was higher. For example, in affluent urban areas, such as London, cocaine use was reported by 11 % of the 16-29 year old age group. A report by the National Centre for Social Research (Boreham & McManus, 2004) presents data from a survey of over 10,000 school children aged between 11 and 15 conducted in 2003. One per cent of all children in this age group reported taking cocaine in the previous year.

Growth of use

Between 1994 and 2000, there was continued growth in cocaine use across all age groups, including 16-19 year-olds, where, between 1999 and 2000, use in last year increased from 1% to 5%. This is despite a fall in use of any drug in this age group between 1994 and 2000. In geographical terms, while use of cocaine was highest in London, its use was growing most rapidly in regional areas, especially in the North of England. The BCS (2000) reported a fall in amphetamine use by almost half in the same period, suggestive of the possibility that some people are switching from amphetamine to cocaine use. Use of ecstasy also started to fall slightly in 2003 (BCS, 2004). It may be that representations of ecstasy as dangerous and potentially lethal have been effective in reducing ecstasy use. However, it is possible that some young people have switched from ecstasy to cocaine as a drug of choice, as cocaine is seen as socially acceptable and less dangerous than other stimulants. Certainly, the 2003 BCS showed an increase in

cocaine use alongside a small reduction in ecstasy use. Cocaine is now the second most commonly used illicit drug in England and Wales, after cannabis (BCS, 2003/4).

Teenagers in Britain have one of the highest rates of illicit substance use in Europe (Swedish Council for Information in Alcohol and Other Drugs (SCIAOD), 2000), and an increase in the number of people trying cocaine may be part of a general cultural change whereby experimentation with illicit drugs has become normalised. There is evidence that culture of 'sensible' (i.e. occasional and controlled) drug use is increasingly the norm among young people (Parker, Williams & Aldridge, 2002)

Prevalence of problem drug use

The most recent estimate of problem drug use in the UK relates to 1996. Frischer et al,. (2001) estimated from their findings that there were 266,000 problem drug users in England, Scotland and Wales in 1996. Cocaine increased as a main drug of use in those seeking treatment from 4% in 1995 to 6 % in 2001 (Dept of Health, 2002).

Mentions of cocaine on the death certificate in drug-related deaths, although still comparatively low when compared to opiates, increased seven-fold between 1993 and 1999 (Corkery, 2000). However, although it is not possible to distinguish between cocaine and crack cocaine in drug-related deaths, the rise in death rate seems to have been related to the rise in use of crack cocaine, rather than cocaine powder. Thus in 2000 the increase in drug-related deaths involving cocaine mirrored the increase in crack cocaine seized (BCS, 2000).

Who uses cocaine?

Rates of use illicit drug use in general in Britain have traditionally been higher among young people, men, single people and frequent drinkers, while there is no significant variation associated with education or socio-economic status (Ramsay, Baker, Goulden et al., 2001). However the gender gap appears to be changing, and Sutherland & Shepherd (2001) found no gender difference on illicit drug use in the schools they sampled.

Consideration of the factors associated with illicit drug use gives some very general indicators of who might use cocaine. However, studies looking at factors associated with recreational drug use tend to lump illicit substances together (e.g. Coullthard, Farrell, Singleton et al., 2002; Sutherland & Shepherd, 2001; Wadsworth, Simpson, Moss et al., 2004). Although these studies give an indication of factors that make it more likely that particular individuals will take drugs, they do not tell us why people take specific drugs. What would be of interest are studies that enquire of individuals what factors led to their trying certain substances, what it is about the experience that leads them to continue to use, and what negative factors may be associated with drug use. Such understanding might lead to improved provision of education aimed at minimising risk of harm.

Action of cocaine

Acute action

The mesolimbic reward pathway

The nucleus accumbens (NAc) is an area of the brain that is key to the experience of pleasure and reward. It is the end of the mesolimbic reward pathway, which is hypothesised to be the 'pleasure centre' of the brain, a central pathway for reward and

reinforcement. It has been found to be activated by all types of reinforcing stimuli in animals and humans, for example, food, sex, and many drugs of abuse. Such stimuli produce increases in the amounts of the neurotransmitter dopamine released in many parts of the brain, and crucially, in terms of their pleasurable effects, in the NAc. When the mesolimbic pathway is stimulated, axons with terminals in the NAc release dopamine into the synaptic clefts, which are then received by neurons in the NAc thus activating the experience of pleasure (Stahl, 2000). Excess dopamine released into the synaptic cleft is reabsorbed by the pre-synaptic terminal.

Experimental evidence suggests that the greatest part of cocaine's effect on behavioural responses is produced via its effect on dopamine. Cocaine binds to dopamine transporters, thus inhibiting dopamine re-uptake and increasing the amount of dopamine available at the synapse (Figure 3.).

One of the areas in the brain that appears most affected by cocaine in acute administration is the ventral tegmental area (VTA). Axons from the VTA extend to the nucleus accumbens where cocaine binds with the dopamine transporter molecules, resulting in an increase in the amount of free dopamine available at the synapse to stimulate the receptor cells in the NAc. Studies using cocaine or cocaine analogues labelled with radioisotopes have also found high densities of cocaine binding to dopamine transporters in the caudate, putamen and nucleus accumbens in rats, monkeys and humans (e.g. Biegon et al., 1992; Staley, Basile, Flynn et al., 1994). These are all areas involved in the experience of pleasure and reinforcement. Horger, Valadez, Wellman et al., (1994) showed that cocaine can produce a 200% increase in extracellular dopamine in the NAc and the medial prefrontal cortex.

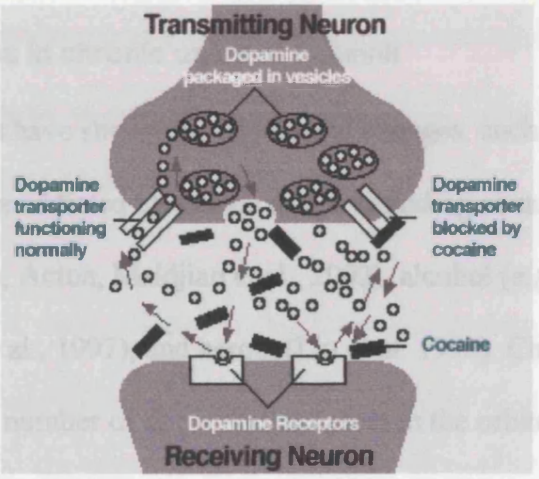

Figure 3. Cocaine blockade increases dopamine availability at D_2 receptors in the nucleus accumbens.

Acute action in the frontal cortex

There is evidence of increased concentration of dopamine in frontal regions in acute drug intoxication (Goeders and Smith, 1986). Acutely, cocaine also causes increased tissue levels of serotonin in the prefrontal cortex and hypothalamus (Yang, Gorman, Dunn, & Goeders, 1992), and chronically, in compensation, it causes an increase in the number of serotonin uptake sites in the prefrontal cortex. The vasoconstriction in the frontal lobes that is seen in the brains of chronic cocaine users, as well as in acute use (Madden & Powers, 1990; Kaufman, Levin, Ross et al., 1998) maybe in part be due to increased levels of serotonin, which is known to be a powerful vasoconstrictor. Pre-frontal activation, as seen in regional cerebral blood flow (rCBF) scans during acute intoxication, is associated with the subjective perception of intoxication or 'high', one of the reinforcing effects of the drug.

Long-term effects of cocaine use

Frontal lobe changes in chronic users of cocaine

Neuroimaging studies have shown morphological changes, such as volume loss, in the frontal lobes of people addicted to various drugs, including cocaine (Liu, Matochik & Cadet, 1998; Franklin, Acton, Maldjian et al., 2002), alcohol (e.g. Pfefferbaum, Sullivan, Mathalon et al., 1997), and heroin (Liu et al. 1998). Chronic use of cocaine results in a decreased number of dopamine receptors in the orbitofrontal cortex and the cingulate gyrus. Positron emission tomography (PET) studies have provided evidence for dysfunction of the orbito-frontal cortex (OFC) in cocaine-dependent individuals (London, Cascella, Wong et al., 1990).

There has been some debate about whether such changes *precede* drug use reflecting pre-morbid psychological characteristics that contribute to drug-experimentation or self-medication and are a vulnerability for drug abuse, or whether they are the *result* of long-term use. Evidence for the latter is provided by studies that show a correlation between degree of volume loss and years of cocaine use (Liu et al., 1998).

Prefrontal volume loss has been hypothesised by Volkow, Fowler & Wang (2003) to be a result of the downregulation of these areas in response to repeated elevations of synaptic dopamine levels. Volkow, Fowler, Wolf et al. (1991) have also found that, while acute use increases prefrontal cortical blood flow, there is a reduction in rCBF in the pre-frontal cortex to below baseline levels in chronic users who are abstaining. This is not as paradoxical as it might seem, as it has been hypothesised to reflect chronic vasospasm in cerebral arteries (Volkow, Mullani, Gould et al., 1988).

Addiction

In order to understand and explore the non-dependent use of cocaine it is necessary to understand the processes of addiction. I will therefore spend some time elucidating theories and concepts of addiction.

The term addiction is used widely in the literature despite the fact there is little consensus on what precisely it means. The Oxford English Dictionary defines the word 'addiction' as physical dependency on a particular substance. Until relatively recent years, addiction was thought to be the result of the highly pleasurable effects of a substance causing a person repeatedly to seek out the same experience until, over a period of time, tolerance develops. Tolerance results in withdrawal symptoms if the drug is not taken and it was once thought that this leads to an overwhelming urge to seek out and consume more of the drug (Dews, 1998). Cocaine was not initially considered a drug of addiction under these terms because it appeared to lack distinct physical withdrawal symptoms. However, chronic use can result in a strong psychological dependency (Gawin & Ellinwood, 1989). There is a vast and growing body of evidence of brain changes in chronic use (e.g. Volkow, Fowler and Wang, 2003). Further, withdrawal after heavy use can result in severe depressive symptoms (Gawin & Kleber, 1986; Markou & Koob, 1991; APA, 1994) due to downregulation of dopamine and serotonin receptors in the mesolimbic system (Gawin & Ellinwood, 1989). Thus, the distinction between psychological and physical dependence may not be as clear as was once thought.

Stahl (2000) defines addiction behaviourally, as a "pattern of drug abuse characterized by overwhelming involvement with the use of a drug (compulsive use) and with the

securing of its supply and by a high tendency to relapse after discontinuation." He distinguishes the terms 'addiction' and 'dependence', which he defines as a physiological state of adaptation necessitating continued use of a substance to prevent the appearance of withdrawal symptoms, within which he includes both the psychological and physical.

The Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV, American Psychiatric Association, 1994) does not use the term addiction, and instead has two separate diagnostic categories. The first of these is 'substance dependence', and the second 'substance abuse'.

Criteria for substance dependence are:

> *"A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:*
>
> *(1) tolerance [...]*
>
> *(2) withdrawal [...]*
>
> *(3) the substance is often taken in larger amounts or over a longer period than was intended*
>
> *(4) there is a persistent desire or unsuccessful efforts to cut down or control substance use*
>
> *(5) a great deal of time is spent in activities necessary to obtain the substance [...], use the substance [...] or recover from its effects*
>
> *(6) important social, occupational, or recreational activities are given up or reduced because of substance use*

(7) *the substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance [...].*"

APA, 2000

Although the explicit tolerance and withdrawal items are not strictly necessary for a diagnosis, their presence may seem to be implied by the other items in any case.

If the criteria for substance dependence are not met, the diagnostic category 'substance abuse' may be used if there is:

"A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one (or more) of the following, occurring within a 12-month period:

(1) recurrent substance use resulting in a failure to fulfil major role obligations at work, school, or home [...]

(2) recurrent substance use in situations in which it is physically hazardous

(3) recurrent substance-related legal problems

(4) continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance"

This definition makes no assumptions about the presence of withdrawal symptoms, tolerance or subjective experience of the 'abuser'. It is an atheoretical diagnostic category. So recreational use of a drug, which does not lead to recurrent problems in the individual's life would not be seen as abuse. Where the term 'addiction' is used in this

thesis, it will be with the implication of dependence (whether physical or psychological), compulsion and craving.

Central questions for scientists involved in addiction research are:

- How does dependence develop?
- Which brain processes are involved?
- How are abuse and dependence to be understood in terms of psychological concepts?

In an attempt to answer some of these questions, I will now give a brief overview of developments in our understanding of addiction. I will go on to consider neurological evidence, gained with the development of neuroimaging, and experimental evidence that has led to current understanding of contemporary models of addiction.

Developments in understanding of addiction

Hedonic theories

Early models of addiction tended to focus only on the reward circuitry of the brain, and described models of addiction in terms of the pleasure of drug use being so great that once it has been taken, the individual compulsively seeks to repeat the experience. Hedonic theorists such as Gawin and Ellinwood (1989) explained addiction in terms of drug-taking being reinforced by intense euphoria, and the contrast with the dysphoric state in abstinence producing severe craving. According to this theory, as a person becomes tolerant to pleasurable effects, the lack of positive reinforcement would eventually lead to extinction of drug-taking if it were not for the negative reinforcement

of the alleviation of withdrawal dysphoria. However, experiences of pleasure and dysphoria do not seem to be the only factors in the reinforcement of stimulant consumption, particularly as compulsive self-administration is seen in addicted individuals even when the experience is no longer perceived as a pleasurable one and may even be aversive (Fischman, Schuster, Javaid et al., 1985). Further, the experience of withdrawal symptoms are most intense within a few day of stopping the drug, yet the craving and susceptibility to reinstatement of drug taking continue for weeks and months ahead (Volkow & Fowler, 2000).

The hedonic theory has another flaw, which is that the pleasurable effects of substances can be experienced by novices as well as by chronic users, and, contrary to popular beliefs, addiction does not occur after a single use, even with the most addictive substances (though there is considerable variation in the rate at which individual animals and humans find cocaine rewarding – e.g. Deneau, Yanagita, & Seevers, 1969; Davidson, Finch & Schenk, 1993; both cited in Schenk & Partridge, 1997).

Pleasure and reward circuits of the brain are a necessary and major part of the addictive process. This is because of their key role in determining which stimuli are unconditionally reinforcing and liable to contribute to repeated self-administration. However, they are not sufficient to explain addiction.

The role of environmental cues

Drug dependence involves complex interactions between biological, psychological and environmental factors. Empirical studies in humans and animals have clearly shown the importance of environmental conditions for cocaine's reinforcing effects. Its

behavioural effects interact with context, and contextual cues associated with drug-taking. Context is crucial in determining the strength and frequency of cravings. Leshner (1998) has given the example of US veterans returning from Vietnam addicted to heroin; they were relatively easy to treat and to keep from relapsing because the environment they returned to had very little in common with that in which they developed their addiction. This is in contrast to addiction treatments generally, which have poor outcomes and high relapse rates (Curran & Drummond, 2005) when patients return to the environments in which their addictions began and were continued.

By what mechanisms do environmental cues exert such a powerful effect? How do cues interact with psychological and neurological processes involved in the craving and compulsivity that characterise addictions?

Incentive sensitisation

Schenk & Partridge (1997) in their paper on sensitisation and tolerance, noted that repeated administration of stimulants *increases* the ability of subsequent exposures to act as positive reinforcers, and that after a history of repeated prior exposure, lower doses than those used initially were capable of maintaining self-administration (e.g. Woolverton, Cervo, & Johanson, 1984; cited in Schenk and Partridge, 1997). How does the development of increased reinforcement potency (sensitisation) at the same time as tolerance to drug effects make sense? Schenk and Partridge suggested that the phenomena both occur but in different phases of the process of drug-taking, affecting separate aspects of the phenomenon of reward. They suggested that once an individual is sensitised, administration of cocaine can elicit 'cocaine-induced craving', leading to compulsive bingeing, and that through associative processes, cocaine-related cues also

take on the property of eliciting appetitive behaviours. Tolerance, on the other hand, is associated with the need for increased doses to produce the same conscious physical effects of drug consumption. Thus each of these phenomenon can both have an impact on the process of addiction.

Parsing of reward

Berridge and Robinson (2003) have made a detailed analysis of the psychological components of reward. They argue, with support from much empirical neurological evidence, that the concept of reward is comprised of three components: (1) learning, (2) pleasure and (3) motivation. Each of these components can be further parsed into explicit (conscious) and implicit (unconscious) processes.

1. Learning

   Unconscious memory includes those resulting from associative conditioning. Craving in drug use involves conditioned response learning and procedural memory, as well as conscious desire and cognitive imaging. Drug use can also be viewed as a habit, or action tendency. Both craving and habitual responding are powerfully affected by discriminative stimuli, i.e. environmental cues.

2. Pleasure

   The affect component of reward – the experience of pleasure – is located neurologically in the NAc as has been noted above.

3. Motivation (or wanting) is closely related to liking, but dissociable from it. This dissociation has been demonstrated in the laboratory using conditioned incentive

experiments (Robinson & Berridge, 2003; Wyvell & Berridge, 2000). The unconscious element of wanting is known as incentive salience, a concept first introduced into addiction theorising by Robinson and Berridge (1993). Incentive salience is an attribution that transforms sensory information about rewards and their cues (conditioned stimuli) into incentives to behavioural responses, that is they elicit appetitive approach (Berridge and Robinson, 2003). Drug cues (conditioned stimuli) can reinstate drug-taking behaviour by eliciting conscious wanting (craving) and/or unconscious wanting (incentive motivation). Thus cues trigger explicit and implicit *memory* associated with *liking* of a drug, and its *incentive salience*, i.e. the degree to which it motivates appetitive behaviour.

Robinson and Berridge have facilitated the understanding of the role of craving in drug dependence. They hypothesise that compulsive appetitive behaviour in cocaine addiction is the result of cocaine's ability to increase the *incentive salience* of cocaine cues when it acts on the NAc, rather than its facilitation of the experience of hedonic reward (or pleasure) (Berridge and Robinson, 1998). This hypothesis has been supported by Wyvell & Berridge (2000) who have shown that amphetamine (a stimulant with a similar neurological effect to cocaine) injected into the NAc increases motivational behaviours in rats in the absence of hedonic enhancement. This effect is particularly characteristic of cocaine, as similar injections of opiates to the same area has been found simply to enhance the experience of pleasure (Dickinson & Dawson, 1987; cited in Wyvell & Berridge, 2000). There is a positive relationship between a drug's ability to reinstate drug-taking behaviour after abstinence and ability to induce psychomotor sensitisation (De Vries, Schofflemeer, Binnedake, Mulder, 1998; De

Vries, Schoffelmeer, Binnedake, Raaso et al., 2002; De Vries, Schoffelmeer, Binnedake, Vanderschuren, 1999;). Therefore, Robinson and Berridge (1993) hypothesise that changes in the NAc that relate to psychomotor sensitisation may also contribute to the incentive motivational effects of the drugs.

Impulsivity and involvement of the prefrontal cortex

Clinical literature suggests that cocaine addiction is the result of a progression from casual, recreational use escalating to compulsive, uncontrolled bingeing, interspersed with periods of abstinence. Indeed, compulsive use, as noted above, is a crucial characteristic of all addictions. In cocaine addiction, the compulsive behaviour seems to be partly an effect of increased incentive salience of drug. However, in recent years, developments in technology, particularly in scanning and imagery, have led to a wealth of evidence pointing to the importance of other areas of the brain in the process of addiction besides the reward pathways of the mesolimbic system. Several theorists have put forward changes in the pre-frontal cortex as an important element of the addictive process. Their models not only take into account the neuroimaging evidence for frontal lobe involvement, but also the perceived loss of control and compulsive intake that seem to characterise drug taking. Theorising of addiction has become concomitantly more complex as it has sought to incorporate this emerging evidence.

Role of the Prefrontal Cortex

The prefrontal cortex is known to mediate a range of cognitive functions that may be impaired through chronic drug use. It is involved in decision making, working memory,

drive, motivation and inhibitory control (e.g. Royall, Leuterback, Cummings et al., 2002).

The orbito-frontal cortex (OFC) is a region of the prefrontal cortex that processes the integration of reward, emotion and decision making – all essential components of motivation-directed behaviour (Bechara, Damasio & Damasio, 2000; Rolls, 2000). It receives inputs from all the sensory areas and is linked to other prefrontal areas and the mesolimbic dopamine system.

Lesions in the PFC have been associated with impairments in inhibitory control, deficits in working memory and a tendency to respond for immediate, small rewards over delayed, bigger ones (Damasio, 1996) in other words, deficits in executive control.

Experimental evidence for executive impairments in cocaine addiction

Several researchers have found increased perseverative errors on the Wisconsin card sorting task in chronic cocaine users (indicating problems with inhibitory control), as well as impairments in delayed recall, and problems with maintaining attention and concentration (e.g. O'Malley, Adamse, Heaton, et al., 1992; Beatty, Katzung, Moreland et al., 1995; Rosselli & Ardila, 1996). These are all reminiscent of frontal lobe syndrome.

Fillmore & Rush (2002) examined general ability to inhibit pre-potent responses (i.e. not simply towards drugs or drug cues) in chronic cocaine users using the 'stop-signal' paradigm. In their task, participants were asked to respond to go-signals except when informed to inhibit response by a competing stop-signal. They found that cocaine users

had impaired ability to inhibit responses compared to controls. This is in direct contrast to studies showing enhancement of response inhibition on stop-signal tasks under acute influence of stimulants (Feola, de Wit & Richards, 2000; Tannock, Schachar & Logan, 1995). It it possible that a preceding deficit is a vulnerability for cocaine use, or that cocaine, which enhances response inhibition in acute use, leads to impairment in chronic use after repeated flooding and depletion of dopamine in the prefrontal cortex. In the context of evidence reviewed above from Volkow and colleagues, it is likely that there is a bi-directional effect, with deficits in response inhibition being a vulnerabity for cocaine use, and chronic use leading to further deficits in ability to inhibit the impulse to take cocaine, resulting in the comupulsive use seen in addiction.

Functional imaging and drug abuse

London, Ernst, Grant et al. (2000) have suggested that "addictive disorders reflect a dysregulation of the ability to evaluate potential reward against harm from drug self-administration", in other words, a dysregulation of motivation-directed behaviour due to impairment in decision making. According to London et al. (2000), one component of motivated behaviour is expectancy, based on predictions of reward, another is compulsive drive (incentive motivation), which is linked to craving, and lastly there is decision making, based on a considered balance between expectation of rewards and losses. London et al. have considered imaging evidence for involvement of each of these components in chronic cocaine users (London, et al., 2000). They found evidence for impairments in decision-making that appeared to be related to the functioning of the OFC.

Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies have also provided evidence for activation of the OFC and its connections accompanying self-reported cocaine craving in experienced users (Childress, Ehrman, Rohsenow et al., 1992; Grant, London, Newlin et al., 1996.) Furthermore, self-reports of craving were positively correlated with metabolic increases in the dorsolateral prefrontal cortex and amygdala, consistent with the function of the OFC in integrating information from the senses, episodic memory (dorsolateral PFC) and emotional coding (amygdala).

When craving was instigated by direct adminstration of a priming dose of cocaine to dependent participants in an fMRI study, it was associated with activation of various cerebral regions including the NAc, the amygdala and parts of the lateral prefrontal cortex (Breiter, Gollub, Weisskoff et al., 1997). The NAc was not shown to be activated in cue-induced craving, only in priming-induced craving. This difference could be due to the fact that cocaine-induced craving was associated with activation of the unconscious incentive motivation system (of the NAc), whereas cue-induced craving had a weaker effect on incentive motivation, but a strong effect on conscious craving associated with activation of the OFC. This idea is supported by the fact that even in the absence of acute administration, cue-induced craving in cocaine abusers is sufficient to activate frontolimbic circuits, as observed by various neuroimaging scanning techniques (Maas, Lukas, Kaufman et al., 1998; Garavan, Pankiewicz, Bloom et al., 2000; Wexler, Gottschalk, Fulbright et al., 2001).

Cocaine is not the only drug of abuse to have chronic effects on frontal regions of the cortex. Chronic exposure to cannabinoids, even when intermittent, can lead to reduced

PFC dopamine transmission (Jentsch, Verrico, Le & Roth, 1998). Chronic heavy use of phencyclidine (PCP), opiates, cannabis and alcohol can produce profound disturbances in learning, working memory, and attention and inhibitory control, even after discontinuation of use. (Hooker & Jones, 1987; Cosgrove and Newell, 1991; Fletcher, Page, Francis et al. 1996; Pope & Yurgelun-Todd, 1996; Rogers, Everitt, Baldacchino et al., 1999). These changes are associated with disturbances in the dopamine circuits in frontal regions. Such evidence suggests that the frontal lobes are involved in addictive processes in general, not just in the abuse of cocaine.

Impulsiveness and aggression as factors in drug use

Volkow and colleagues have described drug addiction as "a disorder that results from the complex interplay of chronic drug administration and genetic and environmental variables." (Volkow, Fowler, Wang et al., 2002).

Impulsivity and aggression are associated with the use of most psychoactive drugs. Cocaine has been related to aggression and violence in the epidemiological literature. (e.g. Chermack & Blow, 2002). Hoaken & Stewart (2003) have suggested this is because drug users are characterologically more likely to try new experiences, impulsivity and aggressive drive being associated with risk taking. It is known that children with externalising problems, including aggressive behaviour and conduct disorder, are more likely to have antisocial personality disorder and to become drug users in adulthood (Kellam, Ialongo, Brown et al., 1989). But could aggression also be the result of acute effects of the drug, or chronic neurotoxic effects, or of withdrawal during abstinence? Murray, Patkar, Mannelli et al. (2003) suggest it could. They found a positive relationship between both aggression and impulsivity with severity of cocaine

use. Moeller, Dougherty, Barratt, et al. (2002) also found an association between chronic cocaine use and impulsivity that was independent of antisocial personality disorder or aggression suggesting that these two characteristics are not necessarily linked.

It is possible there is a bi-directional effect with aggression and impulsivity being predisposing factors associated with drug use, and drug use exacerbating aggression and problems with inhibitory control via frontal lobe damage.

Theoretical integration of prefrontal deficits into processes of addiction

Inhibitory control

Jentsch & Taylor (1999) hypothesised that problems with inhibitory control, due to frontal lobe impairment, were an essential part of addiction. They postulated the existence of an inhibitory control mechanism by which higher mammals can suppress rapid conditioned responses and reflexes to pre-potent responses in order that planned behaviour, driven by slower cognitive processes, can take place. The decoding of the reinforcement value of previously neutral stimuli by learning their association with primary reinforcers, involves not only rapid learning but also rapid relearning and alteration of responses when reinforcement contingencies change (Rolls, 2000). Lesions to the ventromedial (prelimbic) frontal cortex, which projects almost exclusively to the NAc, and is intimately connected with the amygdala, result in impaired extinction of learned operant responding, leading to a continuation of inappropriate responding to no-longer rewarded stimuli (Jones & Mishkin, 1972; cited in Rolls, 2000). This is highly

significant when we consider that addicts' responses to drug cues can fail to extinguish even after many years or even decades of abstinence.

Volkow, Fowler and Wang's (2003) model

One of the most recent models to integrate the role of the frontal lobes in the process of addiction is that of Volkow, Fowler and Wang (2003). Volkow and colleagues have reviewed numerous brain imaging studies and have found contrasting acute and chronic effects of addictive drugs. For example, in one of their own neuroimaging studies (Volkow et al., 2002) they found that while levels of synaptic dopamine were increased after acute administration of cocaine-analogous stimulant, there was a marked *decrease* in available dopamine in chronic users, which also continued long after their detoxification.

In a healthy person, acute intoxication is thought to involve the activation of several parts of the brain involved with reward, memory, drive (or motivation) and control. A visual representation of the model is presented in Figure 4.

Experience of reward is mediated by the nucleus accumbens (NAc) and the ventral pallidum; motivation is mediated by the OFC (and the subcallosum); memory by the amygdala and hippocampus; and executive control is located in the PFC and the anterior cingulate gyrus.

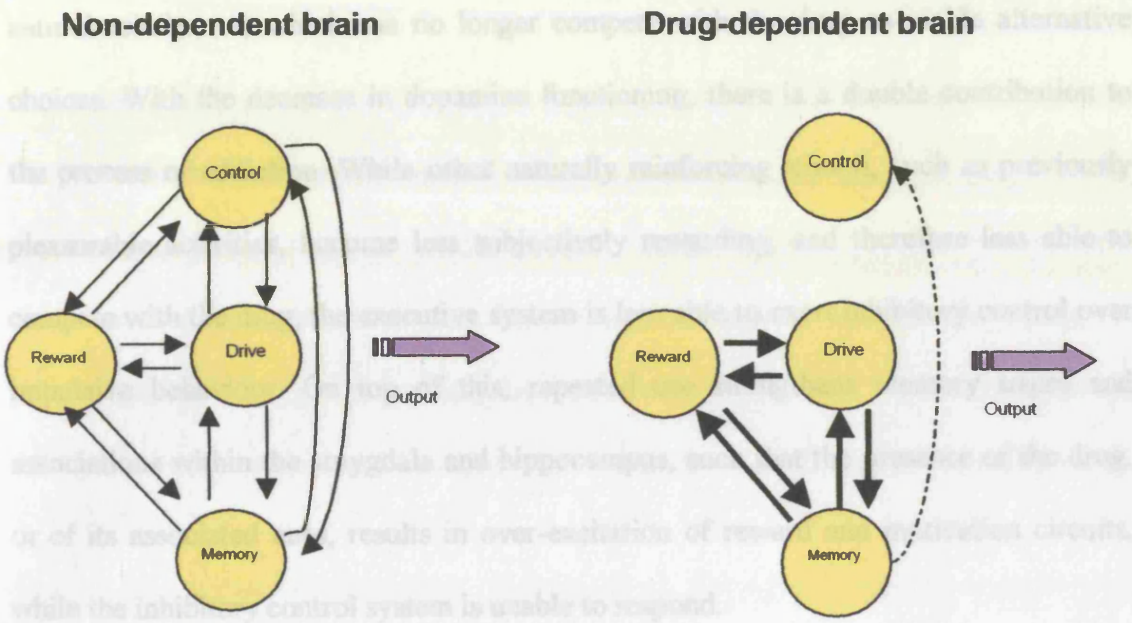

Figure 4. Volkow et al.'s Model of Addiction showing strengthened neural networks involving reward drive and memory, at the same time as executive control becomes weakened.

On withdrawal there is initially a temporary decrease in dopamine availability to below baseline levels. With chronic use the baseline level of dopamine itself actually decreases. This is hypothesised to be due to the downregulation of dopamine receptors in reaction to the repeated increase of available dopamine (Volkow et al., 2003).

The lowered baseline of dopamine functioning with chronic use results in a decrease in the sensitivity of the NAc to natural reinforcers. This contributes to the need to take increasing doses of the drug in order to get a similar effect (tolerance). Impairment in PFC functioning leads to two main effects. Firstly, there is disruption of inhibitory control processes so that behaviour becomes more impulsive and immediate rewards are valued/sought out over long-term rewards. Secondly, there is an increase in the attribution of salience of the drug, so that it becomes more attention-grabbing than other

natural reinforcers, which can no longer compete with the drug as viable alternative choices. With the decrease in dopamine functioning, there is a double contribution to the process of addiction. While other naturally reinforcing stimuli, such as previously pleasurable activities, become less subjectively rewarding, and therefore less able to compete with the drug, the executive system is less able to exert inhibitory control over impulsive behaviour. On top of this, repeated use strengthens memory traces and associations within the amygdala and hippocampus, such that the presence of the drug, or of its associated cues, results in over-excitation of reward and motivation circuits, while the inhibitory control system is unable to respond.

Measuring inhibitory control

The most common paradigm employed for measuring impulsivity is that of response inhibition tasks (Gondo, Shimonaka, Senda et al., 2000). One that has already been mentioned above is the 'stop-signal' paradigm, in which participants are required to respond positively to specific stimuli, but not to respond to the same stimuli in the presence of a stop signal. Such tasks, therefore, involve competing perceptual stimuli. As has been stated, Fillmore & Rush (2002), using a 'stop-signal' task, found chronic cocaine users to have impaired inhibitory control. Another method, is the occulomotor task used by Powell, Dawkins & Davis (2002), in which participants were required to inhibit reflexive saccadic eye movements towards visual stimuli associated with smoking. Those addicted to smoking but abstinent had poorer ability to inhibit reflexive eye movments towards the stimuli than both non-smokers and smokers who had just had a cigarette.

More commonly used, are 'go/ no-go' tasks in which participants are required to respond positively to specific stimuli using computer keys or digital response boxes, and then, in further trials, to inhibit responses to stimuli that previously required a response. Several studies have used this paradigm to explore which brain regions are involved in inhibiting pre-potent impulses to respond (e.g. Casey, Tainor, Orendi et al., 1997) all of which comfirm the the prefrontal cortex is the dominant area involved.

Measuring incentive motivation

Incentive motivation has generally been measured with the use of attentional bias tasks. The Stroop test in which participants are required to respond to the colour of presented words while attempting to ignore their semantic content has been used extensively (e.g. Sharma, Albery & Cook, 2001; Franken, Kroon, Wiers et al., 2000; Waters & Feyerabend, 2000). Colour responses are slower for words semantically salient for the participant. However, MacLeod (1991) has brought attention to the fact that it is unclear whether biases in Stroop tasks are due to interference activities in stimulus selection, or on response selection. In addition, as Jones, Jones, Smith et al. (2002) have commented, Stroop tasks are necessarily limited to word stimuli, when in many cases pictorial stimuli would be richer and more ecologically valid. The dot probe paradigm is one which overcomes both of these drawbacks. Although it can be used with words, the method lends itself to the use of pictures as stimuli. Two pictures are typically displayed briefly on a computer screen side by side, and are replaced by a single dotprobe in line with one of the pictures. Participants are required to respond to the probe as quickly as possible. Response times are faster to words or pictures that are particularly salient to the participant. The dot probe task has successfully been used to measure incentive

motivation in opiate dependence (Lubman, Peters, Mogg et al., 2000), recreational cannabis users (Field, Mogg & Bradley, 2004) and nicotine addiction (Bradley, Mogg, Wright et al., 2003; Bradley, Field, Mogg et al., 2004).

Recreational Use

Very little research on recreational use of cocaine has been published. Recreational use of some other illicit drugs has been less neglected. For example, the mass of research into the effects of MDMA ('ecstasy') (e.g. Curran, 2000; Morgan, 2000) was driven by findings of neurotoxicity in animals. There has been some research into recreational use of cannabis (e.g. Solowij, 1998; Field et al., 2003), ketamine (Curran & Morgan, 2000) and alcohol. Bauer & Cox (1998) found attentional bias on the Stroop task in non-dependent alcohol users. If attentional bias is a measure of incentive motivation, then this suggests that increased incentive motivation can be detectable in substance use in the absence of frank addiction.

Bradberry (2000) has investigated a model of 'recreational' use of cocaine in rhesus monkeys. Small doses, analogous to the amount human social cocaine users might take, where administered to the monkeys in weekly sessions. Extracellular dopamine levels were then measured using brain probes. Bradberry found that a single low dose of cocaine was followed by reduced responses to a similar dose later in the same session, suggestive of acute tolerance. He also found progressively higher levels of dopamine were elicited as the weeks progressed, indicating that a process of sensitisation was taking place. However, this was a measure of physiological sensitisation rather than behavioural sensitisation. He found that even a single low dose of cocaine reduced the brain's response to an identical dose of the drug taken later in the same day. Conversely,

weekly exposure to low doses of cocaine made the monkeys' brains progressively more sensitive to the drug.

There are no theoretical models of the recreational use of cocaine. The effects and processes of regular non-dependent use may be somewhere between the two extremes of Volkow et al.'s model. If so, there should be some increase in salience attribution to the drug and its cues, and there should be some decrease in inhibitory control in recreational cocaine users. Incentive motivation and response inhibition have never been measured in non-dependent cocaine users. However, information about the effects of recreational cocaine use would be useful not only because users can be more informed about the benefits and risks of taking cocaine, but it might also provide insights into the process of addiction itself.

References

American Psychiatric Association (1994). *Diagnostic and Statistical Manual of Mental Disorders, 4th ed.* Washington, DC: APA.

Bauer, D. & Cox, W. M. (1998). Alcohol-related words are distracting to both alcohol abusers and non-abusers in the Stroop colour-naming task. *Addiction, 93,* 1539-1542.

Beatty, W. W., Katzung, V. M., Moreland V. J. & Nixon, S. J. (1995). Neuropsychological performance of recently abstinent alcoholics and cocaine abusers. *Drug and Alcohol Dependence, 37,* 247-253.

Becchara, A., Damasio, H. & Damasio, A. R. (2000). Emotion, decision making, and the orbitofrontal cortex. *Cerebral Cortex, 10,* 295-307.

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

Berridge, K. C. & Robinson, T. E. (2003). Parsing reward. *Trends in neuroscience, 26,* (9) 507-513.

Biegon, A., Dillon, K., Volkow, N. D., Hitzemann, R. J., Fowler, J. S. & Wolf, A. P.(1992). Quantitative autoradiography of cocaine binding sites in human brain postmortem. *Synapse, 10,* 126-131.

Boreham, R. & McManus, S. (2004). *Young people in England in 2002: summary of key findings.* National Centre for Social Research & the National Foundation for Educational Research.

Bradberry, C.W. (2000). Acute and chronic dopamine dynamics in a nonhuman primate model of recreational cocaine use. *Journal of Neuroscience, 20,* 7109-7115.

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,* 29-36.

Bradley, B., Mogg, K., Wright, T. & Field, M. (2003). Attentional bias in drug dependence: vigilance for cigarette-related cues in smokers. *Psychology of Addictive Behaviors, 17,* 66-72.

Breiter, H. C., Gollub, R. L., Weisskoff, R. M., Kennedy, D. N., Makris, N., Berke, J. D., Goodman, J. M., Kantor, H., Gastfriend, D. R., Riorden, J. P., Mathew, R. T., Rosen, B. R. & Hyman, S. E. (1997). Acute effects of cocaine on human brain activity and emotion. *Neuron, 19,* 591-611.

Casey, B. J., Trainor, R. J., Orendi, J. L., Schubert, A. B., Nystron, L. E., Giedd, J. N., Castellanos, F. X., Haxby, J. V. & noll, D. C. (1997). A developmental functional MRI study of pre-frontal activation during performance of a go-no-go task. *Journal of Cognitive Neuroscience, 9,* 835-847.

Chermack, S. T. & Blow, F. C. (2002). Violence among individuals in substance abuse treatment: the role of alcohol and cocaine consumption. *Drug and Alcohol Dependence, 66,* (1) 29 - 37.

Childress, A. R., Ehrman, R., Rohsenow, D. J., Robbins, S. J. & O'Brien, C. P. (1992). Classically conditioned factors in drug dependence. In: *Substance abuse. A comprehensive textbook, 2nd edn.* (Eds: Lowinson JH, Ruiz P, Millman RB, Langrod JG) pp. 56-69. Baltimore, MD: Williams & Wilkins.

Corkery, J. (2000). Snowed under. Is it the real thing? *Druglink,* May/June, 12-15.

Cosgrove, J. & Newell, T. G. (1991). Recovery of neuropsychological functions during reduction in use of phencyclidine. *Journal of Clinical Psychology, 47,* 159-169.

Coulthard, M., Farrell, M., Singleton, N. & Meltzer, H. (2002). *Tabacco, alcohol and drug use and mental health.* London: HMSO.

Curran, H. V. (2000). Is MDMA ('ecstasy') neurotoxic in humans? An overview of evidence and of methodological problems in research. *Neuropsychobiology, 42,* 34-41.

Curran, H.V. & Drummond, C. (2005). State of science review: psychological treatments for substance misuse and dependence. *Foresight Brain Science and Addiction to Drugs Review.* London: HMSO.

Curran H.V. & Morgan C. (2000). Cognitive, dissociative and psychotogenic effects of ketamine in recreational users on the night of drug use and three days later. *Addiction, 95,* 575-590.

Damasio, A. R. (1996). The somatic marker hypothesis and the possible functions of the prefrontal cortex. *Philosophical Transactions: Biological Sciences, 351,* 1413-1420.

Davidson, E. S., Finch, J. F. & Schenk, S. (1993). Variability in subjective responses to cocaine: initial experiences of college students. *Addictive Behavior, 18,* 445-453.

De Vries, T. J., Schoffelmeer, A. N. M., Binnekade, R., Mulder, A. H. & Vanderschuren, L. J. (1998). Drug-induced reinstatement of heroin- and cocaine-seeking behaviour following long-term extinction is associated with expression of behavioural sensitization. *European Journal of Neuroscience, 10,* 3565-71.

De Vries, T. J., Schoffelmeer, A. N. M., Binnekade, R., Raaso, H. & Vanderschuren, L. J. (2002). Relapse to cocaine- and heroin-seeking behavior mediated by dopamine D2 receptors is time-dependent and associated with behavioural sensitization. *Neuropsychopharmacology, 26,* 18-26.

De Vries, T. J., Schoffelmeer, A. N. M., Binnekade, R. & Vanderschuren, L. (1999). Dopaminergic mechanisms mediating the incentive to seek cocaine and heroin following long-term withdrawal of IV drug self-administration. *Psychopharmacology 143,* 254-260.

Deneau, G., Yanagita, T. & Seevers, M. H. (1969). Self-administration of psychoactive substances by the monkey: a measure of psychological dependence. *Psychopharmacology, 16,* 30-48.

Department of Health (2002). *Statistical Bulletin: Statistics from the regional drug misuse database for six months ending March 2001.* Bulletin 07. Department of Health, Office of National Statistics: London.

Dews, P. (1998). Forward. In: *Cocaine Abuse: Behavior, Pharmacology, and Clinical Applications*. Edited by S.T. Higgins & JL Katz. Academic Press: San Diego.

Dickinson, A. & Dawson, F. R. (1987). Pavlovian processes in the motivational control of instrumental performance. *Quarterly Journal of Experimental Psychology B, 39,* 201-213.

Feola, T.W., de Wit, H. & Richards, J. B. (2000). Effects of d-amphetamine and alcohol on a measure of behavioral inhibition in rats. *Behavioral Neuroscience, 114,* 838-848.

Field, M., Mogg, K. & Bradley, B. P. (2004). Cognitive bias and drug craving in recreational cannabis users. *Drug and Alcohol Dependence, 74,* 105-111.

Fillmore, M. T. & Rush, C. R. (2002). Impaired inhibitory control of behavior in chronic cocaine users. *Drug and Alcohol Dependence, 66,* 265-273.

Fischman, M. W., Schuster, C. R., Javaid, I., Hatano, Y. & Davis, J. (1985). Acute tolerance development to the cardiovascular and subjective effects of cocaine. *Journal of Pharmacological and Experimental Therapies, 235,* 677-682.

Fletcher, J. M., Page, J B., Francis, D. J. Copeland, K., Naus, M. J., Davis, C. M., Morris, R., Krauskopf, D. & Saltz, P. (1996). Cognitive correlates of long-term cannabis use in Costa Rican men. *Archives of General Psychiatry, 53,* 1051-1057.

Franken, I. H. A., Kroon, L. Y., Wiers, R. W. & Jansen, A. (2000). Selective cognitive processing of drug cues in heroin dependence. *Journal of Psychopharmacology, 14,* 394-400.

Franklin, T. R., Acton, P. D., Maldjian, J. A., Gray, J. D., Croft, J. R., Dackis, D. A., O'Brien, C. P. & Childress, A. R. (2002). Decreased gray matter concentration in the insular, orbitofrontal, cingulate and temporal cortices of cocaine patients. *Biological Psychiatry, 51,* 134-142.

Frischer, M., Hickman, H., Kraus, L., Mariani, F. & Wiessing, L. (2001) A comparison of different methods for estimating the prevalence of problematic drug misuse in Great Britain. *Addiction, 96,* 1465-1476.

Garavan, H., Pankiewicz, J., Bloom, A., Cho, J-K., Sperry, L., Ross, T. J., Salmeron, B. J., Risinger, R., Kelley, D. & Stein, E. A. (2000). Cue-induced cocaine craving: neuroanatomical specificity for drug users and drug stimuli. *American Journal of Psychiatry, 157,* 1789-1798.

Gawin, F. H. & Ellinwood, M. D. (1989). Cocaine dependence. *Annual Review of Medicine, 40,* 149-61.

Gawin, F. H. & Kleber, H. D. (1986). Abstinence symptomatology and psychiatric diagnosis in cocaine abusers: clinical observations. *Archives of General Psychiatry, 43,* (2) 107-113.

Goeders, N. E. & Smith, J. E. (1986). Reinforcing properties of cocaine in the medial prefrontal cortex: Primary action on presynaptic dopaminergic terminals. *Pharmacology Biochemistry and Behavior, 25,* 191-199.

Goldstein, R.Z. & Volkow, N.D. (2002). Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. *American Journal of Psychiatry,* Oct., 159,10 pp. 1642-1653.

Gondo, Y., Shimonaka, Y., Senda, M., Mishina, M. & Toyama, H. (2000). The role of the prefrontal cortex in the go/ no-go task in humans: a positron emission tomography study. *Japanese Psychological Research, 42,* (1) 36-44.

Grant, S., London, E. D., Newlin, D. B., Villemagne, V. L., Lui, X., Cotoreggi, C., Phillips, R. L., Kimes, A. S. & Margolin, A. (1996). Activation of memory circuits during cue-elicited cocaine craving. *Proceedings of the National Academy of Science USA, 93,* 12040-12045.

Hoaken, P. N. S. & Stewart, S. H. (2003). Drugs of abuse and the elicitation of human aggressive behavior. *Addictive Behavior, 28,* 1533-1554.

Hooker, W. D. & Jones, R. T. (1987). Increased susceptibility to memory intrusions and the Stroop interference effect during acute marijuana intoxication. *Psycho-pharmacology, 91, 20-24.*

Horger, B. A., Valadez, A., Wellman, P. J. & Schenk, S. (1994). Augmentation of the neurochemical effects of cocaine in the ventral striatum and medial prefrontal cortex following preexposure to amphetamine, but not nicotine: An in vivo microdialysis study. *Life Sciences, 55,* (15), 1245-51.

Izenwasser, S. (1998). Basic pharmacological mechanisms of cocaine. In: *Cocaine abuse: behavior, pharmacology and clinical applications.* Edited by S.T. Higgins & J.L. Katz. Academic Press: San Diego.

Jentsch, J. D. & Taylor, J. R. (1999). Impulsivity resulting form frontostriatal dysfunction in drug abuse: implications for the control of behavior by reward-related stimuli. *Psychopharmacology (Berl)* 146: 373-390.

Jentsch, J. D., Verrico, C. D., Le, D. & Roth, R. H. (1998). Repeated exposure to delta-9-tetrahydrocannabinol reduces prefrontal cortical dopamine metabolism in the rat. *Neuroscience Letters, 246,* 169-172.

Jones, B. T., Jones, B. C., Smith, H. & Copley, N. (2003). A flicker paradigm for inducing change blindness reveals alcohol and cannabis information processing biases in social users. *Addiction, 98,* 235-244.

Jones, B. & Mishkin, M. (1972). Limbic lesions and the problem of stimulus-reinforcement associations. *Experimental Neurology* 36: 362-377.

Kaufman, M. J., Levin, J. M., Ross, M. H., Lange, N., Rose, S. L., Kukes, T. J.,

Mendelson, J. H., Lukas, S. E. Cohen, B. M. & Renshaw, P. F. (1998). Cocaine-induced cerebral vasoconstriction detected in humans with magnetic resonance angiography. *JAMA, 279,* 376-380.

Kellam, S., Ialongo, N., Brown, H., Laudolff, J., Mirsky, A., Anthony, B., Ahearn, M., Anthony, J., Edelsohn, G. & Dolan, L. (1989). Attentional problems in first - grade and shy and aggressive behaviors as antecedents to later heavy or inhibited substance abuse. *NIDA Research Monograph, 95,* 368-9.

Kolb, B. & Whishaw, I. Q. (1996). *Fundamentals of human neuropsychology*, 4th edn. New York: Freeman.

Leschner, A. I. (1998). Addiction is a brain disease, and it matters. *Science, 278,* 45-47.

Liu, X., Matochik, J. A., Cadet, J. L. & London, E. D. (1998). Smaller volume of pre-frontal lobe in polysubstance abusers: a magnetic resonance imaging study. *Neuropsychopharmacology, 18,* 243-252.

London, E. D., Cascella, N. G., Wong, D. F., Phillips, R. L., Dannals, R. F., Links, J. M., Herning, R., Grayson, R., Jaffe, J. H. & Wagner, H. N. (1990). Cocaine-induced reduction of glucose utilization in human brain. A study using positron emission tomography and [fluorine 18]-flurordeoxyglucose. *Archives of General Psychiatry, 47,* 567-574.

London, E. D., Ernst, M., Grant, S., Bonson, K. & Weinstein, A. (2000). Orbitofrontal

cortex and human drug abuse: functional imaging. *Cerebral Cortex, 10,* 334-342.

Lubman, D. I., Peters, L. A, Mogg, K., Bradley, B. P. & Deakin, J. F. W. (2000). Attentional bias for drug cues in opiate dependence. *Psychological Medicine, 30,* 169-175.

Maas, L. C., Lukas, S. E., Kaufman, M. J., Weiss, R. D., Daniels, S. L., Rogers, V. W., Kukes, R. J. & Renshaw, P. F. (1998). Functional magnetic resonance imaging of human brain activation during cue-induced cocaine craving. *American Journal of Psychiatry, 155,* 124-126.

MacLeod, C. M. (1991). Half a century of research on the Stroop effect: an integrative review. *Psychological Bulletin, 109,* 163-203.

Madden, J. A. & Powers, R. H. (1990). Effect of cocaine and cocaine metabolites on cerebral arteries in vitro. *Life Sciences, 47,* 1109-1114.

Markou, A. & Koob, G. F. (1991). Postcocaine anhedonia: An animal model of cocaine withdrawal. *Neuropsychopharmacology, 4,* 17-26.

Moeller, F. G., Dougherty, D. M., Barratt, E. S., Oderinde, V., Mathias, C. W., Harper, R. A. & Swann, A. C. (2002). Increased impulsivity in cocaine dependent subjects independent of antisocial personality disorder and aggression. *Drug and Alcohol Dependence, 68,* 105-111.

Murray, H. W., Patkar, A. A., Mannelli, P., DeMaria, P., Desai, A. M. & Vergare, M. J. (2003). Relationship of aggression, sensation seeking, and impulsivity with severity of cocaine use. *Addictive Disorders & Their Treatment, 2,* (4) 113-121.

O'Malley, S., Adamse, M., Heaton, R. K. & Gawin, F. H. (1992). Neuropsycholgoical impairment in chronic cocaine abusers. *American Journal of Drug and Alcohol Abuse, 18,* 131-144.

Parker, H., Williams, L. & Aldridge, J. (2002). The normalization of 'sensible' recreational drug use: further evidence from the North West England Londitudinal Study. *Sociology, 36,* 941-964.

Pfefferbaum, A., Sullivan, E. V., Mathalon, D. H. & Lim, K.O. (1997). Frontal lobe volume loss observed with magnetic resonance imaging in older chronic alcoholics. *Alcohol and Clinical Experimental Research, 21,* 521-529.

Pope, H. C. & Yurgelun-Todd, D. (1996). The residual cognitive effects of heavy marijuana use in college students. *JAMA, 21,* 521-527.

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

Ramsay, M., Baker, P. Goulden, C., Sharp, C. & Sondhi, A. (2001). *Drug misuse*

declared in 2000: results from the British Crime Survey. Home Office Research, Development and Statistics Directorate: London

Robinson, T. E. & Berridge, K. C. (1993). The neural basis of drug craving: an incentive-sensitistaion theory of addiction. *Brain Research Review, 18,* 247-91.

Robinson, T. E. & Berridge, K. C. (2003). Addiction. *Annual Review of Psychology, 54,* 25-53.

Robinson, T. E., Gorny, G., Mitton, E. & Kolb, B. (2001). Cocaine self-administration alters the morphology of dendrites and dendritic spines in the nucleus accumbens and neocortex. *Synapse, 39,* 257-266.

Rogers, R.D., Everitt, B. J., Baldacchino, A., Blackshaw, A. J., Swainson, R., Wynne, K., Baker, N. B., Hunter, J., Carhty, T., Booker, E., London, M., Deakin, J.F., Sahakian, B. J., Robbins, T. W. (1999). Dissociable deficits in the decision-making cognition of chronic amphetamine abusers, opiate abusers, patients with focal damage to prefrontal cortex, and tryptophan-depleted normal volunteers: evidence for monoaminergic mechanisms. *Neropsychopharmacology, 20,* 322-339.

Rolls, E. T. (2000). The orbitofrontal cortex and reward. *Cerebral Cortex* 10: 284-294.

Rolls, E. T., Hornak, J., Wade, D. & McGrath, J. (1994). Emotion-related learning in

patients with social and emotional changes associated with frontal lobe damage. *Journal of Neurology and Neurosurgical Psychiatry, 57,* 1518-1524.

Rosselli, M. & Ardila, A. (1996). Cognitive effects of cocaine and poly-drug abuse. *Journal of Clinical and Experimental Neuropsychology, 18,* 122-135.

Royall, D. R., Leuterback, E. C., Cummings, J. L. Reeve, A., Rummans, T. A., Kaufer, D. I., LaFrance, W. C., Coffey, C. E. (2002). Executive control function: a review of its promise and challenges for clinical research. A report rom the Committee on Research of the American Neurosychiatric Association. *Journal of Neuropsychiatry and Clinical Neurosciences, 14,* 377-405.

Schenk, S. & Partridge, B. (1997). Sensitization and tolerance in psychostimulant self-administration. *Pharmacology Biochemistry and Behavior, 57,* 543-550.

Solowij, N. (1998). *Cannabis and Cognitive Functioning.* Cambridge, England: Cambridge University Press.

Stahl, S. (2000). *Essential psychopharmacology: neuroscientific basis and practical applications.* (2nd Ed.). Cambridge: Cambridge University Press.

Staley, J. K., Basile, M., Flynn, D. D. & Mash, D. C. (1994). Visualizing dopamine and serotonin transporters in the human brain with the potent cocaine analogue [125I]RTI-55: in vitro binding and characterization. *Journal of Neurochemistry, 62,* 549–556.

Sutherland, I. & Shepherd, J. P. (2002). Adolescents' beliefs about future substance use: a comparison of current users and non-users of cigarettes, alcohol and illicit drugs. *Journal of Adolescence, 25,* 169–181.

Tannock, R., Schachar, R. & Logan, G. (1995). Methylphenidate and cognitive flexibility: dissociaed dose effects in hyperactive children. *Journal of Abnormal Child Psycology, 23,* 235-267.

Taylor, S. P., Hulsizer, M. R. (1998). Psychoactive drugs and human aggression. In: Donnerstein, E. & Geen, R. G. (Eds.) *Human aggression: theories, research and implications for social policy.* 139-165. Academic Press: San Diego.

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

Volkow, N. D., Fowler, J. S., & Wang G-J. (2003). The addicted human brain: insights from imaging studies. *Journal of Clinical Investigation, 111,* (10) 144-1451.

Volkow, N. D., Fowler, J. S., Wang, G-J. & Goldstein, R. (2002). Role of dopamine, the frontal cortex and memory circuits in drug addiction: insight from imaging studies. *Neurobiology of Learning and Memory, 78,* 610-624.

Volkow, N. D., Fowler, J. S., Wolf, A. P., Hitzemann, R. Dewey, S., Bendriem, B.,

Alpert, R. & Hoff, A. (1991). Changes in brain glucose metabolism in cocaine dependence and withdrawal. *American Journal of Psychiatry, 148,* 621-626.

Volkow, N. D., Fowler, J. S., Wolf, A. P., Hitzemann, R., Logan, J., Schlyer, D. J., Dewey, S. L. & Wolf, A. P. (1993). Decrease dopamine D2 receptor availability is associated with reduced frontal metabolism in cocaine abusers. *Synapse, 14,* 169-177.

Volkow, N. D., Mullani, N., Gould, K. L., Adler, S., Krajewski, K. (1988). Cerebral blood flow in chronic cocaine users: a study with positron emission tomography. *British Journal of Psychiatry, 152,* 641-648.

Wadsworth, E. J. K., Simpson, S. A., Moss, S. C. & Smith, A. P. (2004). Recreational drug use: patterns from a South Wales self-report survey. *Journal of psychopharmacology, 18,* (2) 228–237.

Waters, A. J. & Feyeraband, C. (2000). Determinants and effects of attentional bias in smokers. *Psychology of Addictive Behaviors, 14,* 111-120.

Wexler, B. E., Gottschalk, C. H., Fulbright, R. K., Prohovnik, I., Lacadie, C. M., Rounsaville, B. J., Gore JC (2001). Functional magnetic resonance imaging of cocaine craving. *American Journal of Psychiatry, 158,* 86-95.

Woolverton, W. L., Cervo, L. & Johanson, C. E. (1984). Effects of repeated

methamphetamine administrations on methamphetamine self-administration in rhesus monkeys. *Pharmacology Biochemistry and Behavior, 21,* 737-741.

Wyvell, C. L. & Berridge, K. C. (2000). Intra-accumbens amphetamine increases the conditioned incentive salience of sucrose reward: enhancement of reward "wanting" without enhanced "liking" or response reinforcement. *Journal of Neuroscience, 20,* (21) 8122-8130.

Yang, X-M., Gorman, A. L., Dunn, A. J. & Goeders, N. E. (1992). Anxiogenic effects of acute and chronic cocaine administration: Neurochemical and behavioral studies. *Pharmacology Biochemistry and Behavior, 41,* 43-650.

Part 2

Empirical Paper

Cognitive and Mood Effects of Recreational Cocaine Use

Abstract

The effects of acute cocaine self-administration in human participants was assessed by a battery of cognitive tasks and mood self-rating scales that were administered to 19 recreational cocaine users and 19 controls on 2 separate test occasions 4 days apart. For the cocaine group, the first test sessions took place after cocaine had been taken in environments familiar to participants. Using a go/ no-go task and a dot-probe task, we found tentative support for small but detectable impairments in ability to inhibit response and an increased incentive sensitisation towards cocaine in the cocaine group. There was no evidence that working memory, focus of attention or speed of comprehension were affected by social cocaine use, either acutely or in abstinence. The cocaine group rated themselves as lower in mood and higher in anxiety and impulsivity, though whether these changes are a result of cocaine use or vulnerability for it is not determined in this study.

Introduction

There is a vast and growing body of research into the effects of psychoactive substances. Much of this has been into the processes and effects of addiction itself. Though some drugs, for example ecstasy, have received attention in terms of the acute and chronic effects of non-dependent recreational use (e.g. Vollenweider, Gamma, Liechti & Huber, 1988; Verheyden, Hadfield, Calin & Curran, 2002), for

other drugs such as cocaine, the overwhelming majority of research has taken place in the context of chronic addiction.

Many areas of the brain are involved in experiencing psychoactive drugs (e.g. Jentsch & Taylor, 1999; Koob, 2000; Robinson & Berridge, 2003). In the last decade there has been a growth in our understanding of the nueural basis of addiction from functional brain imaging (Goldstein & Volkow, 2002). Initially, euphoric effects mediated, it is thought, by the prefrontal cortex and the nucleus accumbens, may lead to a desire to repeat the drug-taking experience, and are in this way an important part of reinforcement. However, other factors also come into play. While the consciously pleasurable effects of some drugs become attenuated with repeated exposure as tolerance develops, leading to the need for increasing amounts for the same effect, psychostimulants, a class of drugs which includes cocaine, also seem to be capable of causing sensitisation, whereby a small dose of cocaine can elicit increased appetitive behaviour for the drug. The co-existence of tolerance and sensitisation might, at first sight, seem to be paradoxical. However, Berridge & Robinson (1998; 2002) have hypothesised that motivation for a drug (or 'wanting'), while closely related to pleasure, is dissociable from it. This dissociation has been demonstrated in the laboratory using conditioned incentive experiments with rats (Robinson & Berridge, 2002; Wyvell & Berridge, 2000). The unconscious element of wanting is known as incentive sensitisation. Incentive salience is an attribution that transforms sensory information about rewards and their cues (conditioned stimuli) into incentives to behavioural responses, that is they elicit appetitive approach (Berridge and Robinson, 2003). Drug cues (conditioned stimuli) can reinstate drug-taking behaviour by eliciting conscious wanting (craving) and/or unconscious wanting (incentive

motivation). Thus cues trigger both explicit and implicit memory associated with liking of a drug, and its incentive salience, i.e. the degree to which it motivates appetitive behaviour. Once sensitised to psychostimulants, administration of even a small amount of cocaine (a priming dose), or conditioned cues, can cause the individual to be highly motivated to seek out more of the drug. The phenomenon of incentive sensitisation is now thought to be an important part of reinforcement in addiction.

While an individual in the process of addiction is becoming increasingly unconsciously sensitised to cues, conscious craving is also experienced, mediated by the prefrontal cortex (Goldstein & Volkow, 2002). These processes work together to make drug cues highly salient so that they increasingly grab the individual's attention. This powerfully increases the likelihood of further drug-seeking and self-administration.

According to Volkow, Fowler & Wang's (2003) theory of substance addiction, in the early stages of repeated exposure to psychoactive drugs, executive functions (working memory, ability to switch attention, decision-making, and ability to inhibit impulsivity) are intact, and are able to override conscious craving and incentive motivation when it would be inappropriate or seriously detrimental for the individual to take drugs. Evidence from animal studies now suggests that, with more frequent and heavier use, the structure of frontal lobe circuits begin to alter in response to repeated dopamine flooding and depletion (Robinson, Gorny, Mitton & Kolb, 2000). In humans reductions in pre-frontal lobe functional activity have also been demonstrated (Volkow, Fowler, Wolf et al. 1991; Volkow, Hitzemann, Wang et al.,

1992; Volkow, Fowler, Wang et al. 1993; London, Ernst, Grant et al., 2000) as well as reduced dopamine D_2 receptor availability.

There has been much discussion about whether frontal lobe impairments precede psychoactive drug use and are a vulnerability for it, or result from neurotoxic damage. Pre-existing differences in frontal lobe function, and therefore of impulsivity and decision making could logically lead to increased vulnerability to addiction through reduced ability to inhibit responses and make profitable decisions. It is likely that there is, in fact a bi-directional process, with any frontal lobe deficits increasing vulnerability to addiction, and drug use contributing to further negative changes to the prefrontal cortex (PFC). It is now accepted that children with frontal lobe deficits such as are seen in attention deficit hyperactivity disorder (ADHD) are more at risk of substance abuse and addiction in adulthood (Lambert & Hartsough, 1998; Molina & William, 2003).

With advances in technology, it has also been possible to demonstrate evidence for PFC changes resulting from substance use (Goldstein & Volkow, 2002; Volkow, Fowler & Wang, 2003) with frontal lobe volume changes being proportional to years of drug use, and decreased D_2 receptor availability in the PFC correlating with years of cocaine use (Volkow, Fowler & Wang et al., 1993).

Impairments in decision-making and impulse inhibition are particularly significant, as they directly contribute to a cycle in which internal or environmental cues activate drug-seeking via increased (unconscious) incentive motivation, and conscious craving, while the ability to inhibit response is compromised, leading to compulsive

seeking-out and taking of drugs. At this point compulsive self-administration may continue even when the individual cognitively understands the disadvantages of continued use, consciously desires to stop, and no longer enjoys the experience *per se*, as opposed to the relief of suppressing withdrawal symptoms (Jentsch & Taylor, 1999).

But how can ongoing, non-dependent recreational use of addictive substances be understood? In many cultures, alcohol is widely used in social settings, frequently quite heavily, while only a minority of people become addicted. It generally needs to be consumed in large quantities over a period of time before addiction takes hold, though there are individual genetic differences in vulnerability to alcohol addiction (Finn, Sharkansky, Viken et al., 1997; Heath, Bucholz, Madden et al. 1997; Long, Knowler, Hanson et al. 1998) and also differences in life experience that might lead to increased consumption of alcohol, or indeed other drugs, as a way of coping with negative affect.

Cocaine's reputation as an addictive substance has varied over time. In the 1970s and early 1980s, it was considered by many to be a safe, non-addictive stimulant (Grinspoon & Bakalar, 1980; National Commission on Marihuana and Drug Abuse, 1973). By the end of the 1980s, the National Institute on Drug Abuse (NIDA) considered that there was a cocaine epidemic in the United States and that it was "the drug of greatest national public health concern." (Adams & Kozel, 1985) while at the same time acknowledging that the majority of stimulant users manage to avoid the problems of dependence, even this was a problem by "promoting the illusion of safety" (Gawin & Ellinwood, 1989). There is plentiful evidence of widespread and

increasing social use of cocaine among the general population in Britain (British Crime Survey (BCS), 2003). In some affluent urban areas of Britain, as many as 11% of the 16-29 year-old age group report having used cocaine, and the number has been rising steadily over the last decade (BCS, 2003).

What effect is this social use of cocaine having on the cognitive functions and emotional well-being of those who take it? If addiction is characterised by disproportionately heightened incentive salience of cocaine and its cues, and an impaired ability to inhibit impulsively responding to such cues, is there any evidence of neuropsychological changes beginning to occur in regular recreational users? Is there a continuum from the cocaine-naïve brain state to the addicted one, with a gradual change from social to compulsive use? Or is there a level of use which can be maintained without some 'threshold' for compulsion or disinhibition being reached?

To investigate these questions the present study was designed to test regular but non-dependent cocaine users for incentive sensitisation and degree of impulsivity. To assess incentive motivation we used the dot-probe paradigm. This is a sensitive way of eliciting attentional bias and unconscious motivation towards particular cues. It has been used successfully to assess salience attribution in a variety of domains including anxiety, delusions and addictions (e.g. Taylor & John, 2004; Franken, Kroon, Wiers et al. 2000; Bradley, Field, Mogg et al., 2004).

To assess ability to inhibit prepotent responses, we used a go/no-go task, the most widely used paradigm to assess response inhibition and impulsivity (Rubia, Smith,

Brammer et al. 2003). This paradigm is a selective attention task in which participants are required to respond to some stimuli and then instructed not to respond to certain stimuli under specific circumstances. Inhibitory difficulty is enhanced by weighting frequencies of stimuli so that the 'go' trials predominate and the 'no-go' trials are random and comparatively infrequent.

As incentive sensitisation is more likely to be elicited after a priming dose of cocaine (Robinson & Berridge, 2003), users were tested on a night when they were using cocaine. There is also anecdotal evidence that people believe cocaine can enhance cognitive functioning such as concentration, memory and speed of thinking. As there is a dearth of research literature on the general cognitive and mood effects of recreational cocaine use, we also decided to administer a range of cognitive tasks and self-rating scales in order to explore the general mood and cognitive effects of cocaine, and users' beliefs about its ability to enhance cognitive functioning.

If recreational cocaine use induces subtle changes similar to some of the characteristics of dependent use, we would predict that: a) in the dot probe task, there will be reduced reaction times in cocaine users, compared to non-using controls, when the probe appears in the same areas as the cocaine-related pictures (a measure of increased salience attribution); b) cocaine users will have increased numbers of false alarms on the go/ no-go task (impaired response inhibition) compared with controls. On the other hand, if recreational use does not induce dependency-like changes, then we would predict no differences between users and controls on these tasks.

Method

Design

A mixed independent groups, repeated measures design was used to compare recreational cocaine users with non-cocaine users at two time points: the night of drug use (day 0) and 4 days later.

Participants

Participants were recruited from individuals known to the researcher, and from their contacts, using the snowball method (Solowij, Hall & Lee, 1992), into either a cocaine group or a control group. The inclusion criterion for the control group was that participants must never have used cocaine, or have only tried it once, and not in the last year. However, they used other recreational drugs, including alcohol.

The study was approved by the local ethics committee and all participants gave written informed consent on both days.

Materials and Procedure

Participants were assessed on day 0 and again on day 4. On each day volunteers were tested individually in a quiet area. They were given written and oral information about the study, and each signed a written consent form on each test day. They then completed the tasks as described below. Participants were asked to take no illicit drugs between the first and second meetings. Different versions of the cognitive tasks were used on the two days and fully counterbalanced across groups and days. (See Appendix for the information sheet, consent form and upublished rating scales).

Go/No go Task

This computer task was designed to assess response inhibition. Stimuli comprised 16 letters of the alphabet organised into two sets of eight, and presented individually. There were 2 blocks of stimuli, the first of which consisted of 30 stimuli and the second and of 100 stimuli. For the first block, participants were instructed to respond by pressing a designated key on the computer keyboard, as quickly as possible, to each letter on the screen. In the second block participants were presented with 100 stimuli, matched for frequency across versions, and were instructed to respond, by the same designated key press to all but two of the eight letters. These two letters constituted the 'No go' trials. Each letter appeared for 800 ms followed by an inter-stimulus interval of 500 ms. The proportion of 'Go' stimuli was 75% and that of the 'No go' stimuli was 25%. All trials were presented on a 1500 MHz Intel Pentium M processor laptop with a standard keyboard and 12" screen. Error rates and reaction times were automatically recorded.

Dot probe task

The dot-probe task was modelled on that used by Bradley, Field, Mogg and De Houwer (2004). The present task was programmed by the author using DMDX programming software.[1] The stimuli consisted of 20 colour digital photographs of cocaine-related material (e.g. a line of cocaine with a rolled note) and 20 pictures not related to cocaine (e.g. a scribbled line with a ball-point pen), but matched as far as possible for composition to the cocaine-related pictures. Examples are seen in Figure 1. An additional 6 pairs of non-cocaine-related pictures were prepared for practice trials. Each trial consisted of the appearance of a central fixation cross for 2000ms,

[1] DMDX was developed by K. I. Forster and J.C. Forster at Monash University and at the Universtiy of Arizona.

followed by a matched pair of pictures for 500ms. When the pictures disappeared, an asterisk appeared immediately in place of one of the pictures. Participants were instructed to press a designated key as soon as they saw the asterisk, which remained in place until the key was pressed. There were four blocks of 80 pseudo-randomised trials in which each picture appeared on each side with an asterisk 'behind' it 25% of the time. Response times and errors were automatically recorded.

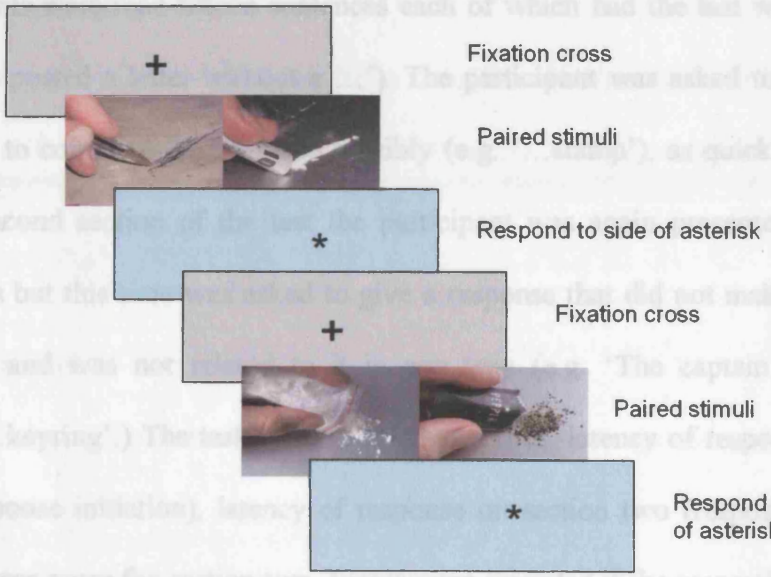

Figure 1. Example stimuli for dot probe task

About 20 minutes after the dot-probe task, a *Picture Rating* sheet was given to each participant on which they rated all the pictures used in the computer task for how arousing and how pleasant they found them using a 9-point Likert scale. The pictures were presented individually in paper format

Digits Forward and Backwards

This sub-scale from the WAIS III (Wechsler, 1997) was used to test working memory. A second version was prepared using pseudo-randomised numbers of sequences of the same length and in the same way as the WAIS III sub-scale.

Hayling Sentence Completion (Burgess and Shallice, 1997)

This task was chosen as a measure of verbal response inhibition. In the first section, participants were read fifteen sentences each of which had the last word is missing (e.g. 'He posted a letter without a ...'). The participant was asked to give a verbal response to complete the sentence sensibly (e.g. '...stamp'), as quickly as possible. In the second section of the test the participant was again presented with fifteen sentences but this time was asked to give a response that did not make sense of the sentence and was not related to it in any way (e.g. 'The captain stood on the sinking...keyring'.) The task yielded three measures, latency of response on section one (response initiation), latency of response on section two (response inhibition), and an error score for section two. Errors were recorded if the respondent completed any sentence so that it made sense, or with a word that was somewhat related to the content and meaning of the sentence. Errors were scored according to the Hayling Test scoring guidelines (Burgess & Shallice, 1997). As there is only one version of this task a second version was created on the advice of Dr Burgess (personal communication), by swapping the second set of sentences to the first part of the task, and vice versa.

Speed of Comprehension (Baddeley, Emslie & Nimmo-Smith, 1992)

This test of the speed of understanding of visually-presented verbal information comprised 100 sentences, half of which were true (e.g. 'Buses have wheels') and half false (e.g. 'Tigers have fins'). Participants were asked to rate as many sentences as they could as true or false within 2 minutes.

Map Search from the Everyday Test of Attention (Robertson, Ward, Ridgeway & Nimmo-Smith, 1994)

This was used to assess ability to focus attention. It is sensitive to visual selective attention deficit, i.e. the ability to pick out targets from a complex array of visual stimuli.

Self-rating Scales

The following list of pencil and paper self-rating scales was administered to each participant:

Metacognitive Estimates. This comprised 5 statements concerning estimates of current cognitive functioning, such as 'My ability to **concentrate** right now is:' followed by a 5- point Likert scale with '1' labelled 'Worse than usual' to '5', 'Better than usual'.

Subjective Effects. This comprised 9 possible 'symptoms' of cocaine use (e.g. 'Heart beating fast/palpitations'), each attached to a visual analogue scale (VAS).

The *Mood Rating Scale* (MRS; Bond and Lader, 1974), the *Aggression Rating Scale* (ARS; Bond and Lader, 1986), the *Impulsivity Self Rating Scale* (ISRS; Bond & Lader, 1974) and *the Beck Depression Inventory* (BDI; Beck, 1978) were completed on each day of testing. The BDI was modified such that the instructions requested participants to rate how they had been feeling over the last 3 days (Curran & Travill, 1997).

Additional tests on Day 4

On day 4, in addition to repeating all the above assessments, participants also completed the *Spot the Word Test* (Baddeley, Emslie & Nimmo-Smith, 1993; an index of premorbid IQ), the *Barrett Impulsivity Scale* (BIS; Barrett, 1985; a measure of trait impulsivity), the *Aggression Questionnaire* (AQ; Buss & Perry, 1992; a measure of trait aggression), and the *Beck Anxiety Inventory* (BAI; Beck, 1974), modified so that participants were requested to rate feelings over the last 3 days. A history of the frequency, amount and duration of all psychotropic drugs was taken for each participant. The cocaine group were in addition given a short interview about their experience of using cocaine, and screened for possible addiction, using the *Severity of Dependence Scale* (Gossop, Darke, Griffiths et al., 1995).

Urine Drug Screen

Each participant provided a urine sample at the end of testing on both days, which was screened for the presence of illicit drugs using the CheckCup^{TM} Immunoassay System for Drugs of Abuse. This system is capable of detecting the presence of very low levels of the following drugs or their metabolites: cocaine, methamphetamine, tetrahydrocannibinol, morphine, amphetamine and phencyclidine.

Table 5. Mean (s.d.) metacognitive estimates (ratings 0 – 5).

	Cocaine group N = 19		Control group N = 19	
	Day 0	Day 4	Day 0	Day 4
Ability to concentrate	2.6 (1.2)	2.8 (0.7)	2.4 (0.7)	3.2 (0.8)
Ability to focus attention	2.7 (1.1)	2.7 (0.7)	2.4 (0.7)	3.2 (0.8)
Speed of understanding	2.9 (0.8)	2.8 (0.7)	2.7 (0.6)	3.1 (0.6)
Accuracy of thinking	2.9 (0.9)	3.0 (0.4)	2.7 (0.7)	3.2 (0.5)
Working memory	3.0 (0.5)	3.0 (0.5)	2.7 (0.7)	3.1 (0.3)

With five rating scales being analysed, the level of significance was set at $p = 0.01$. Only one of the self-rated estimates of cognitive functioning showed a significant effect: a main effect of day for *ability to concentrate* ($F_{1,36} = 8.33$, $p = 0.007$), with both groups rating better concentration on day 4 than day 0.

Subjective effects rating scale (Table 6)

Table 6. Means (s.d.) for Subjective Effects ratings (severity 0-100) and pulse rate.

	Cocaine group N = 19		Control group N = 19	
	Day 0	Day 4	Day 0	Day 4
Palpitations	47.2 (23.4)	8.7 (13.6)	11.2 (16.5)	7.6 (12.6)
High temperature	29.0 (30.4)	5.9 (9.4)	5.6 (15.7)	3.3 (6.4)
Shaking	32.5 (27.5)	3.4 (4.7)	7.6 (15.5)	2.8 (6.4)
Sweating	14.7 (20.6)	11.6 (16.7)	5.1 (15.4)	3.1 (3.8)
Teeth tingling or numb	59.3 (25.5)	2.1 (2.3)	1.0 (1.9)	1.6 (3.0)
Nausea	8.4 (15.2)	2.1 (2.4)	6.5 (17.4)	1.7 (3.1)
Muscle cramps	6.6 (18.4)	4.3 (10.9)	1.4 (2.3)	1.6 (3.0)
High or 'rushing'	54.3 (24.0)	4.3 (8.6)	3.7 (11.2)	1.8 (3.1)
Desire for cocaine	61.5 (36.5)	23.8 (31.7)	0.3 (0.9)	0.7 (1.9)
Pulse (beats/minute)	92.3 (18.2)	72.8 (15.1)	67.8 (12.0)	66.0 (9.5)

As nine different visual analogue scales rating subjective sensations were analysed, the level of significance was set at $p = 0.007$ to adjust for increased family-wise error rates. There was a significant group x day interaction for ratings of palpitations ($F_{1,34} = 32.1$, $p < 0.001$), high temperature ($F_{1,35} = 12.3$, $p = 0.001$), shaking ($F_{1,33} = 16.5$, $p < 0.001$) and 'rushing or high' ($F_{1,35} = 81.5$, $p < 0.001$). On all of these, the cocaine group's ratings were higher than the controls only on day 0. For sweating there was

only a main effect of group ($F_{1,35} = 12.3$, $p = 0.001$), with the cocaine group having higher ratings on both days.

Desire for cocaine were at floor in controls but significantly higher in the cocaine group on day 0 than day 4 ($t_{18} = 3.9$, $p = 0.001$). Ratings for 'teeth tingling or numb' were again at floor in controls but significantly higher in the cocaine group on day 0 than day 4 ($t_{18} = 10.3$, $p < 0.001$). A visual presentation of comparison of mean ratings is seen in Figure 4.

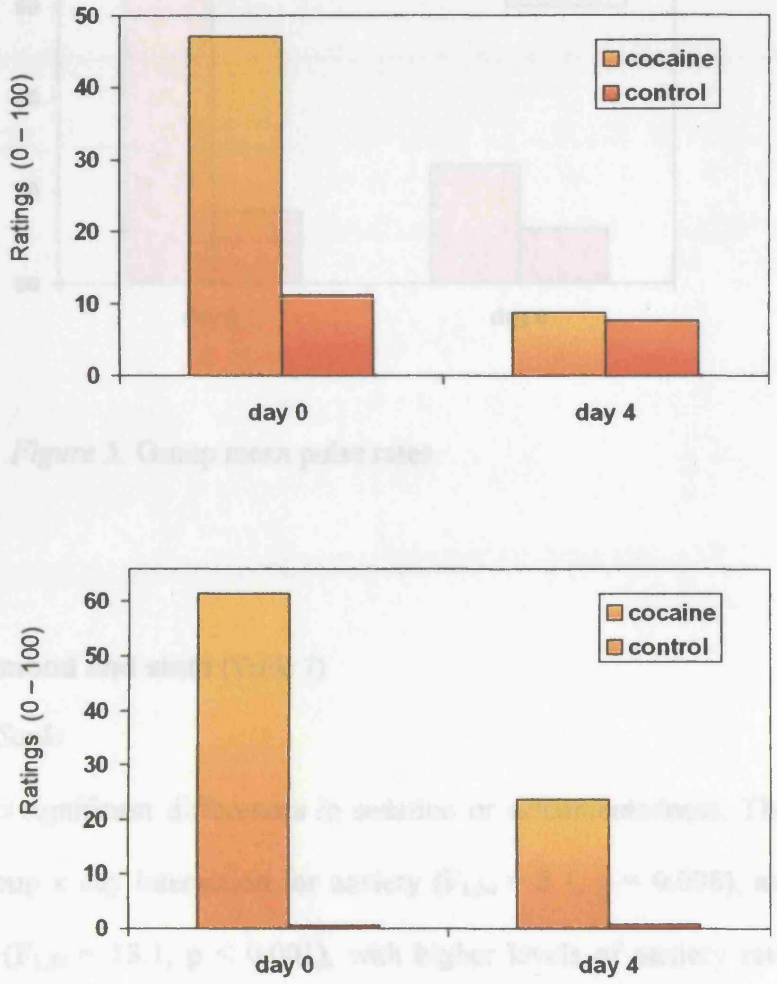

Figure 4. Mean ratings for: (A) severity of palpitations; (B) desire for cocaine.

There were no significant group or day differences on ratings of muscle cramps or nausea.

There was a significant day x group interaction for pulse rate ($F_{1,36} = 20.7$, $p<0.001$), and main effects for both day ($F_{1,36} = 20.7$, $p<0$ 001) and group ($F_{1,36} = 16.0$, $p<0.001$) with elevated pulse rates of the cocaine group only on day 0 (Figure 5). Group means for pulse rate can be seen in Table 6.

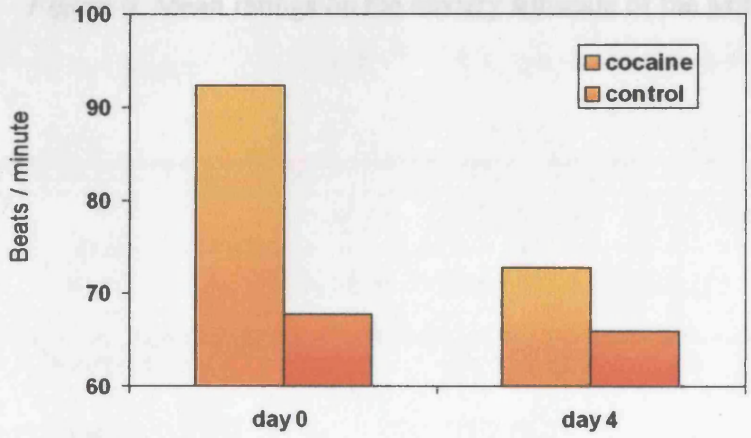

Figure 5. Group mean pulse rates

Measures of mood and state (Table 7)

Mood Rating Scale

There were no significant differences in sedation or discontentedness. There was a significant group x day interaction for anxiety ($F_{1,34} = 8.1$, $p = 0.008$), and a main effect of day ($F_{1,34} = 18.1$, $p < 0.001$), with higher levels of anxiety rated by the cocaine group on day 0 as seen in Figure 6.

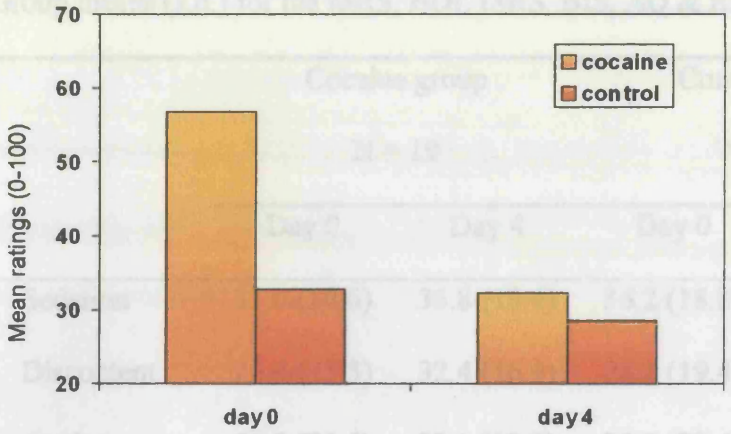

Figure 6. Mean ratings on the anxiety subscale of the MRS

Table 7. Group means (s.d.) for the MRS, BDI, ISRS, BIS, AQ & BAI

		Cocaine group N = 19		Control group N = 19	
		Day 0	Day 4	Day 0	Day 4
MRS:	Sedation	31.0 (14.6)	35.8 (19.4)	36.2 (18.8)	25.9 (14.3)
	Discontent	26.4 (15.5)	32.4 (16.9)	28.1 (19.4)	26.3 (17.1)
	Anxiety	56.8 (21.5)	32.3 (19.0)	32.8 (22.4)	28.5 (21.0)
BDI:	Somatic	3.3 (2.8)	2.2 (1.5)	1.7 (1.8)	1.2 (1.8)
	Non-somatic	6.6 (6.5)	3.6 (2.9)	2.9 (3.8)	2.4 (3.8)
	Total	9.9 (8.2)	5.7 (3.9)	5.8 (8.5)	4.7 (7.2)
ISRS		52.9 (11.6)	29.5 (13.1)	38.0 (14.6)	30.6 (17.2)
ARS		29.4 (14.3)	23.9 (12.8)	20.8 (15.2)	19.9 (16.6)
BIS:	Non-planning	-	26.7 (4.4)	-	25.1 (4.2)
	Motor	-	23.2 (5.3)	-	21.7 (3.8)
	Attention	-	18.4 (3.3)	-	15.6 (2.4)
AQ		-	94.1 (22.7)	-	78.3 (19.3)
BAI		-	7.3 (5.4)	-	4.5 (4.9)

Beck Depression Inventory (BDI)

There was no interaction for BDI total scores, but there was a main effect of group ($F_{1,34} = 6.0$, $p = 0.02$), with the cocaine group reporting lower mood overall than the control group. There was also a main effect of day ($F_{1,34} = 6.8$, $p = 0.013$) with higher scores on day 0.

In terms of the somatic symptoms component, there were again main effects of group ($F_{1,34}$ = 9.3, p = 0.004), and day ($F_{1,34}$ = 6.6, p = 0.015) with the cocaine group reporting more symptoms than the control group, particularly on day 0. For the non-somatic symptoms, there was only an main effect of day ($F_{1,34}$ = 4.6, p = 0.04). Figure 7 shows a comparison of group means for total BDI scores on day 0 and 4.

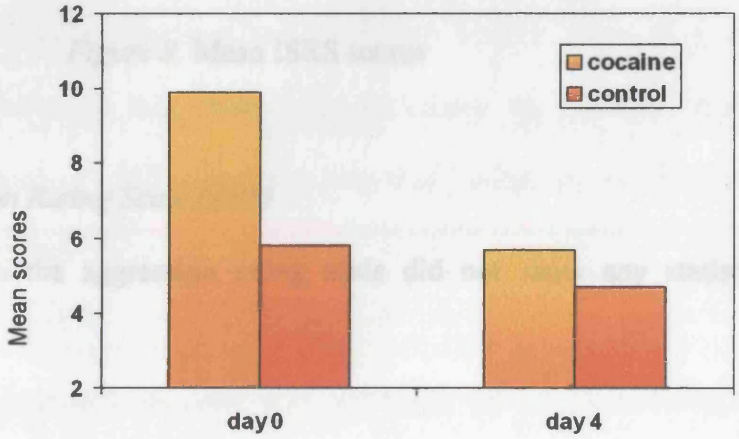

Figure 7. Group mean totals on the BDI

Impulsivity State Rating Scale (ISRS)

For ISRS scores there was a significant group x day interaction ($F_{1,36}$ = 13.3, p = 0.001), and a main effect of day ($F_{1,36}$ = 50.0, p < 0.001). As can be seen in Figure 8, the cocaine group had higher self-ratings on day 0.

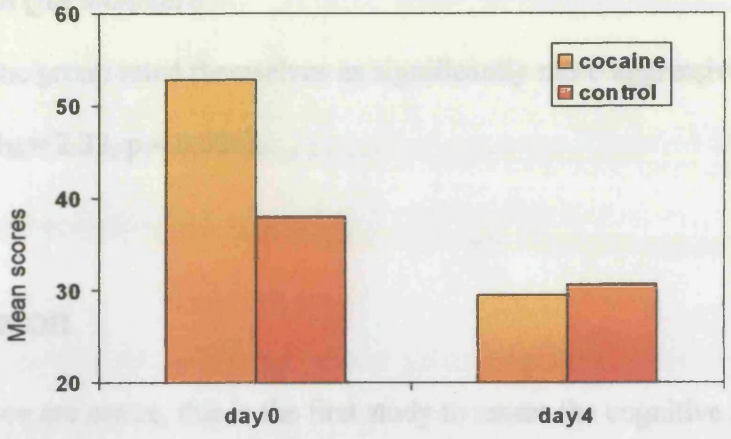

Figure 8. Mean ISRS scores

Aggression Rating Scale (ARS)

Scores on the aggression rating scale did not show any statistically significant effects.

Beck Anxiety Inventory (BAI)

There were no significant differences on the BAI.

Trait measures

Barrett Impulsivity Scale (BIS)

As the total score and 3 sub-scales were all analysed using independent samples t-tests, the significance level was set at $p = 0.01$. When total BIS scores were compared, the cocaine group did not rate themselves as significantly more impulsive. Analysis of the sub-scales showed a difference only on the attentional sub-scale ($t_{36} = 2.9$, $p = 0.006$), with the cocaine group reporting more problems keeping attention on activities.

Aggression Questionnaire

The cocaine group rated themselves as significantly more aggressive on the AQ than controls ($t_{36} = 2.32$, $p = 0.026$).

Discussion

As far as we are aware, this is the first study to assess the cognitive and mood effects of recreational cocaine use, and to explore whether users show mild forms of the cognitive changes that characterise addiction, *viz* increased incentive motivation towards cocaine, difficulties with response inhibition, and impairments in specific executive functions.

It was an opportunistic study with ecological validity in assessing recreational users in the context of their normal intake of the drug in their preferred environment. On day 0, the cocaine group had taken relatively small amounts of cocaine which were enough to elicit clear subjective effects and physiological changes not seen in controls. The increased pulse rate, the subjective rush/high and the greater desire for more cocaine all suggested that cocaine was taken by users on day 0. This was objectively verified by urine screens showing cocaine in the user group but not controls on day 0.

Response inhibition

Impairments in response inhibition are an important part of the process of addiction (Robinson & Berridge, 2002). Anecdotal evidence suggests that recreational cocaine users, if not generally suffering with overt problems of impulsivity, sometimes find it hard to stop taking cocaine once they have taken an initial dose. Indeed, subjective

ratings showed a significantly increased desire for cocaine following use of the drug on day 0. We attempted to test whether recreational users have difficulties with impulsivity in terms of inhibiting pre-potent responses using two separate paradigms – a go/no-go task and the Hayling Sentence Completion.

On the go/no-go task, while the control group improved slightly with practice, the cocaine group showed the opposite direction of change, with fewer false alarms when under acute intoxication than on day 4. This pattern suggests that cocaine had a facilitative impact acutely, in line with what is known about cocaine's effect on the dopamine circuits in the PFC (White & Kalivas, 1998), an area involved in inhibition of responses (Jentsch & Taylor, 1999; Volkow, Fowler & Wang, 2003). Poorer inhibition of the cocaine group, when not under its acute influence, is suggestive of some impairment of response inhibition, which may be due to repeated dopamine flooding and depletion.

If this is the case, why was there no sign of impairment in the cocaine group on the Hayling Sentence Completion? One possible explanation is that the Hayling is not a sensitive enough measure for what could be very subtle changes. The other is the varying strategies that participants reported using on this task during debriefing. Some had found that looking around the room, they prepared themselves simply to name an object in the room whatever the sentence. Testing took place in people's home environments, which were usually rich in possibilities, and such preparation was facilitated by the tester's need to write down response times between sentences. Such a strategy could easily be countered by use of a blindfold. No doubt such a move would make it much harder to disinhibit a prepotent response. However,

another strategy used by some participants was to think of a category of objects and keep listing items in that group whatever the sentence. This strategy would not be so easy to overcome. It is likely that the use of such strategies masked any influence of acute cocaine. Such strategies are unlikely to affect the go/ no-go task.

Incentive Motivation

Increased incentive motivation is an important factor in addictive processes (Robinson & Berridge, 2003). The dot probe task has successfully demonstrated significant differences in incentive motivation in people addicted to cigarettes (Bradley, Mogg, Wright et al., 2003; Bradley, Field, Mogg et al., 2004; Ehrman, Robbins Bromwell et al., 2002). In our study, cocaine users did show increased reaction times to the probe when it was preceded by a cocaine cue, suggesting increased motivation towards cocaine cues. However, the control group also showed this tendency. The most obvious explanation for this is that cocaine pictures were more attention grabbing than non-cocaine pictures to both groups. Explicit representations of cocaine cues and scenes of cocaine taking are relatively unusual, especially when compared to representations of smoking and drinking-related scenes. Cocaine use is also an illicit activity, with actual cocaine use taking place largely hidden from public view, thus making such scenes relatively novel and interesting.

In order to assess the impact of the pictures other than incentive motivation, all participants were asked to rate each picture for how pleasurable and arousing they found it. The cocaine group rated the cocaine pictures as more arousing and more pleasurable both than the non-cocaine pictures and the control group. Further, they rated the cocaine pictures as more arousing and pleasurable on day 0 than they did on

day 4. Controls showed no difference in ratings of cocaine and non-cocaine pictures whilst cocaine users rated cocaine pictures higher on both days. Although some of the day effect may have been due to desensitisation, this cannot be the only explanation as there was no significant day effect for the control group on arousal or pleasure ratings.

These results suggest that cocaine cues have increased salience for recreational users at a conscious level, and that this salience is further increased under acute use, even when that use is a small 'priming' dose. During interview about their use some people spontaneously referred to both conscious and unconscious increased appetite for cocaine when they had taken even a small amount. For example, one said, "The first line does it – after that I can't stop myself." This is highly suggestive of an incentive sensitisation effect.

Other cognitive tasks

The results of metacognitive ratings by participants in this study do not accord with the commonly held belief that people take cocaine to enhance their ability to work. There was no evidence cocaine users had any inflated beliefs about cocaine's capacity to enhance cognitive abilities. On average, cocaine users tended to rate their abilities as the same or slightly worse than usual, as did the control group. Overall, reporteing of attentional abilities was slightly lower on day 0 than day 4. This was largely due to the control group reporting better attentional focus on the second test day, and therefore does not appear to be linked to cocaine use. Interestingly, the attentional subscale of the Behavioural Inhibition Scale showed cocaine users rated more problems maintaining attentional focus than controls.

There was no evidence of actual group or day differences in working memory (digit span), focus of attention (map search), and speed of comprehension. In view of the greater self-reporting of inattention of the cocaine group on the BIS, we might have expected a group difference on this task. The fact that no significant difference was found, however, may be explained with references to the task and again to shades of different meaning in use of the term inattention. Questions on the BIS in the inattention subscale tend to be about whether the respondent can stay on tasks and finish things they start. But there are other reasons for leaving things unfinished apart from lack of attentional focus, for example confidence, boredom, or lack of motivation.

In addition, the map search not only measures ability to focus attention, but also speed of responding. Groups were well matched for age and intellectual ability, but both groups consisted of highly intelligent samples, and this resulted in something of a ceiling effect in both the map search and the Speed of Comprehension test. Any subtle group or day differences may have been more difficult to detect in such circumstances.

Mood and state effects

In terms of mood, the cocaine group reported more symptoms of depression, particularly of somatic symptoms, over the three days preceding both test points. These elevations could be due to effects of drug taking, whether cocaine or polydrug abuse. On the other hand, they may suggest a form of self-medication of cocaine for

pre-existing symptoms. On day 0, seven individuals in the cocaine group scored over 14 points on the BDI compared to only 1 control.

The results of the Mood Rating Scale (MRS) suggested the control group had a higher level of anxiety on day 0. This could be due to the acute effects of cocaine which also caused shaking, palpitations, increased pulse and temperature – all also symptoms of anxiety. There was also a non-significant suggestion from the BAI scores that the cocaine group suffered greater somatic symptoms of anxiety in the 3 days between tests. These symptoms could have been due to cocaine withdrawal, but the cocaine group also took a higher number of drugs between testing on day 0 and day 4, and the somatic symptoms may rather be related to other drug use.

The cocaine group rated themselves as feeling more impulsive on the ISRS on day 0 than on day 4, and more impulsive on day 0 than the control group, while there was no group difference in ratings on day 4. This suggests that cocaine users feel significantly more impulsive when under the influence of cocaine, even though this was not demonstrated in the objective tasks. The reason for this may be that ISRS items are measuring different aspects of impulsivity, ie. feelings of agitation, impatience, and inattention, rather than ability to inhibit specific responses.

Inattention was the one factor of the BIS on which the cocaine group rated themselves significantly more highly. There are a number of studies linking cocaine addiction to problems of impulsivity and attention (Jentsch & Taylor, 1999; Volkow, Fowler & Wang, 2003). It is not clear whether that is the result of cocaine addiction or one of its determinants, and it may be that there is an interactive process with

elements of both occurring. The higher self-rating of trait inattention in the present study is in line with the hypothesis that aspects of trait impulsivity and difficulties with inattention are characteristics that make illicit drug use more likely. It is interesting to note that in children with attention deficit hyperactivity disorder, methylphenidate, a stimulant in the same class as cocaine, can improve attention and reduce behavioural impulsivity. There is evidence that children with ADHD are more likely to have drug problems as adults (Lambert & Hartsough, 1998; Molina & William, 2003). A question raised by the results of the go/ nogo task in the present study is whether higher incidence of illicit stimulant taking in individuals with attentional problems such as ADHD are a result of self-medication, risk-taking behaviour, or the greater vulnerability to addictive processes given predisposing impairments in response inhibition.

Although there were no significant differences in self-rating on the Aggression Rating Scale (ARS), a tool for measuring state aggression, the cocaine group rated themselves as more highly aggressive on each of the subscales of the Aggression Questionnaire (AQ), a trait measure, with significantly higher total scores than the controls. These results suggest a possible association between aspects of trait aggression and substance use. The amounts of cocaine taken before testing were relatively small, and larger amounts may result in more marked differences.

Summary

This study provides tentative support for the hypothesis that recreational cocaine use can lead to small but detectable impairments in response inhibition, and some degree of incentive sensitisation. There was no evidence of cocaine affecting other cognitive

abilities tested in this study. However, the doses taken were small compared to usual amounts taken over a social evening, and both groups were of well above average intellectual functioning, which led to some ceiling effects and therefore lack of sensitivity of the testing.

The cocaine group were lower in mood, and higher in anxiety, self-rated impulsivity and aggression than controls. Whether these characteristics are due to cocaine use, other drug use or precede drug use and are a vulnerability for it is a question that needs addressing in a prospective, longitudinal study.

References

Adams, E., H. & Kozel, N. J., (Eds.) (1985). Cocaine use in America: introduction and overview. In: *NIDA research monograph series, Vol. 61. Cocaine use in America: epidemiologic and clinical perspectives,* 35-49. Washington, DC: US Government Printing Office.

Baddeley, A. D., Emslie, H. & Nimmo-Smith, I. (1992). *The Speed and Capacity of Language Processing (SCOLP) Test.* Bury St. Edmund's: Thames Valley Test Co.

Baddeley, A. D., Emslie, H. & Nimmo-Smith, I. (1993). The Spot-the-Word test: a robust estimate of verbal intelligence based on lexical decision. *British Journal of Clinical Psychology, 32* (1), 55-65.

Barrett, E. S. (1985). Impulsive subtraits: arousal and information processing. In: Spence, J. T., Izard, C. E. (Eds.). *Motivation, emotion and personality*. North-Holland: Elsevier Science.

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

Berridge, K. C. & Robinson, T. E. (2003). Parsing reward. *Trends in neuroscience*, 9, 507-513.

Bond, A. J. & Lader, M. (1974). The use of analogue scales in rating subjective feelings. *British Journal of Medical Psychology, 47,* 211-218.

Bond, A. J., Lader, M. H. (1986). A method to elicit aggressive feelings and behaviour via provocation. *Biological Psychology, 22,* 69–79.

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,* 29-36.

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) 66-72.

Burgess, P. W. & Shallice, T. (1997). *Hayling Sentence Completion Test.* Suffolk: Thames Valley Test Co. Ltd.

Buss, A. H. & Perry, M. (1992). The aggression questionnaire. *Journal of Personality and Social Psychology, 63,* 452–459.

Curran, H. V. & Travill, R. A. (1997). Mood and cognitive effects of +/-3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy'): week-end 'high' followed by mid-week low. *Addiction, 92,* 821–831.

Ermann, R. N., Robbin, 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.

Finn, P. R., Sharkansky, E. J., Viken, R., West, T. L., Sandy, J., & Bueffered, G. M. (1997). Heterogeneity in the families of sons of alcoholics: The impact of familial vulnerability type on offspring characteristics. *Journal of Abnormal Psychology 106,* (1) 26-36.

Franken, I. H. A., Kroon, L. Y., Wiers, R. W. & Jansen, A. (2000). Selective cognitive processing of drug cues in heroin dependence. *Journal of Psychopharmacology 14* (4), 395–400.

Gawin, F., H. & Ellinwood, E. H. (1989). Cocaine dependence. *Annual Review of Medicine, 40,* 149-61.

Goldstein, R. Z. & Volkow, N. D. (2002). Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. *American Journal of Psychiatry, 159,* 1642-1651.

Gossop, M., Darke, S., Griffiths, P., Hando, J., Powis, B., Hall, W. & Strang, J. (1995). The Severity of Dependence Scale (SDS): psychometric properties of the SDS in English and Australian samples of heroin, cocaine and amphetamine users. *Addiction, 90,* 607-14.

Heath, A. C., Bucholz, K. K., Madden, P. A., Dinwiddie, S. H., Slutske, W. S., Bierut, L. J., Statham, D. J., Dunne, M. P., Whitfield, J. B., & Martin, N.G. (1997). Genetic and environmental contributions to alcohol dependence risk in a national twin sample: Consistency of findings in women and men. *Psychology and Medicine 27,* 1381-1396.

Jentsch, J. D. & Taylor, J. R. (1999). Impulsivity resulting from frontostriatal dysfunction in drug abuse: implications for the control of behavior by reward-related stimuli. *Psychopharmacology, 146,* 373-390.

Koob, G. I. (2000). Neurobiology of Addiction: Toward the Development of New Therapies. *Annals of the New York Academy of Sciences, 909,* 170-185.

Lambert, N. M. & Hartsough, C. S. (1998). Prospective study of tobacco smoking

and substance dependencies among samples of ADHD and non-ADHD participants. *Journal of Learning Disabilities, 31,* 533-44.

Long, J. C., Knowler, W. C., Hanson, R. L., Robin, R. W., Urbanek, M., Moore, E., Bennett, P. H. & Goldman, G. (1998). Evidence for genetic linkage to alcohol dependence on chromosomes 4 and 11 from an autosome-wide scan in an American Indian population. *American Journal of Medicine and Genetics 81,* 216-221.

Molina, B. S. G. & Pelham, W. E. (2003). Childhood Predictors of Adolescent Substance Use in a Longitudinal Study of Children With ADHD. *Journal of Abnormal Psychology, 112,* 497-507.

Robertson, I. H., Ward, T., Ridgeway, V. & Nimmo-Smith, I. (1994). *The Test of Everyday Attention (TEA).* Harcourt Assessment Inc.: San Antonio, Texas.

Robinson, T.E. & Berridge, K. C. (2003). Addiction. *Annual Review of Psychology, 54,* 25-53.

Rubia, K., Smith, A. B., Brammer, M. J. & Taylor, E. (2003). Right inferior prefrontal cortex mediates response inhibition while mesial prefrontal cortex is responsible for error detection. *Neuroimage, 20,* 351–358.

Taylor, C. H. & John, J. L. (2004). Attentional and Memory Bias in Persecutory Delusions and Depression. *Psychopathology, 37,* 233-241.

Verheyden, S. L., Hadfield, J., Calin, T. & Curran, H.V. (2002). Sub-acute effects of MDMA (3,4 methylenedioxymethamphetamine, "ecstasy") on mood: evidence of gender differences. *Psychopharmacology, 161,* 23–31.

Volkow, N. D., Fowler, J. S., Wolf, A. P., Hitzemann, R., Dewey, S. L., Bendriem, B., Alpert, R. & Hoff, A. (1991). Changes in brain glucose metabolism in cocaine dependence and withdrawal. *American Journal of Psychiatry, 149,* 621-626.

Volkow, N. D., Hitzemann, R., Wang, G. J., Fowler, J. S., Wolf, A. P., Dewey, S. L. & Handlesman, L. (1992). Long-term frontal brain metabolic changes in cocaine abusers. *Synapse, 11,* 184-190.

Volkow, N. D., Fowler, J. S., Wang, G. J., Hitzemann, R., Logan, J., Schyler, D. J., Dewey, S. L &Wolf, A. P. (1993). Decreased dopamine D2 receptor availability is associated with reduced frontal metabolism in cocaine abusers. *Synapse, 14,* 169-177.

Vollenweider, F. X., Gamma, A., Liechti, M. & Huber, T. (1998). Psychological and cardiovascular effects and short-term sequelae of MDMA ("ecstasy") in MDMA-naive healthy volunteers. *Neuropsychopharmacology, 19,* 241–251.

Wechsler, D. (1997). *Wechsler Adult Intelligence Scale – Third Edition (WAIS–III).* Harcourt Assessment Inc.: San Antonio, Texas.

White, F. J. & Kalivas, P. W. (1998). Neuroadaptations involved in amphetamine and cocaine addiction. *Drug and Alcohol Dependence, 51,* 141-153.

Part 3

Critical Appraisal

Critical Appraisal

This is the biggest piece of research I have ever undertaken and I have learned an enormous amount, both about the subject of drug use and addiction and about the process of conducting research. I had no previous background in drug research and no experience of working in specialist drug and alcohol services. The only time I had come across clients with issues around drug use was in a forensic placement, where the focus was on the links between drug use, mental illness and offending behaviour.

Through understanding the complexity and degree of physical change possible in the brain as a result of chronic substance use, I began to see how an individual can lose ability to have control over compulsive behaviour. On reflection, I realised I had implicitly absorbed a societal association between addictive behaviour and weakness, or lack of will-power. I could start to see how pervasive this attitude might be in relation to other areas such as over-eating where there might be a connection between natural variation in incentive salience to food, for example, and vulnerability to obesity.

The Journey

Searching the literature

Having to plan the research at a detailed level was a daunting process. Where to start with an enormous literature base? Which lines of research were most important to follow? Who were influential figures; which papers were more marginal?

In beginning to look at the literature on cocaine use and its effects, I realised there was a mountain of research. And yet, within this huge wealth of knowledge, I was surprised to find there was virtually no research into the recreational use of cocaine. As a member of the newspaper-reading public, I had seen reference to what appeared to be many findings about ecstasy, and its short- and long-term effects on mood. With cocaine having a much longer history, I expected there to be a similar research base on its recreational use. Not being able to find anything, I thought at first that perhaps I was missing something. Had I not been doing my searches properly? But it became clear that, for some reason, while there was a huge amount known about *chronic* cocaine use and addiction, there were almost no studies of non-dependent use. There seemed to be a strange silence on this area. It was as if recreational use of cocaine did not exist. This is despite the fact that survey research has been revealing increased recreational use of many drugs, including cocaine.

Attitudes to illicit drug use

I began to wonder if one of the reasons for this is an implicit belief by many researchers of cocaine being so addictive that social and controlled use is not possible. Some of the major researchers in this area seem to have a moralistic and judgemental stance about psychoactive drugs. For example, Volkow, who has headed numerous teams reasearching the effects of cocaine, is director of NIDA, the National Institute on Drug Abuse, an American governmental organisation. In NIDA's information pages on their website (www.nida.nih.gov) illicit drugs are not 'used', they are only 'misused' or 'abused'. People dependent on nicotine, are never referred to as nicotine abusers in research papers, and alcohol abusers are often compared with 'social drinkers'. Yet, in

one of Volkow's paper's (Volkow, Wang, Fowler et al., 1999) even college students talking about initial experiences of cocaine, and clearly not referring to problematic use such as is defined by DSM (APA, 1994), are referred to as cocaine 'abusers'. Such language is in danger of confusing unsanctioned use (e.g. use of any drug defined as illicit; excessive drinking in pregnancy; drink-driving) with harmful use that impacts on the individual, their family and often society.

There is a stark contrast here with another harmful potentially compulsive and very damaging behaviour, gambling, which the British government has been actively trying to promote while targeting social cocaine use at 'middle-class dinner parties' for punishment.

Informational websites about psychoactive durgs are mainly produced by government bodies (e.g. the Department of Health) charities (e.g. DrugScope) or parental groups, that have a vested interest in demonising cocaine as a dangerous and extremely addictive drug. In the NIDA webpage that provides information about cocaine, the second sentence of the section on 'effects' reads:

> "Common health effects include heart attacks, respiratory failure, strokes, and seizures."
>
> (NIDA, 2005a)

An acknowledgement that cocaine can be taken occasionally is immediately followed by a strongly-worded caution:

> "Cocaine use ranges from occasional use to repeated or compulsive use, with a variety of patterns between these extremes. Other than medical uses, there is no safe way to use cocaine. Any route of administration can lead to absorption of toxic amounts of cocaine, leading to acute cardiovascular or cerebrovascular emergencies that could result in sudden death."
>
> (NIDA, 2005b)

But presumably, if small non-toxic amounts are taken, it does not lead to acute cardiovascular or cerebrovascular emergencies whichever route is used. Or is that only if it is taken 'medically'? In fact, a report leaked from the government in the week of my writing this thesis, reports that there is 1 death per 100,000 users of cocaine resulting from acute use, or 11 people in the last year. This contrasts with 6,000 deaths in the last year from acute and chronic alchohol use and 100,000 deaths from tobacco smoking.

Surely, understanding why the majority of people can have controlled, social use would contribute to our understanding of why some cannot manage controlled use? There is certainly a need for education, so that people can make more well-informed choices about what they put in their bodies. I wonder if the alarmist tone of much of the information produced is counterproductive. It seems at odds with the experiences of friends and acquaintances of mine who enjoy cocaine 'sensibly', perhaps on special occasions such as birthdays or holidays. I suspect that valuable information is in danger of being dismissed or ignored, when it is buried in such moralistic language and bias of emphasis.

Such language can be contrasted with that of the few websites that have a more balanced approach. For example, Erowid, which combines information about the positive aspects of drugs with sensible harm-reduction advice. Their stated aim is to promote 'respect and awareness' of psychoactive substances by providing non-jdugemental information,

> "...in ways that strengthen [people's] understanding of themselves and provide insight into the complex choices faced by individuals and societies alike."
>
> (Erowid, 2000)

A need for qualitative understandings

After searcing for literature on recreational use of cocaine, almost the only papers I could find were reports of survey data. As useful as it is to know about prevalence, such surveys can only provide us with numbers of users, and sometimes also 'most likely' profiles, but tell us nothing about particular individuals' understanding about why they take particular drugs.

I was disappointed to find that some surveys did not even distinguish between specific drugs, but simply lumped illicit substances together, and there certainly seemed to be a lack of qualitative information about experience, patterns of use, and effects in social use of cocaine.

In my study, I took the opportunity provided by the testing sessions to conduct brief interviews with participants in the cocaine group. This was an enriching and interesting part of the research process, because all the data from the quantitative part of the study

was, for me, embedded with that knowledge of lived experience. I felt that participants in my study had trusted me with intimate aspects of themselves and I became aware that I wanted to produce a piece of work that respected their choices and did not somehow let them down by contributing to an alarmist and moralistic opinion. At the same time, I was aware that result showing potentially negative consequences of recreational cocaine use must be shared.

Learning about the neurobiology of addiction

In terms of the effects of cocaine use, I realised, then, that without a research base in social cocaine use, I could only start with understanding mechanisms of addiction and then attempt to situate recreational use as a 'problematic' phenomenon within this framework. This kind of approach implicitly assumes a continuum concept from no use, through to recreational use and to dependent use at the other extreme.

Understanding the neurobiology and processes of addiction in a relatively short space of time was a difficult task. For a long time, each new paper I read seemed to be embedded in a huge prior knowledge base that I had to try to become familiar with. Many were the papers I had to read and re-read in order to understand the most important areas in the neuropsychology of addiction.

One of the most pivotal parts of my reading was getting to grips with the Berridge and Robinson papers (1993; 2003) on 'parsing reward'. These, more than any others, helped me to understand how tolerance and sensitisation can and do co-occur, and how conscious and unconscious processes combine to create powerful effects on behaviour. I

think for the first time I was really able to understand how addiction can get to the point that the individual is not in control.

My post-training work will initally be in a forensic setting where there is a high level of co-morbid drug and alcohol abuse, which contributes both to relapses in mental illness and to offending behaviour. My deeper knowledge about reward processes, incentive sensitisation, and the effects of frontal lobe damage in chronic drug use will help me better to understand patients' difficulties and to plan treatment. I can already see where I was involved in counterproductive work with patients on placement, and how I might do things differently in clinical work. For example, I was part of a group where film clips of drug use were used to stimulate discussion. I can see now the disadvantages of providing drug cues likely to activate incentive motivation without meaning to, and without being part of a planned programme of exposure.

Writing the dot probe programme

An important part of the study was to assess whether there was any evidence of incentive sensitisation in recreational users. Having read the studies by Mogg and Bradley and colleagues, a dot probe task seemed the most elegant and precise way to do this. We discussed the possibility of using words as the stimuli; words which were cocaine-related and non-cocaine related. One difficulty with this is finding sufficient stimuli related specifically to cocaine rather than a range of recreational drugs that did not also have other meanings (e.g. snort, cut, line, coke). Given the greater richness and immediacy of visual stimuli, we decided to use photgraphic stimuli, as I thought this would be more ecologically valid. I also thought it would be relatively easy to do using

a digital camera. In fact, setting up items for the photographs was time-consuming. It was more difficult that I had anticipated to think of twenty ways of setting up cocaine stimuli sufficiently different that the pictures were not too repetitive. However, this did not turn out to be the most difficult part. When the dot probe task was first suggested, I naïvely thought the department had a programme that I could simply slot the pictures into. It turned out I was to write the programme myself, and this was quite a challenge.

One of the department's research students (Celia Morgan) gave me some tips and directed me to the the DMDX website (DMDX, 2002), where instructions on dot probe programming devised by Forster and Forster are generoulsy freely available. To a novice in research, there seem to be many small snags, with big consequences, in setting up a study. My first problem here was that my computer operating system was too old to support the downloading of zip files needed for the programme. This was eventually solved by my buying a laptop, which would also be well-used in collecting the data. Unfortunately, my research grant did not cover the cost.

For someone with no prior programming experience whatsoever, learning how to do it from a website was not easy. Getting the pictures to come up simultaneously, in the correct positions on the screen , and getting it all to run, was frustratingly difficult. Pseudo-randomising the pairs so that each picture appeared an equal number of times on either side, and an equal number of times with the dot probe following it, and without the cocaine pictures or the probe appearing more than three times in a row on the same side (to avoid a response set) was a fiddly puzzle.

Eventually the task was finished. It looked beautiful. Unfortunately, the results showed that it did not clearly distinguish cocaine users from controls. On a subjective measure of pictures ratings, the cocaine group rated the pictures as more arousing and more pleasant than the control group, which shows that the cocaine-related pictures had heightened salience for users. However, on the probe task, both groups were faster to respond to the probe when it followed on the side of a cocaine-related picture. My explanation of this is that the cocaine cues were also highly attention-grabbing for controls, but perhaps for different reasons, i.e. they were novel and more interesting in content that non-cocaine pictures. I had been careful to match the paired pictures for composition, but in retrospect it might have been better to match them for arousingness of content. However, this would have entailed a fairly exensive pilot study in order to rate degree of arousingness of many pictures in order choose pairs that matched.

Ethics

It is impossible currently to do laboratory studies in which cocaine is given to participants, so the only window of opportunity for a study like mine is to ask for recreational users to let me test them when they are under the influence of cocaine. I was able to confirm the presence or absence of the drug using both objective measure (urine analysis) as well as known signs (e.g. elevated pulse rate) and subjective effects ratings (e.g. shaking, temperature rise, tingling, rushing). For me there was an ethical question of whether I was encouraging people to take part in illegal activity. I had to make arrangements with individuals to come and test them at specific times, and so their use was linked to my testing. On the other hand, all participants were volunteers who used cocaine in a controlled non-dependent pattern, who were allowing me access

to test them on a night of usual use. On balance I feel my own role in the procedure was justified in that it is, as far as I am aware, the only study so far to assess the acute effects of cocaine in a non-dependent group of users.

However, there were problems that resulted from the procedure I went through for gaining ethical approval. I had no wish to act unethically with regard to participants. Though I did not consider the concept of testing recreational users on a night they planned to use cocaine anyway to be unethical, my supervisor and I were unsure how the university ethics board might receive the idea. Therefore, my supervisor rang the chair of the ethics committee to discuss the project before it was well-advanced. She described the procedure planned for the research and the my supervisor and the chair agreed that it would be acceptable for us to request a simple extension of a previous study run by my supervisor with another research student. This outcome had the benefit of saving a great deal of time in making a new application.

I had some reservations about my lack of involvement in the process of approval for a project which I myself was carrying out. In retrospect, I feel I should have made a more detailed assessment of what the previous research involved, and what the extension of approval covered. Despite the time advantage of gaining approval in this way, there was also a disadvantage.

Being covered by an extension meant using the same participant information sheet used by the previous study, as this was the sheet seen and approved by the Ethics Committee. However, this information sheet did not cover all points of interest to the participants, and did not point out that they would be asked for urine samples. I had no interest in

deceiving participants or persuading them to take part in something of which they did not have full knowledge. Therefore, was careful to provide verbally details not covered by the sheet. I had doubts about this being correct, but perhaps did not express them strongly enough to my supervisor who was confident that we had followed an acceptable procedure. In the planning stage of the project we did not envisage taking urine samples because of lack of resources (each screen costs £25). However, a commercial drug screen company then provided us with free screening kits which we used to give an objective index of drug use. It was an oversight of me and my supervisor that this information was not added to the information sheet and approved by the Ethics Committee.

All participants had full information of what would take place, were allowed to have all questions answered and were made fully aware of what the testing sessions would involve. This information was given to potential participants in advance. If they indicated they would be happy to take part, they then contacted me to let me know when they were next taking cocaine. All participants were made aware that they were under no obligation to continue at any point if they changed their minds, and all participants signed the consent form twice, before the testing sessions, and in the case of the cocaine group, before taking cocaine on the first testing session. However, though the written information sheet stated that questions about drug-taking would be asked, and implied that the effects of drug-taking on variations in mood and concentration were of interest to the researchers, it did not specifically state that the focus of the study was on the effects of recreational cocaine. This information was clearly stated to each participant in the verbal explanation, but this would leave me vulnerable to any doubts that participants had been given enough information about the study should any of them feel

negatively affected by taking part, and then make a complaint, with potential negative consequences for all parties involved. Fortunately, in the event, there were no such difficulties: all participants were happy with the information given and the testing procedures. I have learnt, though, that a clear, rigorous and unambiguous ethical application prodecure is intended both for the proper protection of participants and for the protection of all interested research parties. In future research I intend to follow the usual route for assessment of ethical standards by a committee scrutinising full written details of all aspects of the planned research, and to be fully involved at every step of the ethical procedure.

References

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

Berridge, K. C. & Robinson, T. E. (2003). Parsing reward. *Trends in neuroscience, 26,* 507-513.

DMDX. (2002, April 12). DMDX display software. *U-arizona.edu*. Retrieved July 10th 2004, from http://www.u.arizona.edu/~kforster/dmdx/dmdx.htm

Erowid. (2000, March 15). About Erowid. *Erowid.org*. Retrieved July 6th, 2005, from

http://www.erowid.org/general/about/about.shtml

NIDA. (2005a, April 12). Cocaine. *NIDA.nih.gov.* Retrieved July 7th 2005, from http://www.nida.nih.gov/DrugPages/Cocaine.html

NIDA. (2005b, February 4). Research report series – Cocaine abuse and addiction. How is cocaine used? *NIDA.nih.gov.* Retrieved July 7th 2005, from http://www.nida.nih.gov/ResearchReports/Cocaine/cocaine3.html

Volkow, N. D., Wang, G-J., Fowler, J. S., Logan, J., Gatley, S. J., Gifford, A., Hitzemann, R., Ding, Y-S. & Pappas, N. (1999). Prediction of reinforcing responses to psychostimulatns in humans by brain dopamine D2 receptor levels. *American Journal of Psychiatry, 156,* 1440-1443.

The Joint UCL/UCLH Committees on the Ethics of Human Research: Committee Alpha
The Joint UCL/UCLH Committees on the Ethics of Human Research: Committee A
The National Hospital for Neurology and Neurosurgery and the Institute of Neurology Joint Research Ethics Committee

THE JOINT UCL/ULCH ETHICS COMMITTEE ON HUMAN RESEARCH
COMMITTEE ALPHA

AMENDMENT APPROVAL FORM

Full Title of Study: Weekend and week-day variation in mood and concentration

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REC Study No: 98/0173

Drug Company protocol no. (if applicable): N/A

Amendment Number and Date:	Amendment 1, June 2004

The REC has reviewed your amendment.

The REC has no comments.

Your amendment has been:

Approved

The LREC will be notified of the amendment at the next committee meeting on 8 July 2004

Your amendment should be forwarded to appropriate LRECs:

For Information

Signed Ethics Administrator:

Print Name:

Date of Report: 18 June 04

The form should be attached to the amendment approval request form sent by you to the REC.

Volunteer Information Sheet

A Study of Weekend and Weekday Variation in Mood and Concentration

Purpose:
I am inviting you to participate in a study which will look at how people's mood varies over the week and whether mood affects concentration.

Although it is commonplace to talk of feeling happier at weekends ("That Friday Feeling") as compared to the start of the week, it is unclear how people's mood changes over the week. We know very little about whether such mood changes affect people's ability to concentrate.

Volunteers are needed to help us learn more about these mood changes.

What's involved?
If you agree to take part, you will be asked to fill in some questionnaires about your mood and to carry out some straightforward tests of concentration and memory on two separate occasions: on the weekend, and then four days later mid-week. On each occasion, there will be a brief interview and you will be asked for information on any alcohol or drug use that day, or any other factors that might have affected your mood and concentration.

All your identifying details will be kept entirely confidential.

If you have any questions you would like to ask relating to the study, feel free to do so now.

Investigators:
Libby Barnardo & Professor Val Curran
Sub-Dept of Clinical-Health Psychology

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

All proposals for research using human participants are reviewed by an ethics committee before they can proceed. This proposal was reviewed by UCL Ethics Committee.

University College London
Consent Form

ID No._____

Project Title:
A Study of Weekend and Week day Mood and Concentration

	Yes	No
Have you read the Participant Information Sheet?		
Have you received enough information about the study?		
Have you received satisfactory answers to all your questions?		
Do you understand that you are free to withdraw from the study at any stage?		
Do you understand that your participation is completely confidential?		

Signed:..... **Date:**.....

Full name in capitals:.....

Signature of Witness:..... **Date:**.....

Full name in capitals:.....

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Comment or concerns during the study
If you have any comments or concerns you should discuss these with the Principal Researcher (Prof Val Curran, Sub-dept of Clinical Health Psychology, UCL, . If you wish to go further and complain about any aspect of the way you have been approached or treated during the course of the study, you should email the Head of the Graduate School who will take the complaint forward as necessary.

No. _____ Date _____ Day _____

Picture Ratings

Please rate on scale of 0 –9 the level of arousal and level of pleasantness each picture invokes.

LOW 0 1 2 3 4 5 6 7 8 9 HIGH

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Picture	Arousing	Pleasing
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