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An investigation into the executive functioning of methadone-maintained patients

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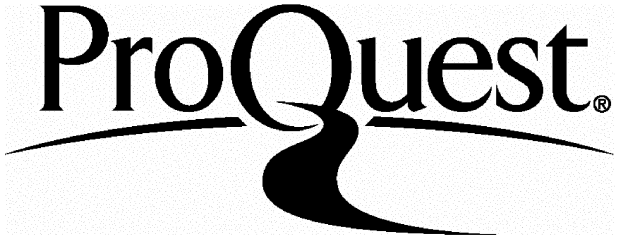

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ABSTRACT

Recent studies of cognitive deficits associated with substance use have converged with extant neuroimaging literature upon the notion that chronic substance users exhibit impairments on executive-type tasks mediated by orbitofrontal and ventromedial prefrontal cortex. However, few studies have examined the executive functioning of patients on daily methadone-maintenance treatment. This thesis aimed to investigate the executive abilities of 16 methadone-maintained, chronic polydrug-using, patients compared with 14 non-drug using individuals. The groups did not differ significantly on premorbid IQ, current non-verbal reasoning, gender, ethnicity and employment status. Executive abilities related to response initiation and inhibition, responsivity to reward and rule attainment were explored because impairments on these tasks have been described as being of clinical significance. Executive skills related to planning and multi-tasking behaviour were also assessed on an "ecologically-valid" Hotel task, designed to mimic the skills involved in open-ended everyday activities faced in real-world settings. Self-ratings of executive problems on a dysexecutive questionnaire were explored in relation to independent ratings by patients' keyworkers and performance on executive tasks.

Methadone-maintained users performed significantly more poorly on multitasking and appeared to use less efficient strategies compared with controls. These group differences were robust to covariance of depression, age and years of education. However, the same covariates influenced findings on tasks tapping response inhibition, reward responsivity and rule attainment. There was no evidence that substance users lacked insight into their

executive difficulties, moreover keyworkers rated their patients' difficulties as less severe than patients' self-ratings. The results imply that methadone-maintained patients may have more difficulty than non-drug using individuals on activities that require intact planning and organisation skills, a finding which may have implications for their ability to engage in the tasks of therapy and rehabilitation. Similarly, the results suggest that cognitive deficits may underlie many of the difficulties faced by chronic substance users' in organising and maintaining their everyday lives. Techniques utilised in neurological rehabilitation research are discussed as potentially having a useful role in reducing the impact of executive deficits on substance-users' everyday lives.

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CHAPTER 1

Introduction

Traditionally, chronic opiate use has been linked to alterations in dopaminergic pathways in the limbic system. Recently, a more rarefied view has been articulated, based on neuroimaging findings that demonstrated links between changes in the functioning of orbitofrontal and ventromedial prefrontal cortex and impairments in decision-making, reward expectancy and craving in opiate users (London, Ernst, Grant, Bonson & Weinstein, 2000). The role of the orbitofrontal cortex in executive, inhibitory control processes is well documented, the question is whether cognitive and behavioural impairments associated with frontal dysfunction in brain-injury provide a useful model of the neurocognitive consequences of prolonged substance use. This thesis aims to investigate the executive abilities of methadone maintained individuals, in particular whether they exhibit deficits in response initiation and inhibition, reward responsivity and real-world skills of planning and multi-tasking, compared to matched controls.

The first chapter begins with an outline of the effects of opiate use and reviews recent accounts of drug addiction, in which frontal dysfunction has been postulated to play a key role in the transition from drug use to addiction. Many theories confer etiological significance to impaired response inhibition in the formation of drug-related motivational states (Goldstein & Volkow, 2002; Kosten & George, 2002). A critique of methadone maintenance treatment of opiate addiction will follow, and will outline the

pros and cons of a maintenance approach. Although the methodology employed in the current study cannot answer questions related to the effects of methadone *per se*, it is anticipated that this research will contribute to the issue of whether the current cognitive status of individuals receiving methadone treatment facilitates or impedes their engagement in the tasks of rehabilitation.

Following this, a review of recent neurocognitive research will outline substance users' performance on experimental neuropsychological measures. Findings from this research have converged with neuroimaging studies upon the notion that, chronic opiate use is associated with frontal dysfunction. Experimental tasks purported to measure ventromedial-mediated aspects of decision-making (assessed using gambling tasks) have suggested that opiate users base their decisions on the saliency of immediate, large rewards and fail to take into account future negative consequences. Gambling tasks are inherently complex, however, and are hampered by interpretational difficulties related to vast number of potential component skills that they tap. A purer measure of reward-oriented behaviour, 'reward responsiveness' (CARROT: Powell, Al-Adawi, Morgan & Greenwood, 1996), has been found to correlate with clinical motivation and performance on several executive tests. Impairments in reward responsivity have been demonstrated in abstinent nicotine-addicted individuals and brain-injured patients. The current study will compare methadone maintained patients' sensitivity to incentive with matched controls using this measure. Performance of substance users on other aspects of executive function will be outlined at this point also.

Finally, perceived gaps in knowledge concerning opiate users real-world executive skills will be discussed. As yet, explorations of executive functioning in opiate users have been limited to performance on standard neuropsychological tests of short duration with task requirements that are highly cued by test stimuli or experimenter. Most standardised measures do not capture the nature of open-ended activities faced in real-world settings related to planning, multitasking and prioritising competing demands. It has been demonstrated that individuals with frontal lobe damage can have severe impairments in real-life despite performing well on neuropsychological tests (Eslinger & Damasio, 1985; Shallice & Burgess, 1991). Little assessment has been made of the real-world skills of opiate users, therefore the current study aims to assess these skills using a test of multi-tasking of high-ecological validity ('Hotel test': Manly, Hawkins, Evans, Woldt & Robertson, 2002).

1.0. Characteristics of opiate use and addiction

1.1. Neuropharmacology of opiates

The perception of pain in humans is modulated by naturally occurring, endogenous opioids in the nervous system: endorphins, encephalins and dynorphins (Lishman, 2002). Endogenous opioids comprise neuropeptides (proteins) that are stored in neurons and released during opiate action (Teeson, Degenhardt & Hall, 2002). Opiate drugs mimic the action of endogenous opioids by binding mainly at three receptor sites in the brain (mu, delta and kappa receptors) and eliciting analgesic effects to different degrees. Ingestion of opiates produces a variety of effects on the central and peripheral nervous

system and the autonomic system. Opiate drugs fall into two categories: naturally derived i.e. morphine and diamorphine (heroin) and synthetic types i.e. methadone, pethidine, buprenorphine, dipapanone, codeine, dihydrocodeine, dextromoramide. Opiate drugs also vary in terms of their pharmacological action at receptor sites and are divisible into those with agonist action and those with mixed agonist-antagonist/partial agonist action. Methadone is an opiate agonist, which exerts primary action at mu receptors (Kosten & George, 2000).

1.2. Short and long-term effects of heroin use

Although the major medicinal property of opiates is pain relief, they are widely abused because of their euphoriant effects. In the case of heroin, administration by intravenous injection is accompanied by almost immediate (7-8 seconds) onset of euphoria because of spontaneous conversion of heroin in the body (to morphine) and rapid binding to opioid receptors (NIDA, 2000). Other forms of administration (e.g. intra-muscular injection, smoking) produce slower and less intense effects. Short-term effects also include feelings of well-being, mental detachment and sensations of sedation, heaviness, dry mouth, flushed skin and itchiness. The sedative effects last for several hours (Kosten & George, 2000) and exist on a continuum of dangerousness from drowsiness and loss of concentration to severe respiratory depression (due to neurobiological changes in the brain stem), which can lead to respiratory arrest and death (Lishman, 2002). A number of adverse heath risks are associated with heroin use: contraction of blood-borne infectious disease (primarily HIV and hepatitis B and C), drug dependence (which carries its own particular risks) and overdose-related morbidity (Hall, Lynskey & Degenhardt, 1999b).

1.3. Drug dependence and addiction

The phrases drug addiction and drug dependence are often used interchangeably, although they have distinct meanings. Dependence is generally used in clinical settings to define the physical syndrome associated with chronic drug use and it is generally accepted that the neurobiological changes that underlie drug dependence are better understood than the process of addiction. Addiction is considered to result from a complex interaction between environmental effects, psychological conditioning and genetic predisposition (Kosten & George, 2002). Robbins and Everitt (1999) have argued that there is a need to understand how addiction works at cognitive, behavioural and neuropsychological levels.

1.3.1. Neural substrates of the dependence syndrome

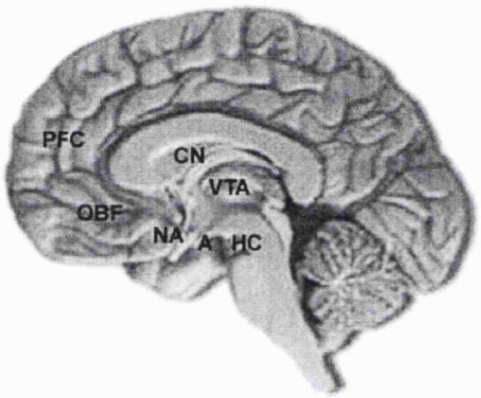
When heroin crosses the blood-brain barrier it attaches rapidly to mu receptors on opiate sensitive neurons and initiates a chain of biochemical processes. These processes reward people with pleasurable feelings similar to those released by eating and sexual activity (Kosten & George, 2002). Two systems in the brain are primarily involved in the reinforcement of drug-taking behaviours implicated in addiction: the mesolimbic and mesocortical dopamine systems (Goldstein & Volkow, 2002).

1.3.2. The mesolimbic system and the dopamine hypothesis

The functioning of the mesolimbic reward system is central to most aspects of drug-related behaviours, although it is particularly involved in reinforcement, emotional and motivational features of drug-taking (Goldstein & Volkow, 2002). It is located in the ventral tegmental area of the brain and includes the nucleus accumbens, amygdala and

hippocampus (see Figure 1.). The binding of heroin to opiate receptors in the mesolimbic system increases the activity of dopamine neurons projecting to the prefrontal cortex, nucleus accumbens and caudate nucleus (striatum).

Figure 1. The mesolimbic dopamine system, originates in the ventral tegmental area (VTA), and projects to the nucleus accumbens (NA). The amygdala (A), hippocampus (HC) and medial prefrontal cortex (PFC) including medial orbitofrontal cortex (OBF) receive input from and send projections to the nucleus accumbens (NA). Caudate nucleus (CN).
(Adapted from Robbins & Everitt, 1999)



Crucially, the release of dopamine at the nucleus accumbens is responsible for the sensation of pleasure, a process that is implicated in the action of many drugs of abuse and led to the generation of the 'dopamine hypothesis' in the early 1990's (Robbins & Everitt, 1999). Dopamine has been the traditional focus of research into drug addiction and its' role in drug reinforcement has been well supported by studies of repeat self-administration of morphine by rats (Bozarth & Wise, 1981) and living brain tissue analysis (Rossetti, Melis, Carboni, & Gessa, 1992). Indeed drug addiction has been characterised as a dopamine-dependent learning disorder (Di Chiara, 1999). The ability of drugs of abuse to increase brain dopamine concentration in limbic areas is central to their reinforcing effects (Goldstein and Volkow, 2002: p1642), this propensity to repeat

behaviours that lead to rewarding drug effects (experience of pleasure) is considered to be an example of 'positive reinforcement' (Robbins & Everitt, 1999: p.567). Other areas of the brain record the experience in memory and create associations ('conditioned associations'-see section 1.4.4.) between the pleasant feelings and the behaviours and circumstances of drug administration.

1.3.3. The inhibitory role of the mesocortical system

The mesocortical system operates in parallel with the mesolimbic system, but importantly, both systems interact in a circular nature. The mesocortical system comprises a circuit of projections between the prefrontal cortex, orbitofrontal cortex and the anterior cingulate and has a central role in behaviours related to intoxication, drug incentive salience, craving and compulsive administration behaviour. Crucially, the orbitofrontal cortex exerts an inhibitory function over these behaviours.

1.3.4. Tolerance and dependence

Repeated administration of opiates causes a process of neuroadaptation to occur in the brain: brain function adapts to the presence of exogenous opioids such that it operates close to a normal state when the drugs are present and abnormally when they are not. With repeated use, tolerance develops quickly so that high doses, which would have been dangerous previously, can be administered. Tolerance occurs because neurons with mu receptors gradually become less responsive to opioid stimulation and more opioid is required to initially stimulate the neurons in mesolimbic system to release the same quantity of dopamine.

Koob and LeMoal (2001) encapsulated this process in the 'changed set point' model of addiction whereby normal, baseline levels of dopamine are altered so that non-drug activities no longer produce pleasure when opiates are not present. Higher doses of drugs leads to severe physical dependence, which becomes apparent when administration stops and withdrawal symptoms emerge. Therefore, the process of neuroadaptation is the underlying neurobiological driving force in the development of tolerance and the dependence syndrome.

1.3.5. The withdrawal syndrome

Withdrawal involves the locus ceruleus at the base of the brain, which produces the neurotransmitter noradrenaline – a chemical modulator of wakefulness, breathing and blood pressure. In the presence of opioids, noradrenaline release is suppressed in neurons in the locus ceruleus, resulting in drowsiness and depressed breathing. However, neuroadaptation in an opiate-dependent user causes neurons to increase their activity levels (and noradrenaline levels) to maintain the status-quo in order to permit approximately normal levels of wakefulness. Therefore, when opioids are absent, the increased activity of neurons leads to excessive amounts of noradrenaline precipitating withdrawal symptoms including jitters, sweating, diarrhoea, runny eyes and nose, increased blood pressure, cramps, insomnia and fever. Withdrawal peaks during the third and fourth days of abstinence and subsides within 7 days. Traditionally, it was believed that withdrawal was the key feature of addiction, but craving and relapse can occur weeks, even months after withdrawal symptoms have disappeared which suggests that psychological mechanisms are also important (NIDA, 2000).

1.3.6. Diagnosis of substance-dependence

The diagnostic and statistical manual of mental disorders (DSM-IV; APA, 1994) lists two substance-related diagnoses: substance-induced disorder (behavioural syndrome caused by direct effect on the central nervous system) and substance use disorder (describes pattern of problematic substance use and dependence). Twelve classes of substance are recognised within the substance-related diagnoses including opioids. Opioid dependence is classified according to the criteria below. Criteria 1 and 2 refer to features of physiological dependence and criteria 3-7 refer to compulsive use.

Criteria for opioid dependence - 304.00 (DSM-IV, 1994)

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 twelve-month period.

1. Tolerance, as defined by either of the following:
   a) A need for markedly increased amounts of the substance to achieve intoxication or desired effect.
   b) Markedly diminished effect with continued use with the same amount of the substance.
2. Withdrawal
   a) Characteristic withdrawal syndrome, as manifested by either of the following:
      (A) i. Cessation or reduction in opioid use that has been heavy and prolonged (several weeks or longer)
      ii. Administration of an opioid antagonist after a period of opioid use.
      (B) 3 (or more) of the following, developing within minutes to several days after criterion (A): dysphoric mood; nausea or vomiting; muscles aches; lacrimation or rhinorrhea; papillary dilation, piloerection or sweating; diarrhoea; yawning; fever; insomnia.
   b) The same or closely related substance is taken to relieve or avoid withdrawal symptoms.
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 (e.g. visiting multiple doctors or travelling long distances).
6. Important recreational, social or occupational activities are given up or reduced because of substance use.
7. The substance is continue despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance e.g. current cocaine use despite recognition of substance induced depression.

Specify if: With physiological dependence-evidence of tolerance or withdrawal.
Without physiological dependence-no evidence of tolerance or withdrawal.

1.4. The development of frontal theories of drug addiction

In the late 1980's and early 1990's, several papers were published that linked drug use to changes in prefrontal cortical function: reinforcing effects of cocaine in medial prefrontal cortex (Goeders & Smith, 1986) and reductions in frontal metabolism as a result of cocaine addiction (Volkow, Fowler, Wang et al., 1993). A few years later, research interest extended to the effects of chronic opiate use also. In recent publications, deficits in so-called 'frontal functions' have assumed an etiological role in theories of drug addiction, most of which place a common emphasis on the role of impaired inhibitory processes in addiction.

Enhanced spatial resolution of new generation imaging scanners (e.g. PET, fMRI) has permitted detailed in-vivo analysis of neurobiological functioning functions associated with diverse aspects of drug addiction. However, imaging studies alone cannot answer questions of causation, as they intrinsically provide correlative data only and are associated with complicated interpretative issues (imaging studies will be discussed briefly only). However, recent neurocognitive research (discussed in section 1.10.) has converged with the results of imaging research upon the notion of impaired frontal functioning as a result of chronic substance use (London, Ernst, Grant, Bonson & Weinstein, 2000).

1.4.1. Neuroimaging evidence of orbitofrontal dysfunction in drug addiction

London et al. (2000) hypothesized a central role of the orbitofrontal cortex in drug addiction. The authors reviewed imaging studies of polydrug and cocaine users in relation to three key aspects of addiction: expectancy behaviour (based on predictions of

reward and probabilistic associations to stimuli), craving to use drugs and decision-making (based on weighing-up of immediate and long-term costs and benefits). An integrative function of the orbitofrontal cortex in these three aspects was supported by findings across studies of increased glucose metabolism in orbitofrontal cortex during conditions of expectancy of drug effects and correlations between self-reports of craving and metabolic increases in medial orbitofrontal cortex (and 5 other areas). Findings related to decision-making will be discussed in the neurocognitive section 1.3. Moreover, the authors characterised the orbitofrontal cortex as a 'critical node' in the processing of different aspects of addictive processes mediated by different cortical circuits. A view shared by Jentsch and Taylor (1999), who previously posited the inhibitory control of reward-seeking behaviour as dependent upon corticostriatal projections from medial frontal cortex to the caudate nucleus and the nucleus accumbens.

1.4.2. Cognitive deficits model (Kosten & George, 2002)

Addiction has been described in terms of a cognitive deficits model by Kosten and George (2002). They proposed that the signalling function of prefrontal cortex (to the mesolimbic reward system) is compromised in drug addiction. The authors accounted for clinical observations that drug addicts have a reduced ability to use judgement to constrain their responses, in terms of impaired inhibitory signalling to the dopamine neurons in the ventral tegmental area of the mesolimbic system.

1.4.3. Impaired response initiation and salience attribution (I-RISA) model (Goldstein & Volkow, 2002)

Goldstein and Volkow (2002) claimed that the central tenet of the dopamine hypothesis – that the reinforcing effects of increased dopamine concentration in the brain lead to addiction was insufficient to account for the transition from drug use to addiction. They hypothesized that changes in the functioning of the striatal-thalamo-orbitofrontal circuit were more important because of its inhibitory function over behaviour. Drug addiction was conceptualised as a syndrome of 'impaired response inhibition and salience attribution' (I-RISA), wherein inhibitory, prefrontal top-down processes are reduced consequently releasing behaviours that were previously under control. Within the I-RISA model, continual motivation to use drugs is the result of behaviour becoming increasingly captured ('stimulus-driven') by schema-like memory structures containing drug-related knowledge ('action tendencies') (Goldstein & Volkow, 2002: p.1643). Action tendencies contain information related to positive and negative reinforcement of intoxicating drug-effects and therefore drive the user's motivational state. Attribution of primary salience to drug-related stimuli occurs rapidly and other potential rewarding stimuli become less salient to the user.

Relapse and bingeing were hypothesized to be the result of impulsive responding (i.e. response disinhibition) to immediate and salient drug-related rewards (Goldstein & Volkow, 2002; p.1648). They hypothesized that response inhibition deficits are linked to changes in orbitofrontal, anterior cingulate cortex and the striatum on the basis of convergent findings from imaging studies that found greater activation in orbitofrontal and anterior cingulate cortex during several tasks requiring response inhibition.

1.4.4. Associative learning in drug addiction

The orbitofrontal cortex has been linked to the process of associative learning in drug addiction (as well as the amygdala, hippocampus, nucleus accumbens and striatum). Robbins and Everitt (1999) described the progression to addiction as a process of 'aberrant learning', wherein drug-related behaviours become powerfully associated with cues in the environment ('conditioned stimuli'), so that these areas are activated merely by the sight of drug-related paraphernalia and relevant situational contexts. Within this model, 'addictive behaviour [such as drug-seeking] is, to some extent, ultimately divorced from the original drug effect that generated its development' (p.569). Substitute prescribing treatments (e.g. methadone), which provide an alternative drug effect may be limited in their ability to prevent users engaging in habitual behaviours. Impairments in inhibitory processes (widely associated with prefrontal cortical function) may contribute to increased impulsivity and risk-taking, which consequently may lead to relapse among abstinent users. Robbins and Everitt (1999) proposed that treatments that focus on conditioning and memory retrieval processes may reduce cue-induced drug-seeking.

1.5. Heath and social problems associated with heroin addiction

Pure opiates are relatively non-toxic to living tissue and organs, indeed a long-term user supplied with pharmaceutical opiates is unlikely to experience the organ damage associated with alcohol and cigarette use (Teeson, et al., 2002). However, many health complications arise as a result of injecting practices: scarred and/or collapsed veins, bacterial infection of the blood vessels and heart valves, abscesses and other soft-tissue infections and liver, kidney and lung disease. There is a high prevalence of additives in street heroin that clog blood vessels and cause infection (NIDA, 2000). High rates of

psychological disorder are documented among heroin users also, most commonly depression, anxiety disorders and antisocial personality disorder (Darke and Ross, 1997). The social ramifications of heroin addiction are serious including social exclusion, high rates of criminality and high-risk behaviour (DOH, 2001).

1.6. Risks associated with heroin overdose

The risk of overdose is high with opiates such as heroin – a median of three life-time overdoses per user has been measured in a sample of 329 heroin users (Darke, Ross & Hall, 1996). Overdose has been linked to variations in the user's tolerance to opiates, contrary to popular beliefs regarding fluctuations in the purity of street drugs (Teeson et al., 2002). Estimates of mortality rate among heroin users is 1%, which is 13 times higher than age-matched peers (English, Holman, Milne, Winter, Hulse, Lodde, et al., 1995). Studies of non-fatal overdose prevalence among regular users suggest that it is high (Warner-Smith, Lynskey, Darke & Hall, 2001) and is associated with extensive overdose-related morbidity. Warner-Smith, Darke and Day (2002) found that in an Australian sample of 198 heroin users, 69% had experienced a heroin overdose which led to physical injury (40%), burns (24%), assault whilst unconscious (14%), peripheral neuropathy (49%), temporary paralysis of limbs (26%) and seizure (2%). A more serious consequence of overdose relates to hypoxic brain damage, which results in diffuse neuronal death and has been associated with permanent cognitive slowing, memory and attention deficits and impaired reasoning abilities (Darke, Sims, McDonald & Wickes, 2000).

1.7. Epidemiology of opiate abuse

The number of opiate users presenting for treatment to UK health services has increased steadily for the past decade. During a 6-month period in 2000, 64% of 33,093 drug users who presented for treatment identified heroin as the main drug of use, which represents an increase from 46% of 16,810 users presenting for treatment in 1993 (DOH, 2001). Prevalence estimates of the total number of opiate users in the UK vary greatly according to the measurement method employed: in 1996 estimates ranged from 162,544 (treatment demographic method) to 251,000 (Household survey) (DOH, 2001).

1.8. Methadone maintenance treatment

1.8.1. Characteristics of methadone treatment

Methadone is the most widely used pharmacotherapy for the treatment of heroin addiction and represents the most commonly offered medical treatment to users presenting to health services (Teeson, Degenhardt & Hall, 2002). The selection of methadone as a treatment was guided by a number of pharmacological features of opioids and the prevailing 'harm-minimisation' ethos of drug services of the late 1980's, which accepted that abstinence-based approaches were not popular among users. Opioid analgesics can be substituted easily for each other and methadone, if calibrated to the correct dose, prevents the onset of withdrawal symptoms. Methadone is a long-acting opioid – its effects last for approximately 24 hours (six times as long as heroin), which means it need only be taken once per day. Also, methadone can be administered orally, thus reducing risky injecting practices and the spread of infectious disease. Patients are typically commenced on a daily dose of 20 mg to 30 mg, with titration in 5 mg steps up

to a dose of 60-100 mg per day (although doses may exceed this amount). Methadone does not tend to produce feelings of euphoria associated with heroin and, in long-term methadone users, methadone may even block the euphoric effects of heroin (NIDA, 2000). Higher doses are documented as fully suppressing opioid craving (Kosten & George, 2002).

In a meta-analytic review of methadone maintenance therapy outcomes, Mattick, Breen, Kimber and Davoli (2003a) found that methadone had superior retention rates compared to waiting-list, placebo and detoxification controls. In studies conducted in Thailand and USA, methadone treatment has been found to reduce the user's heroin use (Vanichseni & Wongsuwan, 1991; Strain, Stitzer, Leibson & Bigelow, 1993). Ward (1992) demonstrated that methadone treatment improved outcome for users as a function of correct dosing, the intensity of services offered and the quality of relationships with staff. In a later study, Ward, Mattick and Hall (1998) found that methadone maintenance reduced prevalence of infectious disease, injection-related pathology and psychological problems.

However, methadone treatment has been subject to a degree of controversy on account of conflicting evidence regarding outcomes and differing views related to the ethos of a maintenance approach – these issues are briefly discussed as follows.

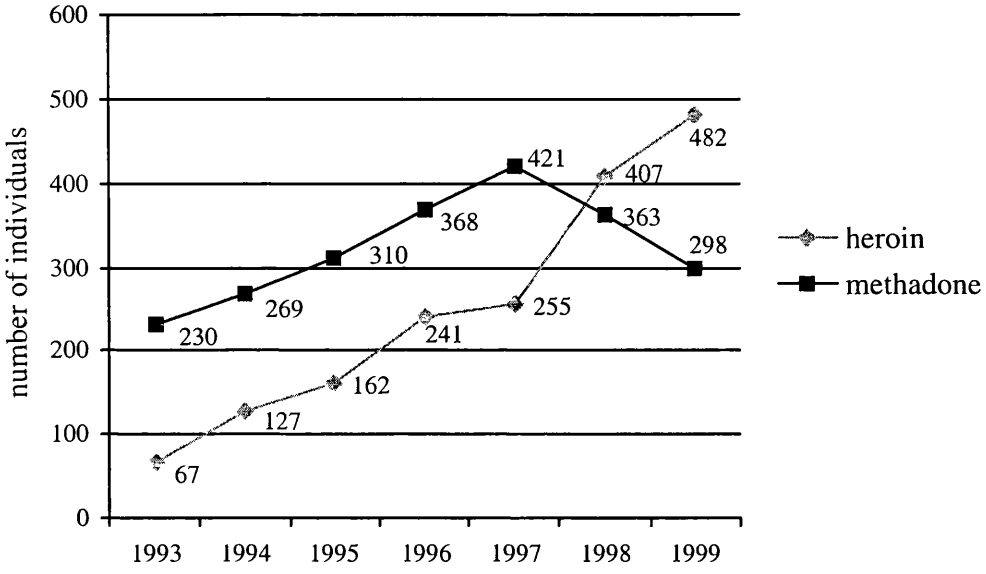
1.9. Controversial issues in methadone maintenance treatment

1.9.1. Outcomes in methadone treatment

The Department of Health report on drugs (2001) noted that recent media attention has focused increasingly on the question of legalisation, in terms of asking the general public to question whether it is the substance heroin *per se* which causes most damage or the ramifications of it being illegal. Methadone maintenance is widely considered to remove the need for the user to engage in criminal activity to fund the purchase of heroin (average monthly expenditure of a regular user of heroin has been estimated at £709.60: DOH, 2001). It has been argued, however, that many users continue to inject illicit heroin despite receiving oral methadone (Meyers, 1995). In Mattick et al.'s (2003a) meta-analytic review, it was found that engagement in methadone maintenance treatment did not significantly reduce criminal activity, although there was a trend towards lower numbers of convictions among those in treatment.

Similarly, Mattick et al. (2003a) found no evidence that methadone significantly reduced the number of drug-related deaths. Indeed, statistics published by the Department of Health (2001) indicated that, until very recently, more deaths in England and Wales were associated with methadone than heroin use (see Figure 2.). The potential for methadone to be diverted onto the black market is high and obviously carries serious repercussions. Clearly, methadone is a highly dangerous medication and because of its full agonist action at the mu receptor site, there is no ceiling to the level of respiratory depression that it can induce (Mattick et al., 2003b).

Figure 2. Number of deaths where methadone & heroin were mentioned on the death certificate, England & Wales, 1993-1999 (ONS 2000a, 2000b, 2001 cited in DOH, 2001)



1.9.2. Methadone dependence

Methadone causes severe physical dependence in the user and is associated with a similar withdrawal syndrome as heroin. Moreover, the degree to which a methadone maintenance treatment addresses the underlying causative factors in addiction is limited, given that lifelong treatment has been advocated for many users and relapse is common when maintenance is discontinued after 2 years or less (Kosten & George, 2002). Meyers (1995) took a sceptical view of the 'treatment' capacity of methadone, noting that patients often find little relief from anxiety of 'withdrawal from the major pharmacological-reward' such as that produced by injected heroin and consequently seek higher doses of methadone. Higher doses, he claimed, lower the patients' capacity to function and increase their dependency-'if the goal of the program is control of the

user-that is, a reduction in criminal activity-the course will be judged satisfactory. It cannot, however, be called treatment' (Meyers, 1995: p.464).

1.9.3. Differentiating the cognitive effects of methadone

Evidence is accumulating which suggests that chronic opiate use is associated with cognitive impairment (Rogers, Everitt, Baldacchino et al., 1999; Curran, Kleckham, Bearn, Strang, & Wanigaratne, 2001; Darke, Sims, McDonald & Wickes, 2000; Grant, Contoreggi & London, 2000; Ornstein, Iddon, Baldacchino et al., 2000; Specka, Finkbeiner, Loemann, Leifert, Kluwig & Gastpar, 2000; Davis, Liddiard & McMillan, 2002; Lyvers & Yakimoff, 2003). However, Rogers and Robbins (2001: p.254) noted that it is often difficult to interpret findings as, given the high incidence of methadone treatment, results may reflect an amplification of deficits on account of the pharmacological features of methadone. Many methodologies employed in opiate research do not control factors associated with methadone use, acute versus chronic effects, head injury and employment status (Mintzer & Stitzer, 2002) – these issues are discussed in section 1.15.

1.10. Neurocognitive research in chronic opiate use

1.10.1. Mixed findings on traditional measures

Early views on the neurocognitive effects of chronic opiate use lacked consensus, partly as a result of the relative paucity of research findings on which conclusions were drawn and partly because of the methodological problems of extant research. Until very

recently, less research had been conducted on the cognitive effects of chronic opiate use relative to research on the effects of cannabis and stimulants (Robbins & Rogers, 2001). Conflicting results were found in studies conducted in the 1970's and 1980's utilising traditional neuropsychological battery tests (e.g. Wechsler Adult Intelligence Scale). Evidence of impairment in polydrug users and heroin users was found by Korin (1974), Grant, Adams, Carlin, Rennick, Judd & Schoof (1978) and Hill & Mikhael (1979), in contrast, no evidence of impairment was reported by Bruhn & Maage (1975), Lombardo et al (1976) and Rounsaville, Novelly, Kleber & Jones (1981). Studies that compared the performance of methadone maintenance patients and controls suggested that simple reaction time was relatively preserved (Gordon, 1970; Rothernberg, Schottenfeld, Meyer, Krauss & Gross, 1977), whereas more complex measures of psychomotor processing speed showed evidence of impairment (Appel & Gordon, 1976).

As will be discussed, many of these early studies were methodologically flawed (Mintzer and Stitzer, 2002). Indeed, Roger and Robbins (2001) have proposed that recent improvements in the sensitivity of neuropsychological measures has allowed previously unrecognised cognitive deficits associated with frontal lobe dysfunction in opiate users to be recognised, a view which has received support from a variety of perspectives e.g. neuroimaging (see review by Jentsch & Taylor, 1999; London et al., 2000; Goldstein & Volkow, 2002) and neuropsychology (see review by Robbins & Everitt, 1999). Similarly, the existence of memory impairment in methadone maintained patients has been documented in recent research (Curran, Kleckham, Bearn, Strang & Wanigaratne, 2001).

The following discussion will focus exclusively on recent developments in executive function research in substance use, in particular, hypothesised sub-component processes related to decision-making, reward responsivity, response inhibition, impulsivity, concept-attainment and set-shifting and proceed to perceived gaps in knowledge regarding the executive abilities of substance users. The clinical implications of executive dysfunction in opiate users will also be discussed as well as methodological issues associated with measurement of these aspects of cognition.

1.11. Clinical and Experimental findings of executive dysfunction

Until very recently, exploration of the putative functions of the frontal lobes was mostly restricted to the dorsolateral regions with the exception of work on ventromedial aspects conducted by Antoine Bechara, and Hanna and Antonio Damasio. I propose that their work is highly relevant to understanding the everyday ramifications of chronic opiate use, particularly their findings of specific deficits in real-life decision-making of patients with damage to the areas of the brain (ventromedial prefrontal, amygdala) that are also believed to be affected by the major drugs of abuse. The following discussion of substance-related executive dysfunction will proceed from the work of Bechara and colleagues to perceived gaps in knowledge surrounding the executive abilities of substance users.

Although studies on opiate users are sparse in number (Ornstein et al., 2000) in comparison to research on other drugs of abuse (Roger & Robbins, 2001), recent findings have converged upon the notion of impairment of cognitive functions associated with the orbitofrontal cortex (Rogers et al., 1999) and ventromedial (Bechara,

Dolan, Denburg, Hindes, Anderson & Nathan, 2001) areas of the brain in particular. Making the link between frontal cortical dysfunction and drugs whose primary action is situated in the limbic system (e.g. opiates) has been a lengthy process, given that the reciprocal relationships between the limbic system and prefrontal cortex were delineated over 30 years ago (Nauta, 1971).

Various taxonomies of cognitive function have been developed to describe the functions of the frontal lobes, although there is widespread agreement that they subsume a 'supervisory' or 'executive' role in cognition (Lezak, 1995). However, Reitan and Wolfson (1994) noted that generalizations about behavioural correlates of frontal lobe pathology had been uncritically accepted in the literature, which has led to the dubbing of many tests as ubiquitous 'frontal measures'. As will be discussed, generalizations of opiate-related 'executive dysfunction' based on poorer task performances in opiate users, must be viewed cautiously, given the long-standing theoretical issues related to the sensitivity and specificity of executive function measures.

1.11.1. Decision-making and gambling tasks

Bechara et al. (2001: p.376) noted similarities in the decision-making and behaviour of substance-dependent individuals and those with bilateral lesions to ventromedial cortex: (1) denial or lack of awareness of having a problem; (2) a tendency to choose immediate rewards, at the risk of future negative consequences including loss of job, reputation, home and family. This impaired decision-making, dubbed 'myopia for the future' (Bechara, Damasio & Damasio, 2000), was explained as a failure of a somatic (emotional) signalling system that acts to bias or guide decisions towards advantageous

outcomes. Within this account, decision-making is not an exclusively cognitive process, rather individuals are proposed to make judgements 'not only by assessing the severity of outcomes and their probability of occurrence, but primarily in terms of their emotional quality' (Bechara et al., 2000: p.305). Damasio (1994) originally described the emotional signalling process in the 'somatic marker hypothesis'[1], which proposed that both the ventromedial prefrontal cortex and the amygdala are critical structures in the neural system necessary for activation of somatic states that guide decisions.

Damage to the ventromedial prefrontal cortex has been found to disrupt social behaviour profoundly, manifested as an inability to follow social conventions, to make disadvantageous decisions in occupational, domestic and financial settings and inability to sustain gainful employment (e.g. bankruptcy of patient EVR described by Eslinger & Damasio, 1985). Psychophysiological research concurs with this view. Patients with damage to ventromedial cortex showed diminished skin conductance responses (SCR's) when they recalled situations in which they experienced fear and punishment, in contrast to having normal SCR's when recalling other emotions (Bechara, Tranel, Damasio and Damasio, 1996; Bechara, Damasio, Tranel and Damasio, 1997). This selective inability

[1] The somatic marker hypothesis was predicated by Bechara, Damasio and Damasio (2000) on the basis of the assumption that decision-making is the product of multi-layered neural processes, some of which are conscious and overtly cognitive and depend on the support processes of attention, working memory, emotion. This view posited an emotional component within conditions of uncertainty (or risk) in decision-making, as opposed to traditional views of decision-making as a purely cognitive activity devoid of emotional content. The ventromedial cortex was proposed to provide the substrate for conditioned associative learning, whereby it holds linkages between attributes of a situation and the bioregulatory states (emotion) that were previously paired similar situations within the individual's experience (called 'somatic markers') (Bechara et al, 2000: p.296). Ventromedial linkages precipitate alarm or incentive signals (overt or covert) based on somatic states aroused by a situation, which leads to rapid rejection or endorsement of option-outcome pairs. Thus when functioning normally, somatic markers restrict the decision-making space to allow logic-based, cost-benefit analyses to be conducted more quickly and efficiently.

to re-experience the emotional state associated with fear and punishment led to the conclusion that ventromedial damage leads to a failure of triggering of fear-related somatic states when weighing-up the options for a decision. Later work by Bechara, Damasio, Damasio and Lee (1999) suggested that, the amygdala played a more pivotal role in sensitivity to fear and punishment, as it was found that damage to the amygdala, not the ventromedial cortex, prevented the evocation of somatic states of punishment after winning or losing money on a gambling task.

Gambling tasks are regarded as a tapping a fundamental aspect of addictive behaviour pertaining to the persistence of a positively rewarded behaviour despite negative future consequences. They simulate real-life decision-making and are regarded as having strong face validity (Grant, Contoreggi & London, 2000). The original gambling task developed by Bechara, Damasio, Damasio and Anderson (1994) required participants to repeatedly pick cards from 4 decks, after which they received a monetary reward. The key manipulation in the task was that, unknown to the participant, different underlying contingencies of reward (payout) and punishment (penalty) were associated with the decks. Two of the four decks had large rewards and large, infrequent penalties, which would lead to an overall loss. The other two decks had smaller rewards and small, infrequent penalties which would maximise their reward and lead to an overall gain. Patients with damage to ventromedial cortex and the amygdala typically chose cards that gave large immediate gains with poor future outcomes, unlike patients with damage to dorsolateral prefrontal cortex (Bechara, Tranel, Damasio & Damasio, 1996, 1997). Bechara (2000) later characterised the deficit observed in ventromedial patients as an

'insensitivity to future consequences' (as opposed to an insensitivity to punishment or hypersensitivity to reward).

Several studies utilising gambling tasks have suggested that abuse of many substances leads to impairments of this type of decision-making. Using a similar computerised task, Bechara, Dolan, Denburg, Hindes, Anderson amd Nathan (2001) compared the performances of 5 ventromedial patients, 40 normal controls and 41 substance-dependent individuals (heterogeneous substance use including alcohol, cocaine and metamphetamine) who had been abstinent for 15 days. The substance-dependent group showed wide variation in their performance, although a substantial sub-group (61%) performed as poorly as the ventromedial patients, compared to (31%) of controls who performed at the same level. The ability to hold and maintain gainful employment was one of the few demographic predictors of performance on the gambling task. Drug of choice was not significantly correlated with performance, rather performance was best predicted by an index which included factors of duration of abstinence, years of abuse, relapses and times in treatment and employment. Moreover, intelligence, memory and performance on other neuropsychological measures (e.g. Stroop, WCST, WAIS-III) were not highly correlated with this type of decision-making, which suggested that impairments were not attributable to generalized frontal lobe dysfunction.

Large individual variability in quality of decision-making between substance users was also found in a study by Grant, Contoreggi and London (2000). Impaired performance on the gambling task was found in 30 substance users (history of opioid or stimulant use) compared to 24 un-matched, healthy controls. Almost 50% of the substance users

made poor decisions that resulted in long-term losses and obtained scores similar to ventromedial patients in the Bechara et al. (1994) study. However, the authors were unable to attribute the observed deficits in the substance users to a specific drug of abuse, as most reported histories of polysubstance use.

Gambling task performance, future orientation and the ability to conceptualise the future (as measured by the Future Time Perspective (FTP) inventory) was assessed by Petry, Bickel and Arnett (1998) in 34 opiate users in buprenorphine maintenance treatment. Opiate users were found to be less likely to predict events far into their future, less likely to systematically organise the future and tended to choose cards on the gambling task that had poor future outcomes compared to controls. The underlying causal mechanism of a 'shortened time horizon' (Petry et al., 1998: p.735) was not explained fully however, and the authors could not distinguish between competing hypotheses that, either it reflected a pre-existing risk factor for developing addiction, or alternatively, that it resulted from drug-induced functional and physiological change.

A psychopharmacological perspective on substance-users' deficits on the gambling task has been advanced by Rogers et al., (1999) who claimed that, opiate-related deficits were best understood in terms of short-term changes in the neuromodulation of circuitry of the ventral prefrontal cortex, ventral striatum and the amygdala. Rogers et al. (1999) assessed the hypothesis that different patterns of impairment would be found between stimulant and opiate users due to different sites of receptors implicated in the respective substances. Performance on a computerised version of the gambling task was compared in 18 amphetamine users, 13 opiate users (10 methadone maintained), 20 patients with

frontal lobe damage (10 orbitofrontal, 10 dorsolateral/medial) and 26 healthy age- and IQ-matched controls. Opiate users, orbitofrontal patients and amphetamine users took significantly longer to choose between two possible decisions than controls. However, the quality of opiate users' decision-making was not impaired as found in the former two groups, which suggested that opiate users were equally able to choose advantageously. As commonly found in substance-use research, the drug-taking profiles of the groups posed problems for the interpretation of findings as all substance users were engaged in polysubstance use: the authors noted a high rates of opiate use among the amphetamine users. Qualitative differences have also been found between a group of 22 heroin users (20 methadone maintained, 2 naltrexone maintained) and 23 active amphetamine users (10 taking prescribed dexamphetamine), whereby heroin users made significantly less use of an efficient strategy on a spatial working memory task (Ornstein, Iddon, Baldacchino, Sahakian, London, Everitt & Robbins, 2000).

Evidence of dissociations in performance between different neuropsychological tasks was found by Mintzer and Stitzer (2002). They compared 18 methadone-maintained patients to 21 matched-controls on a variety of neuropsychological tests including a modified gambling task. Impairments in working memory, metamemory, slowed psychomotor performance and sensitivity to interference effects on the Stroop test, contrasted with relatively preserved time estimation and recall and recognition of words. The methadone patient group exhibited a selective impairment in decision-making on the gambling task, whereby they made significantly more disadvantageous decisions only when choosing cards from decks with a low frequency of penalties. Mintzer and Stitzer (2002) hypothesised that the decision-making impairments observed in opiate

users could be minimised therefore, by increasing the saliency of perceived penalties by manipulation of frequency contingencies.

Gambling tasks, modelled on the Bechara et al. (1994) task, have revealed qualitative differences in the decision-making of substance users that may mirror real-life decision-making under conditions of risk, reward and uncertainty. Modifications of the parameters of tasks have further delineated opiate users' decision-making related to increased delibaration time (Rogers et al, 1999) and possible insensitivity to low salience stimuli (Mintzer & Stitzer, 2002), although, as yet, it is unknown whether Bechara's depiction of ventromedial patients as 'insensitive to future consequences' applies equally to substance users. Reward responsivity (discussed in following section) is a simpler index of sensitivity to environmental incentives and is considered to be meritous in providing a relatively purer measure of reward-related motivational state.

1.11.2. Reward responsivity

The effects of chronic psychostimulant use such as cocaine on reward-related brain circuitry is now well-documented (see Porrino & Lyons, 2000), however much less is known of the effects of chronic opiate use. Recent imaging studies (PET) have found differences in brain activation during the processing of reward in opiate users compared to non-drug using controls (Martin-Soelch, Chevalley, Künig, Missimer, Magyar, Mino, Schultz & Leenders, 2001). Non-monetary reinforcement appeared to have insufficient motivational value for opiate-dependents as indicated by lower activation levels, a finding also obtained in smokers (Martin-Soelch Magyar, Künig, Missimer, Schultz & Leenders, 2001). Powell, Dawkins and Davis (2002) hypothesised that activation of

reward-related circuitry in the brain is compromised in substance-dependents including nicotine-addicted smokers. According to this view, drug-induced activation leads to further priming of drug-taking behaviours and that repeated activation of reward pathways (including prefrontal cortex), as a result of chronic substance use, has a facilitative effect on executive functions 'in the organisation and execution of an effective plan directed at the acquisition of the desired reinforcer' (p.152). In contrast, it was proposed that withdrawal from drugs (or acute abstinence) is associated with a motivational disturbance, which manifests as a lowering of desire for non-drug incentives/rewards and may be linked to reductions in dopamine transmission in the ventral striatum that occur during withdrawal states (Altmann, Everitt, Glautier, Markou, Nutt, Oretti et al., 1996 cited in Powell et al., 2002). Likewise it was predicted that acute withdrawal states would also be associated with impairments in executive abilities (Powell et al, 2002). As previously discussed, it is well documented that chronic opiate use leads to alterations in neural circuitry supporting dopamine transmission. However, little is yet known of how these physiological changes translate at a behavioural level, in terms of reward-related behaviour and responsivity.

To test the hypothesis that acute abstinence was associated with weakened incentive motivation, Powell, Al-Adawi, Morgan and Greenwood (1996) designed a reward responsiveness task-Card Arranging Reward Responsivity Objective Test (CARROT) which measures the extent to which individuals increase their performance speed when offered a financial incentive. In essence, the CARROT is a psychomotor task (see Method for details), which yields measures of card sorting speed under conditions of reward and non-reward. Reward responsiveness performance was found to be

dissociable from simple psychomotor speed (as measured by the digit-symbol coding test) (Powell & Al-Adawi, 1997). Clinical motivation, operationally defined as the level of active participation in treatment, was significantly correlated with accelerated card-sorting speed induced by financial incentive in 54 brain-injured patients undergoing in-patient rehabilitation (Al-Adawi, Powell & Greenwood, 1998). Powell et al. (1996) suggested that, motivational deficits such as failing to respond to prompts and encouragement have repercussions for progress in rehabilitation. Reward responsiveness was also found to correlate highly with performance on executive function measures of verbal fluency, set-shifting (modified WCST; Nelson, 1976) and planning (Tower of London; Shallice, 1982). Al-Adawi and Powell (1997) found that reward responsiveness increased to normal levels in abstaining smokers after smoking a single cigarette. A comparable improvement in performance of verbal fluency and digit span was also found after smoking.

1.11.3. Response inhibition and cognitive impulsivity

Chronic opiate users have been found to score highly on trait impulsivity scales of personality inventories (Rogers & Robbins, 2001) and exhibit impulsive responding on experimental tasks (Madden & Petry, Badger, Bickel, 1997; Lee & Pau, 2002), findings that have important clinical implications for treatment. Jentsch and Taylor (1999: p.379) proposed that the impulse to seek drugs, results from subcortical dopaminergic enhancement of stimulus-reward learning. Importantly, they argued, this impulsivity is reinforcing because repeated drug consumption further impairs the frontostriatal inhibitory processes that combat impulsivity. This process of reciprocal reinforcement has been linked to recidivism and susceptibility to relapse among drug users.

Unfortunately, the complexity of many experimental tasks employed coupled with the lack of comparison neuropsychological measures (e.g. Lee & Pau, 2002) has made it difficult to differentiate loss of inhibitory control from more generalised attentional difficulties.

1.11.3.*i. Stroop test*

The Stroop colour-word paradigm (Stroop, 1935) is widely considered to measure response inhibition or suppression of a habitual response (Perret, 1974). It assesses the ability to selectively attend to one stimulus attribute (name the ink colour of a written word e.g. red) when another stimulus attribute is incongruous (the word spells the name of a different colour e.g. green), thus naming the word requires the suppression of an irrelevant word. The increase in time to respond is believed to be a measure of response inhibition and has been found to be longer in methadone maintained patients compared to controls (Mintzer & Stitzer, 2002).

However, Bechara, Damasio and Damasio (2000) differentiated two types of impulsivity: 'motor impulsiveness' was equated to the concept of response inhibition, typically measured by tasks that require inhibition of a previously rewarded or cued response. Whereas 'cognitive impulsiveness' was described in terms of an inability to delay gratification, and represents a more complex form of disinhibited behaviour. Ventromedial patients were found to switch decks on a gambling task when they received a penalty, which suggested that they were able to inhibit responses that had been previously rewarded. Bechara et al. (2000) proposed that ventromedial patients' impaired decision-making instead reflected cognitive impulsiveness because they

appeared unable to resist the gratification of large immediate reward decks by their tendency to return to disadvantageous decks quickly. Interestingly, in another study, Bechara et al. (2001) found that substance users' decision-making was significantly impaired on the gambling task, although to a lesser degree than ventromedial patients, yet both groups were found to perform at a similar level on the Stroop task. This finding suggests that subtle differences exist between these two groups that are difficult to tease apart utilising these two complex tasks. Moreover, there is little agreement in the literature on what underlying processes are tapped by the Stroop, indeed some view it as more of a test of general concentration (Lezak, 1995).

1.11.3.*ii. Verbal fluency*

Perret (1974) found that brain-injured patients who did badly on the Stroop test were most likely to have reduced verbal fluency for words, which led him to conclude that both tasks tapped similar underlying cognitive processes. The Controlled Oral Word Association Test (Benton, 1968; Benton & Hamsher, 1976) is the most widely used test of executive functioning associated with the frontal lobes (Parker & Crawford, 1992). The test is easy to administer, reliable and has good discriminatory power (Denckla, 1994). It has been found to be particularly sensitive to left frontal damage and its sensitivity is partially believed to derive from the fact that generation of words based on an initial letter is a highly novel task that requires participants to formulate their own strategy (Parker & Crawford, 1992). Although some view reduced fluency as a problem of response initiation, Perret (1974) proposed that fluency tasks demand the suppression of normal word retrieval strategies (usually based on word meaning). Fluency tests therefore require novel, effortful retrieval strategies and performance is largely

determined by the efficiency of the strategy employed (Baddeley, 1990). Reduced word fluency has been found in heroin and amphetamine users (Ornstein et al., 2000) and methadone maintained patients (Darke, Sims, McDonald & Wickes, 2000; Davis, Liddiard & McMillan, 2002) suggesting reduced strategy efficiency in these groups.

The assumption that fluency reflects executive function is widely debated, given that some frontal patients with executive difficulties perform well on fluency (Shallice & Burgess, 1991). Also, it is known that fluency performance is related to verbal intelligence, education and age in normal individuals, which suggests that letter fluency deficits should not automatically be assumed to reflect dysexecutive problems. However, Phillips (1997: p.198) noted that the associations between fluency and intelligence may not exclude the role of executive processes in task performance, given that several recent accounts have claimed that 'individual differences in intelligence reflect the efficiency of executive control over cognitive function'.

1.11.3.*iii. Hayling sentence completion test (Hayling; Burgess & Shallice, 1996a)*

Burgess and Shallice (1996) noted that it was difficult to make interpretations regarding the executive abilities of frontal patients' (in particular their response initiation and inhibition abilities) on the basis of fluency and the Stroop test when the characteristics of each test differed greatly. The authors developed the Hayling Sentence Completion test (Hayling) to overcome this issue, by designing a task with two component parts that separately measured initiation and inhibition but comprised the same underlying structure. The Hayling consists of 30 sentences in which the last word is missing, whereby the meaning of the sentence acts as a cue to the missing word so that there is a

high probability of a specific word being chosen by the participant (see Method section). In the initiation condition, the participant is required to give a word that completes the sentence, whereas in the inhibition condition, the participant must give a word that makes no sense in the sentence. In a study utilising the Hayling (Burgess & Shallice, 1996), patients with lesions that included the frontal lobes (anterior group) showed deficits in initiation and inhibition compared to age- and IQ-matched controls and patients with lesions in posterior regions. The anterior group also made more erroneous straightforward completions in the inhibition condition and gave more answers that were semantically related to the sentence.

Nathaniel-James, Fletcher and Frith (1997: p.560) proposed that, in the initiation part of the Hayling, words are accessed via an automatic association process, whereas effortful, strategic processes governed by the Supervisory Attentional System[2] (Norman & Shallice, 1980) are required for correct completion of the inhibition section. Burgess and Shallice (1996) found that although unilateral frontal patients (left and right) were impaired on both parts of the test, their performance of the initiation part was not correlated with performance on the inhibition part, thus they deduced that initiation and inhibition problems could be impaired singly. Nathaniel-James et al. (1997) explored

[2] Norman and Shallice (1980) originally developed a model of attention, in which they made the distinction between automatic and effortful attentional mechanisms governing the selection of actions: *Contention scheduling* is the process of routine selection of routine actions, whereas situations involving planning, decision-making, error-correction and the suppression of a habitual response require the second selection mechanism-the *Supervisory Attentional System* (SAS). The SAS was postulated to operate by biasing the contention scheduling process and to be intrinsically domain non-specific, exerting an executive role over the selection of behaviour. Shallice (1988) hypothesised that the SAS was localised within prefrontal cortex and cited the rigidity, stuck-in-set perseveration, distractibility and stimulus-bound behaviours of frontal lobe patients as supportive evidence.

cortical activations (via PET imaging) during Hayling performance in healthy volunteers and found overlaps in terms of activation of the medial prefrontal areas (including anterior cingulate) during both conditions. This led the authors to conclude that damage to medial prefrontal regions such as the anterior cingulate could be sufficient to impair performance on both parts of the Hayling. However, it is unknown whether cortical activations are representative of the cognitive strategies being employed during performance of the task. As yet, the Hayling test has not been applied to the assessment of response initiation and inhibition in substance-users.

1.11.4. Concept attainment and set-shifting

1.11.4.*i. Wisconsin card sorting test (WCST; Milner, 1963)*

Tests of concept attainment attempt to measure an aspect of abstract reasoning related to the ability to conceptualise abstract rules (conceptual set attainment) and shift behaviour in response to changes in set (set-shifting). A cardinal feature of a 'frontal' deficit on set-shifting tests, such as the WCST, is a higher rate of perseveration on previously active sets. Such perseverative responding has been explained in terms of an inhibition failure, whereby the individual becomes stuck-in-set because the currently active sets are not inhibited in response to new stimuli. Perseverative behaviour on the WCST is widely considered to be of clinical significance (Parker & Crawford, 1992).

Evidence of drug-related deficits on tests of set-shifting behaviour is mixed (Ornstein et al., 2000). A recent study found increased perseverative responding on the WCST in a group of methadone maintained patients in early withdrawal (24 hours after last dose)

(Lyvers & Yakimoff, 2003). Higher perseverative errors and responses were correlated with greater severity of opioid dependence. However, findings are by no means consistent. Results of earlier studies of set-shifting behaviour found no evidence of impairment on the WCST in polysubstance users (Grant et al., 2000) or in the category-shift performance of heroin users (Ornstein et al., 2000). A key difficulty with the WCST relates to its purity as a measure of executive function as the test is highly complex and probably requires the synthesis of many component skills. Likewise, the status of the WCST as a measure of frontal lobe function has been strongly contested by Reitan and Wolfson (1994) on the grounds that the test does not reliably differentiate groups of patients with frontal and non-frontal lesions.

1.11.4.*ii. Brixton test (Brixton; Burgess & Shallice, 1996b)*

The Brixton test was inspired by the WCST, but it was developed as a less complex measure of rule attainment abilities. The test assesses the ability to predict the spatial position of a circle that moves around a stimulus array according to a series of simple rules. The participant must induce the rule from the previous position of the circle and be alert to unpredictable changes in the active rule. Burgess and Shallice (1996b) aimed to assess the propensity of participants to make bizarre guesses on the basis of incomplete information, a characteristic that has been noted in frontal-lobe patients (Miller, 1992). Responses on the WCST are highly constrained by having few alternative responses, each of which is guided by perceptually salient aspects of the task (colour, shape and number attributes of card stimuli). The Brixton allows guessing to be detected more easily than is possible on the WCST by having rules based on abstract relationships that are not easily defined in terms of the perceptually salient card

attributes. In a study of Brixton performance in 77 brain-injured patients, frontal-lobe patients performed in a qualitatively different manner from non-frontal patients and made more errors overall. There was no evidence that frontal damage was associated with perseveration, instead there was a higher rate of bizarre responding which was defined as arising 'from a preference which is not based on a rational response to the current task situation'. Burgess and Shallice (1996b) considered two alternative explanations of bizarre guessing behaviour: 1) guessing as the result of 'cognitive risk-taking/ impulsivity'; 2) a failure to check the plausibility of choices and/or to modify their choice in the face of the results of their check'. The Brixton has never been administered in substance-using populations, but its simplicity and its apparent sensitivity to deficits of rule/concept attainment, make it a suitable candidate for the assessment of the cognitive abilities of substance-users.

1.12. Gaps in understanding of executive abilities of opiate users: real-world skills

Although there have been several studies of opiates users' performances on traditional, laboratory-based measures of executive function, there has been little assessment of their real-world skills. Shallice and Burgess (1991) demonstrated that many standard executive measures do not pick-up the deficits often exhibited by patients with frontal lobe damage in real-life, such as situations where they have to organise or plan their behaviour, react to novelty or prioritise competing tasks. Individuals with executive dysfunction are problematic to assess because their individual component abilities may be intact, but their ability to synthesise and initiate these skills is often impaired (Burgess & Alderman, 1990). Several cases have been documented of frontal-lobe patients who have performed well on neuropsychological tests but experienced severe

difficulties in everyday life such as maintaining gainful employment (Eslinger & Damasio, 1985; Shallice & Burgess, 1991). This raises the question of whether the real-life difficulties of substance-users have a cognitive basis that is similarly being overlooked by standard neuropsychological tests.

Two tasks were developed by Shallice and Burgess (1991): the Six Elements Test and the Multiple Errands Test – in an attempt to capture those aspects of executive function that are not tapped by traditional measures. Successful performance of both tasks required participants to plan, organise and execute a number of sub-tasks in order to achieve an overall goal. Each task therefore taxes effortful, 'multi-tasking' abilities, a characteristic that simulates the type of planning and decision-making involved in many everyday activities such as shopping or preparing meals. Shallice and Burgess (1991) demonstrated that these two tasks were sensitive to the dysexecutive impairments of 3 frontal-lobe patients, who had severe impairments in everyday activities, but whose performance on standard IQ tests (WAIS) was above average. Shallice and Burgess (1991) claimed that most accounts of planning behaviour did not fully explain the opportunistic nature of human planning, whereby the initial plan may not correspond to the completely worked out course of action or well-developed strategy (p.737). They reasoned that there must be a process analogous to intentions, whereby the individual can adapt their plan according to on-line changes that arise and realise their intentions at later points. They invoked the concept of "markers" which are messages *"that some future behaviour or event should not be treated as routine and instead, some particular aspect of the situation should be viewed as particularly relevant for action. If the behaviour or event does occur later, then the marker would be triggered and this would*

lead to the inhibition of the activity being carried out" (p.737). Marker creation and triggering processes were considered part of the "bridge processes" governed by the Supervisory Attentional System. The authors classified frontal lobe patients' errors during multi-tasking performances (on the Six Elements and Multiple Errands tests: Shallice & Burgess, 1991) according to the proposed stage of planning at which the error occurred and found that marker errors were a particularly important problem for frontal lobe patients. Marker errors were manifested as spending too long on a single subtask without switching and not complying with task rules and requirements, behaviours that the authors suggested could be linked to a "failure to inhibit central sets" (p.739) i.e. currently active schema. A key difficulty with Shallice and Burgess's argument, however, relates to the untestability of their hypotheses; it is impossible to empirically distinguish a marker creation error from a marker triggering failure.

Wilson, Evans, Emslie, Alderman and Burgess (1998) aimed to develop an ecologically-valid assessment tool that would 'map onto real-life behaviours' (p.226) and, consequently, constructed a battery of tests – the Behavioural Assessment of the Dysexecutive Syndrome (BADS) – which included a modified version of the Six Elements Test. They also developed a Dysexecutive Questionnaire (DEX), to capture the full range of problems the individual may experience in daily life. Two versions of the DEX were developed: a self-report version for patients and an independent-rater version where people who know the patient well (e.g. relatives, carers, health professionals) can rate their observations of the patients' difficulties. Interestingly, it was found that frontal lobe patients rated themselves as having fewer dysexecutive problems than independent-raters, which the author claimed was due to a lack of insight in brain-injured patients

(Burgess, Alderman, Evans, Emslie & Wilson, 1998). Control participants, on the other hand, did not rate themselves differently to independent-raters. Following factor-analysis of DEX scores, Burgess et al. (1998) derived five separate factors from the DEX related to inhibition, intentionality, executive memory, positive affect and negative affect. Given the possibility that opiate users may experience difficulties in many domains of real-world skills, it seems pertinent to assess their perceptions of their own difficulties, and compare these to the views of health professional involved in their treatment such as keyworkers.

A modified version of the Six Elements test, arguably with more ecological face validity – the 'Hotel test' – was developed by Manly, Hawkins, Evans, Woldt and Robertson (2002) in a study of rehabilitation of brain-injured patients. In the Hotel test, participants were required to undertake five distinct activities that were analogous to the types of activities involved in running a hotel e.g. compiling hotel bills, organising conference name tags, opening delivery doors by pressing buttons at a specified time etc. The key skill assessed related to the ability to organise the limited time available so that equal time was given to each task. In order to achieve this, an appropriate strategy must be developed at the outset and the overall goal must be held in conscious awareness throughout so that behaviour did not become 'captured' by the current activity, leading to a disproportionate amount of time being spent on one task to the exclusion of others. Manly et al. (2002) reported that a group of 10 brain-injured patients were impaired on the task relative to 24 age- and IQ-matched controls in the following ways: patients attempted fewer tasks, they demonstrated larger deviations from optimal time allocation and they deviated greatly from the specified time to press the buttons during the task. It

is proposed, therefore that the Hotel test may represent a fairly ecologically-valid means of assessing a hitherto unexplored aspect of substance users' executive abilities. Interestingly, the provision of periodic, non-predictive alerting tones improved the performance of frontal-lobe patients to within the range of the control group. Manly et al. (2002: p.280) proposed that hearing a tone caused participants to suspend their activity, providing 'a window in which evaluation of actions against the goal is more likely to occur'.

1.13. Limited generalisability of executive function findings

Investigations of executive deficits in substance users are subject to the same long-standing caveats that have hampered the progress of understanding the complex functions of the frontal lobes. Many executive function measures have been criticised for not being specifically sensitive to frontal lobe damage (e.g. WCST; Reitan & Wolfson, 1994). Indeed there is a lack of evidence that certain measures selectively tap executive skills, as opposed to more diffuse cognitive dysfunction. A related issue lies in the interchangeable use in extant literature of the terms 'executive function' and 'frontal function', a substitution which Tranel, Anderson and Benton (1994: p.125) proposed is *"..indefensible, confusing as it does an neuroanatomical term that refers to a region of the brain, with a neuropsychological term denoting particular cognitive operations"*. Evaluation of any observed deficits on executive measures must clearly be preceded by consideration of the limits of generalisability of these measures; one cannot infer that the existence of cognitive impairment is equated with the existence of frontal pathology.

1.14. Clinical implications of dysexecutive syndrome

Aside from the aforementioned impairments in activities of everyday living (e.g. employment) executive dysfunction carries substantial clinical implications for substance users' engagement in therapy and rehabilitation. The possibility that many of substance users' difficulties may be mediated by cognitive deficits of an organic basis, necessitates a different interpretation of difficulties of impulsivity and decision-making. Moreover, it is proposed that, aspects of psychotherapy such as cognitive-behavioural therapy for substance abuse (see Beck, Wright, Newman & Liese, 1993) require a degree of self-initiation and self-monitoring in order to carry out many of the tasks of therapy. For example, a key component of relapse prevention is that the individual identifies high risk situations in advance, plans strategies to cope and gradual exposure to high risk stimuli. Psychotherapeutic techniques have been adjusted to compensate for the memory deficits of brain-injured individuals (Judd, 1999). Thus the question remains whether substance-users have cognitive deficits that, likewise, necessitate the modification of standard therapies.

1.15. Methodological considerations

1.15.1. Extraneous influences on task performance

Mood disturbance is common among substance users, although few studies take full account of this factor, which makes it difficult to differentiate the underlying cause of observed impairments on cognitive tasks (Davis, Liddiard & McMillan, 2002). It is therefore considered important to assess the influence of mood within the current experimental framework. Likewise, evidence of reduced psychomotor processing speed been found in methadone maintained patients (Darke et al., 2000; Mintzer & Stitzer, 2002) and may contribute to poorer performance on many tasks, particularly if the task contains a speeded component. It is important to extricate the influence of reduced processing speed from problems of an executive origin, thus the current framework has also taken account of this possibility and included a measure of processing speed (assessed by the Digit-symbol coding task: Wechsler, 1997). A further potentially confounding factor in substance use research relates to the lack of appropriately matched control groups, as substance users are often known to differ in terms of years of education and employment status, therefore the current framework seeks to match opiate users and healthy control participants in terms of employment status.

1.15.2. Characteristics of substance using populations

Many of the studies described previously in this chapter utilised groups who were engaged in polydrug use. As Ornstein et al. (2000: p.114) noted, 'substance users are a heterogeneous group and primary users of one drug will inevitably at some point in time have used drugs of another class. However within this spectrum of use one can separate

out groups on the basis of preference and relative frequency and duration of use'. Accordingly, the current study selected potential substance users on the basis of opiates being identified as their preferred and most frequently consumed drug of choice. Evidently, however, the common occurrence of polydrug use greatly reduces the specificity of conclusions regarding the effects of any particular substance *per se*, indeed many studies in extant literature are constrained by this factor. Studies also vary greatly in the degree to which they exclude the possibility of acute intoxification and many do not employ urine screening tests (including Petry et al, 1998; Rogers et al, 1999; Darke et al., 2000; Ornstein et al., 2000; Bechara et al., 2001; Lee & Pau, 2002; Lyvers & Yakimoff, 2003). As this factor is more easily controlled for, than say polydrug use history, it was considered important to include urine screening in the current investigation.

As there is a high rate of co-morbidity between substance dependence and other psychiatric diagnoses (Darke & Ross, 1997), it can be argued that the exclusion of individuals with co-morbid diagnoses reduces both the representativeness of the sample and the generalisability of the findings to the real settings. As previously discussed (see section 1.6.), non-fatal overdose may lead to subtle neuropsychological deficits through anoxic brain damage, but many studies fail to measure the incidence and severity of overdose in research participants (see exception Davis, Liddiard & McMillan, 2002).

1.16. Rationale for current study

Converging evidence from neuroimaging and neuropsychological research has linked alterations in neural activation in orbitofrontal and ventromedial prefrontal cortex to executive impairments of motivation, impulsivity and loss of inhibitory control in chronic opiate users. There is no clear evidence that opiate users have difficulty initiating tasks, whereas there is substantial evidence that they experience problems related to inhibitory control. Findings have been inconclusive in specifying whether observed deficits reflect problems of a purely executive nature however, as opposed to simply reflecting difficulties with component characteristics of complex experimental tasks e.g. gambling tasks, WCST, Stroop test. The current study will look at the performance of methadone maintained opiate users and controls on tasks purported to have reduced the influence of complex test stimuli such as the Hayling and Brixton tests, whilst also including a traditional measure of executive function-word fluency. Likewise, users' sensitivity to a financial incentive will be assessed using an uncomplicated measure (CARROT), which yields an index of enhanced reward responsivity in terms of changes in speed only. Performance of this test correlates with indices of clinical motivation and therefore has implications for understanding opiate users' ability to be motivated during treatment by clinically-relevant incentives such as positive encouragement. It is proposed that separating-out executive impairments such as response initiation versus response inhibition, is considered crucial to understanding the relevance and feasibility of therapeutic targets in treatment of substance use.

Real-world executive skills, as yet, have not been assessed in opiate users. The current study will investigate these abilities utilising an open-ended, ecologically-valid test

designed to simulate the multi-tasking and planning skills involved in running a hotel. Research suggests that brain-injured patients often evaluate their executive difficulties differently from people who know them well. Such differences in perceptions between patients and significant others may lead to the formation of attributional biases and lack of understanding of an individual's problems. Therefore, the current study will explore whether substance users' perceptions also differ from keyworkers who are actively involved in their treatment.

1.17. Hypotheses

1. The methadone group will not show sensitivity to the effect of reward on the CARROT, unlike the control group who will be significantly faster than the methadone group on the reward condition of the CARROT. Therefore, there will be a significant interaction of group x reward condition on the CARROT. Speed on the non-reward condition of the CARROT will not differ significantly between the two groups.

2. The methadone group will perform significantly worse than healthy controls on the measures of response inhibition including the Hayling test (inhibition section) and verbal fluency.

3. The methadone group will perform significantly worse than healthy controls on the Brixton and Hotel tests.

Differences between the methadone and control groups' self-rated factor scores on the DEX will be explored, in addition to differences between the self- and independent-rated factor scores. The relationship between self-rated factor scores and executive test performance will be explored also.

CHAPTER 2

Method

2.1. Research Setting

The research was undertaken within two settings: the Sub-Department of Clinical Health Psychology at University College London and South Camden & South Islington NHS Drug Service located at the Margarete Centre, London. The Sub-Department of Clinical Health Psychology at University College London is the location of the teaching of the Doctoral course in Clinical Psychology and the research was conducted in a small, quiet laboratory there. The Drug Service provides a number of outpatient services to the boroughs of Camden & Islington including daily dispensing pharmacy (DDP) of methadone, community specialist methadone maintenance prescribing (e.g. keyworker prescribing), community care assessments, outpatient detoxification, hospital liaison and psychology services. There are two multi-disciplinary teams based at the Margarete Centre (one each for South Camden and South Islington) comprised of key workers, nurses, doctors, clinical psychologists and social workers. The Drug Service liases closely with an on-site Primary Care Unit (PCU) team, which provides shared care for a number of patients. During a 12-month period ending in March 2003, the Drug Service treated 625 individuals with community methadone prescribing (3:1 male to female ratio, mean age 34.4 years). The ethnicity of individuals treated by the drug service was recorded as: 63% white-British; 19% white-other; 7% other; 4% black (includes British,

Caribbean, African, black-other); 4% mixed-race; 3% Asian (includes Indian, Pakistani, Bangladeshi, other).

2.2. Ethical Approval

Ethical approval was obtained from the ethics committees of University College London and Camden and Islington Community Health Services NHS Trust in August 2002 (for approval letter see Appendix I). Recruitment began in November 2002 and testing ran from January 2003 to May 2003.

2.3. Recruitment Procedure

2.3.1. Recruitment of methadone maintenance patient group

Two groups of patients were identified as suitable for the research: those who received methadone supervised in the community and those who were dispensed methadone daily at the centre.

Supervised self-administration (SSA) patients: key workers at the Margarete Centre were asked to nominate suitable patients for the research. Initially, the key workers were given an information sheet which explained selection criteria and what would be involved for the patient, (see Appendix II). They reviewed their caseloads and identified suitable patients (see criteria below). They then asked suitable patients if they would be interested in finding out more about participating in the research. If the patient expressed interest in taking part, the trainee clinical psychologist (who will be referred to as the trainee) arranged to meet the patient with their keyworker and the trainee discussed the research fully with the patient.

Daily dispensing pharmacy (DDP) patients: the trainee reviewed the case notes of all patients registered for the DDP service to determine suitability. Suitable patients were approached by the trainee in the waiting room of the centre when they arrived for dispensing. If they expressed interest in finding out more information, then they were taken to a consulting room where the research was discussed fully.

All patients (SSA & DDP) who expressed interest were given an information sheet, (see Appendix III) and invited to ask questions. If patients wished to take part, then written consent was sought at this point (see Appendix IV for consent form). An appointment was arranged for the research that fitted in with the patient's next appointment at the centre.

2.3.2. Recruitment of control group

The trainee approached a North London employment centre and requested permission to recruit volunteers from the service. Permission was granted for the trainee to approach employment seekers who were in the waiting room of the service either waiting for an appointment or checking employment notices. The trainee approached an individual and asked permission to speak to them regarding volunteering for research. If the individual was interested in finding out more they were taken to a desk where a discussion could be held in private. The trainee discussed the research, gave the individual an information sheet (see Appendix V) and invited questions. If the individual wished to take part, then written consent was sought at this point (see Appendix VI for consent form). An appointment was arranged for the individual to attend the laboratory at the Sub-Department of Clinical Health Psychology in order to undertake the research.

2.4.Participants

2.4.1. Methadone maintenance patient group

Selection criteria for the recruitment of the methadone group from the Margarete Centre are outlined below.

Inclusion Criteria

1. Patients aged 18-50 years.
2. Patients received current prescribed methadone for at least 1 month.
3. Patients identified opioids as major drug of use e.g. methadone, heroin.
4. Patients had English as first language and possessed basic literary skills.

Exclusion Criteria

1. History of alcohol dependence
2. Acute alcohol intoxication
3. History of significant head injury resulting in loss of consciousness
4. History of neurological condition including epilepsy, dementia
5. History of significant medical problem including diabetes, Human Immunodeficiency Virus (HIV)
6. History of major psychiatric disorder including schizophrenia

Sixteen opioid-dependent methadone patients (7 men, 9 women) were recruited from the Margarete Centre for participation in the study (6 from SSA, 10 from DDP). Psychometric and demographic information are detailed in section 3.3.

2.4.2. Control group

Selection criteria for the recruitment of the control group from the Employment Centre are outlined below.

Inclusion Criteria

1. Aged 18-50 years.
2. Had English as first language and possessed basic literary skills.

Exclusion Criteria

1. History of substance dependence including alcohol (past recreational drug use and current occasional use of marijuana or alcohol were permitted).
2. Acute alcohol intoxication
3. History of significant head injury resulting in loss of consciousness
4. History of neurological condition including Epilepsy, Dementia.
5. History of significant medical problem including Diabetes, Human Immunodeficiency Virus (HIV)
6. History of major psychiatric disorder including Schizophrenia

Fourteen participants (8 men, 6 women) were recruited from a North London Employment Centre. The control group was selected in order to match as closely as possible to the methadone group in terms of sex, age, employment status and premorbid verbal IQ as assessed using the National Adult Reading Test-modified (NART-2; Nelson & Willison, 1991). Psychometric and demographic information is shown in section 3.3.

2.5. Experimental Design

A quasi-experimental, between-subjects design was employed. There were two groups, one substance-dependent group who received methadone and another, non substance-dependent, control group who did not receive methadone. The research was not undertaken under blind conditions, i.e. the trainee knew which group each participant belonged to.

During the initial recruitment meeting (when information and consent were discussed) participants were asked to abstain from all drugs and alcohol (except methadone in methadone group and nicotine in smokers) for 12 hours prior to the arranged testing session. The methadone group attended the test session at the Margarete Centre and the control group attended the test session at the Sub-Department of Clinical Health Psychology. The trainee tested each participant individually. At the beginning of the testing session, the methadone group were asked to provide a urine sample for a urine test (patients had been informed of this at the initial recruitment meeting). Participants were informed that all test results were confidential and would not be reported to their key workers. The test determined the presence of cocaine, opiates, methadone, cannabis, amphetamine and benzodiazapine in the individual's urine (see section 3.4.2. for results). If the patient received daily dispensed methadone at the centre, then their test session was scheduled to commence immediately after they had taken their dose of methadone (within 5 minutes). If the patient received their methadone in the community in supervised self-administration, then it was arranged that they received a supervised dose at the centre prior to the test session. If the patient was prescribed unsupervised self-administration methadone, then they were advised to bring their dose to the centre

and to take it immediately prior to the commencement of the test session. The test session lasted approximately 1.5 hours in total and followed a standard protocol (see section 2.9.). The testing session was concluded with a debriefing of the experiment, during which participants were invited to ask questions. Control participants received a cash reimbursement of expenses and methadone participants received reimbursement in the form of vouchers for a high street store.

2.6. Drugs administered in methadone group

The methadone group all received their usual dose of methadone approximately 5 minutes prior to commencement of the test session. Ten patients received methadone dispensed at the pharmacy at the DDP and six self-administered their usual methadone dose. The methadone dispensed at the DDP consisted of Methadose 10mg/ml oral concentrate. The methadone mixture dispensed to SSA patients at community pharmacies consisted of 1mg/ml oral solution. There are no differences between the different concentrations of methadone in terms of physical effects, contraindications or side effects.

2.7. Measures

Premorbid General Intellectual Functioning

National Adult Reading Test – modified (NART-2; Nelson & Willison, 1991)

Nelson (1982) developed the National Adult Reading Test (NART) for use with the WAIS, as a means of estimating the premorbid intelligence of patients suffering from cognitive deterioration as a result of a dementing condition. The theoretical rationale of

the test is based on findings that vocabulary and general intellectual ability were highly correlated and that word-reading ability was well-maintained in a group of dementing patients (Nelson & McKenna, 1975). A corollary of these findings was advanced that, in an individual suffering dementia, the level of their residual vocabulary will be the best indicator of their premorbid general ability. Nelson and O'Connell (1978) proposed that the pronunciation of phonetically-irregular words provided the best estimate of a person's prior familiarity with a word, as the application of standard phonetic rules would not elicit the correct pronunciation. The test has been restandardized (NART-2; Nelson & Willison, 1991) to allow NART-2 scores to be converted to WAIS-R scores.

The NART-2 comprises 50 phonetically-irregular words (e.g. ache, rarefy, syncope) that are read aloud by the participant and it takes approximately 10 minutes to administer. An error score is compiled by subtracting the number of correct pronunciations from the total number of words (50). The error score is used to calculate estimated WAIS-R Full-scale I.Q, Verbal I.Q. and Performance I.Q. using a table provided in the manual (Nelson & Willison, 1991). Special provision is made for poor readers, whereby if fewer than ten words are read correctly then the accuracy of I.Q. prediction is enhanced if the NART results are combined with the results of the Schonell Graded Word Reading Test (GWRT; Schonell, 1942), which comprises 100 words and yields an error score, which is added to the NART score. The addition of the GWRT extends the range of prediction beyond the average range to the borderline range. The NART-2 has been described as among the most reliable tests in clinical use (Spreen & Strauss, 1998), with internal consistency reliability of .90 (Crawford, Stewart, Garthwaite, Parker & Besson, 1988), test-retest reliability of .98 (Crawford, Stewart, Garthwaite, Parker & Besson, 1988) and

high inter-rater reliability .88 (O'Carroll, 1987). NART-2 performance is correlated with education and social class, whereas age and gender exert little influence on scores (Crawford et al., 1988) and it is resistant to the effects of depression (Crawford, Besson, Parker, Sutherland & Keen, 1987). A factor analytic study by Crawford, Stewart, Besson, Parker and DeLacey (1989) found that the NART predicted 72% of the WAIS Verbal I.Q. variance but only 33% of the WAIS Performance I.Q. variance, which suggests that the test is a good predictor of Verbal I.Q. but relatively poor at predicting Performance I.Q. Watt and O'Carroll (1999) compared three commonly employed measures of premorbid ability in 114 healthy controls and found high correlations of current WAIS-R verbal IQ with the NART-2 (.72) and the Cambridge contextual reading test (.71), but relatively lower correlations with the spot the word test (.54). This suggests that the NART-2 provides a relatively accurate estimate of premorbid verbal intellectual ability based on predicted WAIS-R scores.

Current Non-Verbal Intellectual Reasoning

Matrix Reasoning Test (MR; Wechsler, 1997)

The Matrix Reasoning test is part of the Wechsler Adult Intelligence Scale-3rd Edition (WAIS-III; Wechsler 1997). It was included in the battery as a measure of abstract fluid intelligence and assesses nonverbal reasoning, ability to conceptualise spatial relationships and problem solving under un-timed conditions. It consisted of a series of 26 coloured pattern problems and multiple-choice answers; each problem comprised a pattern with a piece missing and the participant is instructed to select the missing piece from 5 possible answers. The pattern problems increase in difficulty level in a linear fashion. The score is based on the total number correct. It has value over other tests of

fluid reasoning as a brief and quick to administer measure. The test-retest reliability of the MR when averaged across ages 16-89 years is .77 (Wechsler, 1997). The correlation between performance on the MR with WAIS-III Full Scale I.Q. is .69, with Verbal I.Q. is .64 and with Performance I.Q. is .65 (Wechsler, 1997). This suggests that performance on the MR may give a relatively good indication of current intellectual ability.

Psychomotor Processing Speed

Digit Symbol-Coding Test (DSCT; Wechsler, 1997)

The Digit Symbol-Coding test is part of the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III; Wechsler 1997). It is a paper and pencil test which measures psychomotor processing speed and, in particular, eye to hand speed. The participant is presented with a box containing numbers (1-9) each of which has a unique symbol associated with it. The task for the participant is to copy symbols associated with a series of numbers presented in 7 rows of boxes. There is a 120 second time limit after which the participant is instructed to stop. The score is based on the number of correct symbols copied. The test-retest reliability of the DSST when averaged across ages 16-89 years is .86 (Wechsler, 1997), which suggests that it is a fairly robust measure over time.

Attention

The Digit Span test (DS; Wechsler, 1997)

The Digit Span (Forward) test is part of the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III; Wechsler 1997). In the DS, the participant's task was to repeat back a digit sequence presented verbally by the trainee. The participant was presented with two sequences of the same length until the participants fails a pair of sequences. Digit

span was calculated as the longest digit sequence repeated correctly and a score was derived based on the total number of sequences correctly recalled. The test-retest reliability of the DS when averaged across ages 16-89 years is .83 (Wechsler, 1997), which suggests that it is a fairly robust measure over time.

Verbal Fluency

Controlled Oral Word Association Test (COWAT; Benton & Hamsher, 1976, 1989)

The COWAT was developed by Benton and Hamsher (1989) as part of the Multi-lingual Aphasia Examination and measures word generation ability. The underlying premise of the test is that the quantity of words produced within a restricted time limit will be determined by the participant's ability to use an effective strategy. There is substantial debate in the literature regarding the underlying processes governing letter fluency performance. Phillips (1997) has questioned the widespread assumption that fluency reflects executive functioning and she has listed potential determinants of performance as differences in retrieval strategies, word storage, search speed and creativity. The test consists of three trials in which the participant is required to generate as many words as possible beginning with a specified letter within one minute. Letter fluency has been found to decline with age (Daigenault, Braun & Whitaker, 1992; Mittenberg, Seidenberg, O'Leary & DiGuilio, 1989), which Phillips (1997) attributed to peripheral factors such as processing speed and to individual differences in general intellectual ability. Crawford, Moore and Cameron (1992) have formulated regression equations, which allow the estimation of premorbid performance on the fluency task based on performance on the NART. The discrepancy between the obtained fluency score and the NART predicted fluency score, allows one to ascertain whether a low obtained fluency

score reflects impairment or a below-average premorbid ability. Letter fluency tasks have been found to be sensitive to the effects of brain injury, particularly if the site of injury is situated in the left frontal lobe anterior to Broca's Area (Milner, 1975), although PET studies have revealed bilateral temporal and frontal participation in fluency tasks (Parks, Lowewenstein, Dodrill, Barker, Yoshii, Chang, Emran, Apicella, Sheramata & Duara, 1988).

The letters CFL were selected by Benton and Hamsher according to the frequency of words beginning with these letters in the English language: the letter C has a high frequency, the letter F a lower frequency and the letter L an even lower frequency. Test instructions specified that participants should say aloud as many words as they can that begin with the specified letter, but that words should not consist of proper nouns or words with the same root but different suffix e.g. shop, shops, shopped. A practice trial with the letter S verified that participants had understood the task requirements. The score was the sum of acceptable words generated across the three trials (repetitions are excluded) and was adjusted for age, sex and education.

Reward Responsivity

Card Arranging Reward Responsivity Objective Test (CARROT; Powell, Al-Adawi, Morgan & Greenwood, 1996).

The CARROT is a psychomotor task, which yields a behavioural measure of responsiveness to financial incentive known as 'reward responsivity'. It measures the degree to which an individual changes their speed of performance of card sorting and therefore involves within-subject comparisons of speed. The participant was given a

stack of cards each of which are approximately the size of playing cards upon which were displayed 5 vertically arranged digits (random selection of digits from 1 to 9). Each card contained a 1, 2 or a 3 within the 5 digits and the participant was required to sort the stack into 3 correspondingly numbered piles as quickly as possible.

The tasks involved four trials (T1, T2, T3 and T4). The first trial (T1) established the individual's baseline sorting speed (BASETIME); the participant was asked to sort 60 cards and the time taken was set as their BASETIME. This individually determined time was used in subsequent trials as a time limit for sorting, which allows trial times to be calibrated to control for individual variability in motor functioning and psychomotor processing speed. In trials T2-T4, the participant was asked to sort 100 cards as quickly as possible within their BASETIME and the number of cards sorted was recorded as a score. T3 differed from T2 and T4 as it involved a financial incentive; the participant was informed that they would be rewarded with 10 pence for every five cards sorted. Coins were placed on the table in view of the participant during this trial. Response times on the reward trial (T3) and the initial non-reward trial (T2) were compared to ascertain whether the participant increased or decreased their sorting speed when presented with a financial incentive.

Executive Function

Hayling Sentence Completion Test (Hayling; Burgess & Shallice, 1996a)

The Hayling test was developed by Burgess and Shallice (1996a) as a measure of task initiation speed and response suppression. It consists of 30 sentences in which the final word had been omitted and it is divided into two sections (1 and 2) containing 15

sentences each. The sentences were chosen by the authors such that there was a high probability of a specific response occurring. In section 1, straightforward completion of the sentence was assessed and it is a measure of response initiation ability; the sentences were read aloud and the participant was instructed to give a word, which completed the sentence. In section 2, the sentences were read aloud and the participant was instructed to give a word, which did not fit the sentence in any way. It was assumed that section 2 measured the ability to inhibit a highly cued, prepotent response (response inhibition). In section 2, if the participant was unable to think of an unrelated word, then the trainee offered an example word of 'banana'. Also, if during section 2, the participant gave a word, which fitted the sentence, then they were instructed (on one occasion only) that the word was too related. In both parts, the participant was instructed to give their response as quickly as possible and their response was recorded verbatim. The time taken for the participant to give a response (response latency) was recorded with a stopwatch from the time the last word had been read to the point at which they commenced their response. Response latencies of less than one second are scored as zero and latencies greater than a second were rounded down to the nearest second. If a participant was unable to produce a word within 60 seconds, then that trial was terminated and a time of 60 seconds recorded. A practice trial of 2 sentences was given prior to commencement of each section.

Performance on section 1 was based on the sum of the response latencies. On section 2, errors were classified in addition to the sum of the response latencies. Errors were classified into two categories (A and B) (see overleaf for examples from the manual) and awarded a point if they belonged a category.

Sentence	Category A error	Category B error
The Captain wanted to stay with the sinking...	Floating vessels e.g. boat, ship, tug, raft, buoy or parts thereof (e.g. sail, propeller)	(i) Aircraft e.g. aeroplane, helicopter, balloon *or* (ii) Water-based creatures e.g. fish, hippopotamus *or* (iii) Answers strongly semantically connected to 'sinking' e.g. sea, water, 'going down'

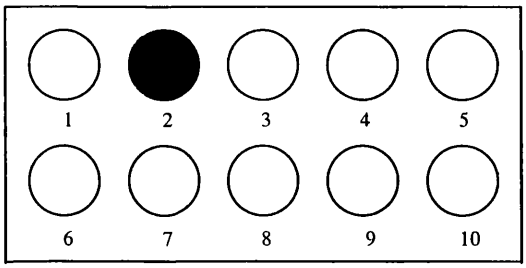
Category A errors were words that were straightforward completions of the sentence i.e. words that fitted the sentence completely. Category B errors comprised words that were semantically connected to the sentence (included opposites of a sentence completion and socially inappropriate responses also). Category A errors received more points than category B errors. The sum of points from both categories was used to determine the level of performance. There were three main measures derived from the Hayling test which have test-retest reliabilities as follows: initiation latency score (from section 1) .62, response inhibition latency score (section 2) .78 and response inhibition error score (section 2) .52. The scores were classified according to the scaling system outlined in the manual. Raw scores were converted to scaled scores (1-10) corresponding to percentiles e.g. a scaled score of 10 (99^{th} percentile) was classified as 'superior', a scaled score of 6 (50^{th} percentile) was classified as 'average' and a scaled score of 1 (out of normal range) was classified as 'impaired'.

Brixton Spatial Anticipation Test (Brixton; Burgess & Shallice, 1996b)

The Brixton test was developed as a measure of 'rule attainment', although failures on the task may represent difficulties of perseveration, strategy misapplication and bizarre responding (Burgess & Shallice, 1996b). It consists of a series of 56 A4-sized pages bound together in a spiral booklet. Each page was presented sequentially and contains

the same design: a rectangle containing an array of circles (2 rows of 5 circles) numbered 1 to 10 (see Figure 3). One of the circles is always shaded. The position of the shaded circle varies from page to page according to a simple rule (e.g. alternate between position 4 and 10), which changes without warning after 3 to 8 pages. The task involves eight rule changes and six different rules. The participant was instructed to predict the position of the circle on the next page. Therefore the participant determined the new position by deduction from the previous pages what rule was governing the changing of position. The performance measure was the number of errors made. The scores were classified according to the scaling system outlined in the manual (same system as described in previous section on Hayling). It has a test-retest reliability of .62.

Figure 3. Brixton test stimulus array



Hotel task (Manly, Hawkins, Evans, Woldt & Robertson, 2002)

The hotel task developed by Manly et al. (2002) is a modification of the Six Elements task (SE; Shallice & Burgess, 1991). The SE task was originally designed as an analogue of open-ended multiple, subgoal planning commonly found in everyday activities, those aspects of executive function not routinely captured in standard neuropsychological tests. It required 3 tasks (each task comprised 2 parts) to be performed (dictation, picture naming and arithmetic) under rule constraints and within a

short time limit. The aim was to attempt all 6 parts in the time available. The key aspect of the task was the need to constantly self-monitor one's performance and move onto the next task. Shallice and Burgess (1991) demonstrated that 3 patients with frontal lobe damage performed poorly on the SE, despite consistently good performance on a number of standard tests. The hotel task was designed to mimic the types of activity involved in the running of a hotel and consisted of 6 tasks as follows:

(1) Compiling guest bills: the participant was presented with the till roll of the hotel register which listed services used by guests and associated costs, and a booklet containing bill forms for eight guests. Their task was to scan the till roll for services used by the particular guest and transfer relevant items onto the bill form.

(2) Sorting the charity collection: a box which contained 196 coins (21 foreign; 175 British including 24x20p, 46x10p, 96x5p, 4x2p, 5x1p) and 10 bank bags were presented to the participant. The participant was instructed to sort the British coins from the foreign coins and fill the bags to the value of £1.00 (any mixture of denominations).

(3) Looking up telephone numbers: the participant was given a Yellow Pages phone directory and a list of 34 local companies. They were instructed to find the telephone numbers of the companies and record them on the list.

(4) Sorting the conference labels: the participant was presented with a pile of 100 cards each with the name of a guest attending a conference. Their task was to sort the cards into alphabetical order based on the surname of the guest.

(5) Proof reading the hotel leaflet: the participant was asked to read a nine-page draft leaflet for the hotel and circle double-letter spelling mistakes.

(6) Opening and closing the garage doors: at two pre-defined times, the participant was instructed to open and close hypothetical garage doors to allow deliveries. A box containing a black button and a red button was placed on the table beside the participant. The doors were to be opened by pressing the red button at 11.06am and closed by pressing the black button at 11.12am.

In a pilot study, conducted by Manly et al. (2002), it was estimated that it would take in excess of 1 hour to complete all of the tasks. At the beginning of the Hotel task administration, participants were instructed that they had 15 minutes in total for the task. The materials were arranged in the same order on a desk for each participant. A covered digital clock was placed on the desk for the participant to check as often as they wished. It was covered to allow the trainee to verify the number of times they checked the clock. The instructions were read aloud by the trainee (see below), the participant's understanding was verified and a written summary of each task was placed beside the task. During testing the trainee recorded the times at which a task was started and ended, the number of times the clock was checked and when the buttons were pressed.

> *"In this task you are asked to imagine that you are working in a hotel. Your manager is keen for you to try each of these everyday activities during the next 15 minutes so that you can get feel for the work-and make an informed estimate of how long the work would take to complete. Your main job is to try to do some of all of these 5 tasks over the next 15 minutes. There are 5 main tasks to do. Each of the tasks may well take longer than 15 minutes to complete on its own, so there is no way that you will be able to complete them all. The most important thing is to try to do something from each task-spending as much time on each as possible in the time available."*

Dysexecutive Syndrome Questionnaire (DEX: Wilson, Alderman, Burgess, Emslie & Evans, 1996)

The DEX questionnaire forms part of the Behavioural Assessment of Dysexecutive Syndrome test battery (Wilson et al., 1996) and was developed to sample four broad areas of change associated with dysexecutive syndrome: (1) emotion and personality, (2) motivation, (3) behaviour, and (4) cognition. It comprises 20 questions related to the most frequently reported symptoms derived from interviews with carers of frontal lobe patients (see Table 1. taken from Burgess, Alderman, Evans, Emslie & Wilson, 1998). There are two versions of the DEX: one to be completed by an independent rater e.g. carer, keyworker (see Appendix VII) and another to be self-rated by the individual/patient (see Appendix VIII). The rater is asked to give a rating on a 5-point Likert scale how often the symptom occurred i.e. never (rated 0) - very often (4).

Table 1. Characteristics of the Dysexecutive syndrome addressed by questions in the DEX questionnaire (taken from Burgess et al., 1998)

Question number	Behavioural characteristic	Question number	Behavioural characteristic
1	Abstract thinking problems	11	Shallowing of affective responses
2	Impulsivity	12	Aggression
3	Confabulation	13	Lack of concern
4	Planning problems	14	Perseveration
5	Euphoria	15	Restlessness-hyperkinesis
6	Temporal sequencing deficits	16	Inability to inhibit responses
7	Lack of insight and social	17	Knowing-doing dissociation
8	Apathy and lack of drive	18	Distractibility
9	Disinhibition	19	Poor decision-making ability
10	Variable motivation	20	No concern for social rules

All participants were asked to complete a self-rated DEX questionnaire. For the methadone group only, the keyworker linked to the participant was asked to complete an independent-rater DEX questionnaire, based on their prior knowledge of the participant. An overall score for the self-rater and independent-rater DEX questionnaires was calculated based on the sum of the ratings (higher scores represented higher degrees of impairment). For the methadone group, a discrepancy score was calculated based on the difference in score between the self and independently rated DEX questionnaire. Burgess et al. (1998) performed a factor analysis of 92 DEX questionnaires completed by independent-raters of head-injured patients and derived five separate factors including: 1) inhibition; 2) intentionality; 3) executive memory; 4) positive affect and 5; negative affect. The self-rated scores of methadone and control participants (and independent-ratings in methadone group) were compared across the five factors derived by Burgess et al. (1998). Self-rated and independent-rated DEX factor scores were compared in the methadone group. Scores on neuropsychological tests were correlated with scores in each of the five factors for both groups also.

Mood

Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983)

This is a self-rated questionnaire in widespread clinical use, which assesses symptoms of depression and anxiety experienced by the rater in the previous week. Scores are summed for the depression and anxiety scales separately and compared to clinical cut-off points.

2.8. Additional information collected

All participants were asked to provide basic demographic information (age, ethnicity, years of education, employment status). In the methadone group, information related to substance use was collected (type of substances used, methadone dose, duration of methadone and heroin use, age first used). It was important to find out if participants in the methadone group had experienced loss of consciousness associated with drug use and, in particular, overdoses. Loss of consciousness can lead to deprivation of oxygen to the brain (hypoxia) and neuronal death as a result. Hypoxic brain damage and may represent a common form of brain injury in opiate users presenting to acute services (Darke, Sims, McDonald & Wickes, 2000).

2.9. Test Protocol

Tests were administered to each participant in the same order as follows:

NART-2

HADS questionnaire

DEX questionnaire

Digit span

Digit symbol substitution

Verbal fluency

Matrix reasoning

Hayling test

Brixton test

CARROT

Hotel task

CHAPTER 3

Results

3.1. Procedures to control sampling error

3.1.1. Normality of distributions

Prior to the application of statistical tests all variables were examined to see if they were normally distributed. The normality of the distribution of each variable was assessed by examination of histograms and statistics related to skewness and kurtosis. In the case of a non-normally distributed variable, then a transformation was applied (square-root and reflection) to improve the fit with the normal distribution. Square-root transformations were applied to the following variables as they were found to be significantly skewed: Hayling section 1 time; Hayling section 2 time; Hayling section 2 errors (category b); CARROT trial 3 time; hotel task time deviation; DEX self-ratings and other ratings.

3.1.2. Outliers

The data were also examined for the presence of outliers by saving the variables as standardised z-scores after transformations were performed. An outlier was defined as a score of more than 3 standard deviations from the mean of the scores of the variable. Two outliers were found in the hotel door time deviation (Z=-3.41, Z=-3.14) and two in the number of hotel door button presses (Z=-3.03; Z=-3.47) variables. The outliers were excluded from the analyses of the variables.

3.2.1 Statistical analyses performed

Differences in task performance between the two groups were assessed using Independent-samples and Related-samples t-tests, Pearson's chi-square, Univariate Analysis of Variance with covariates and Repeated-measures Analysis of Variance with covariates using SPSS-version 10. The relationships between selected variables were explored with Pearson correlations (2-tailed).

3.2.2. Analysis of covariance

Individual methadone participants were not matched with a corresponding control subject on age, years of education, IQ or mood levels. Group differences were found in variables related to age, years of education and levels of depression and anxiety. Therefore, there was potential for these variables to contribute to neurocognitive test performance. The influence of these variables on task performance was examined by using these variables as covariates. As anxiety and depression scores were found to be significantly correlated (r= .657, $p<.001$), it was deemed pertinent to assess the influence of mood by using only depression as a covariate. An analysis of co-variance was therefore used to assess group differences in the neurocognitive tasks using age, years of education and depression score as covariates.

3.3. Characteristics of methadone and control groups

There were no significant differences in the gender distribution between groups ($\chi^2(1)=.91$, $p=.34$). There were 7 men (44%) and 9 women (56%) in the methadone group and 8 men (57%) and 6 women (43%) in the control group.

The ethnic distribution of the groups was representative of the ethnic distribution of clients attending the Drug Service. In the methadone group, 13 participants described themselves as British-white (82%), 1 as British-black (6%), 1 as British-mixed race (6%) and 1 as non-British-white (6%). In the control group, 11 participants described themselves as British-white (79%), 1 as British-mixed race (7%) and 2 as non-British-white (14%).

The groups differed significantly on several demographic variables (means and results of t-tests are reported in Table 2.). The groups differed significantly in terms of age ($t(28)=3.16$, $p=.004$), whereby the mean age of the methadone group was seven years higher than controls. The methadone group had significantly less years of education than controls ($t(28)= -3.94$, $p<.001$).

Table 2. Means (standard deviations) of characteristics of methadone and control groups.

variables	mean (*s.d.*)		t	*p*
	methadone	control		
Age (years)	36.1 (*6.6*)	29.0 (*5.6*)	t(28)=3.16	*p*=.004
Estimated pre-morbid IQ	103.4 (*11.0*)	109.0 (*10.0*)	t(28)= -1.46	ns
Current fluid reasoning	18.1 (*3.5*)	19.9 (*4.5*)	t(28)= -1.23	ns
Education (years)	11.4 (*1.6*)	13.8 (*1.6*)	t(28)= -3.94	*p*<.001
HADS depression	6.5 (*4.1*)	2.7 (*2.1*)	t(28)=3.12	*p*=.004
HADS anxiety	8.9 (*3.9*)	5.6 (*3.1*)	t(28)=2.52	*p*=.018

There were significantly higher HADS scores in the methadone group compared to the control group (see Table 2.). Similarly, HADS anxiety scores were significantly higher

in the methadone group compared to the control group. 31% of methadone participants reached clinically-significant levels of depression (as defined by the cut-off point of 8-10), compared to 8% of controls. Similar numbers of participants across groups reached clinically-significant levels of anxiety: 44% of methadone and 39% of control participants.

3.4. Drug use in methadone group

Measures of drug use must be interpreted cautiously as precise information related to duration of drug use was unattainable because of limitations of participants' recall and inconsistencies in case notes held by the Drug Service. Moreover, drug histories varied greatly between individuals e.g. variation in number of episodes, frequency, duration of drug use and polysubstance use. As most of this information was subject to limitations that called into question its reliability, it was not considered useful to use it in analyses. The measures that were considered more reliable related to methadone dose, current duration of methadone and heroin use, the number of overdoses and the results of urine screening. Information related to methadone and heroin use, polysubstance use and urine screening is discussed below.

3.4.1. Methadone and heroin use

The median prescribed methadone dose was 65mls and the range was large 40-170mls (see Table 3.). The median duration of the current methadone treatment was 487 days (approximately 16 months). Seven participants (44%) had experienced overdoses (heroin mostly), which had led to a loss of consciousness of more than a few seconds. Many participants (56%) did not report having an overdose. Some participants (31%)

reported 1-3 overdoses and one participant reported 12 overdoses. One participant estimated having 50 overdoses over a three-year period (this case constituted an outlier and therefore the data was excluded from calculation of mean, median and s.d.).

There were problems in data collection related to duration of methadone use: frequently participants had taken street methadone prior to engagement in methadone maintenance treatment. Also, several participants had experienced intermittent engagement in methadone treatment over a number of years. As an approximate estimate of duration of use, the length of time was calculated from the age that participants' first considered methadone/heroin to be a problem to the present. The median duration of methadone and heroin use was 5.5 years and 15 years respectively (see Table 3.).

Table 3. Methadone and heroin use by the methadone group

	median	mean (*s.d.*)	range (*min.-max.*)
Methadone dose (mls.)	65	71.88 (33.41)	40 - 170
Current treatment duration (days)	487	609.56 (673.61)	28 - 2717
Time since methadone 1st a problem (years)	5.5	8.0 (5.23)	2 - 19
Time since heroin 1st a problem (years)	15	14.92 (9.09)	3 - 36
No. of overdoses	0	1.47 (3.11)	0-12

3.4.2. Polysubstance use

Results of urine screening was available for 15 individuals only. Results showed that 73% of methadone participants were engaged in polysubstance use (see Table 4.). Importantly, all of the polysubstance users had recently used cocaine in addition to methadone. Results showed that a substantial proportion (40%) used extra heroin and cocaine in addition to their prescribed methadone dose.

Table 4. Urine screening results

substances	Number of methadone participants
Methadone only	4
Methadone + cocaine	1
Methadone + cocaine + heroin	6
Methadone + cocaine + benzodiazepine	2
Methadone + cocaine + heroin + benzodiazapine + amphetamine	2

3.5. Neurocognitive test results

3.5.1. Digit-symbol coding test

A significant group difference was found on digit-symbol coding ($F(1,28)=26.95$, $p<.001$), wherein the methadone group coded significantly fewer symbols than controls (see Table 5.). The group difference remained after age, years of education and depression score were controlled for as covariates in the analysis.

3.5.2. Digit-span test

Methadone participants' mean digit span total score was lower than controls' ($F(1,28)=5.80$, $p=.023$) and the methadone group's span length was significantly shorter than the control group's ($F(1,28)=7.04$, $p=.013$) (see Table 5.). The difference between groups in digit span total score and span length was no longer significant when age, years of education and depression score were controlled for as covariates.

Table 5. Means (standard deviations) of methadone and control groups on digit-symbol coding and digit span tasks (before controlling for age, years of education and depression score).

	mean (*s.d.*)		*F*	*p*
	methadone	control		
Digit-symbol coding	60.75 (*13.99*)	88.86 (*15.67*)	F(1,28)=26.95	$p<.001$
Digit span length	6.69 (*1.20*)	7.79 (*1.05*)	F(1,28)=7.04	$p=.013$
Digit span total score	8.19 (*2.10*)	9.93 (*1.82*)	F(1,28)=5.80	$p=.023$

3.5.3. Hotel task

3.5.3.i. Deviation from optimal time allocation

A Univariate ANOVA was performed on transformed data (square-root transformation) of the measure of total deviation from optimal time allocation (300 seconds) to each task (time deviation). A significant group difference was found (see Table 6.) which was unchanged by the addition of all covariates to the analysis. The methadone group mean was 121.3 seconds higher than the control group mean (see Table 6.).

3.5.3.ii. Number of tasks attempted

Groups did not differ significantly on the number of tasks attempted (F(1,28)=2.75, ns), and this was not changed after controlling for the influence of covariates. Results suggested that both groups were performing close to ceiling levels (max=5).

3.5.3.iii. Number of clock checks

The mean number of clock checks was significantly lower in the methadone group than the control group (F(1,28)=7.24, p=.012) (see Table 6.). The pattern of results was unchanged by the addition of covariates to the analysis.

3.5.3.iv. Number of garage door presses

The means of both the methadone group (1.87±0.35) and the control group (2.00±0.0) were close to ceiling level (max=2) on this measure. Therefore analysis of a group difference was not conducted.

3.5.3.v. Garage door time deviation

Groups did not differ significantly in terms of the deviation from the correct time to press the garage door buttons (F(1,26)=3.51, ns), but when age was controlled as a covariate a significant group difference emerged (F(1,25)=9.53, p=.005).

Table 6. Mean scores (standard deviations) on the hotel task by methadone and control groups (before controlling for age, years of education and depression score).

	mean (*s.d.*)		*F*	*p*
	methadone	control		
Time deviation (secs.)	347.44 (*146.09*)	226.14 (*53.72*)	F(1,28)=8.41	p=.007
No. of tasks attempted	4.31 (*.79*)	4.71 (*.47*)	F(1,28)=2.75	ns
No. clock checks	5.75 (*2.65*)	8.93 (*3.79*)	F(1,28)=7.24	p=.012
Door time deviation (secs.)	7.13 (*1.55*)	7.85 (*.55*)	F(1,26)=2.51	ns

3.5.4. Reward responsivity task (CARROT)

3.5.4.i. Baseline sorting times

There was a significant group difference in baseline mean sorting time (T1) ($F(1,28)=28.76$, $p<.001$) which remained after age, years of education and depression score were controlled for as covariates ($F(1,25)=11.38$, $p=.002$). The methadone group took significantly longer (mean=62.06±11.23 seconds) to sort 60 cards than the control group (mean=44.57±5.06 seconds).

3.5.4.ii. Comparisons across reward and non-reward conditions

The mean number of cards sorted in non-reward trials 2 (T2) and 3 (T4) and in the reward trial (T3) for each group is shown in Table 7. Results showed that the number of cards sorted increased across the trials for both groups, which indicated that a practice-effect occurred. The measure of reward responsivity score was derived by comparing the number of cards sorted in the non-reward trial 2 with the number of cards sorted in the reward trial 3. An explanation of the omission of trial 4 in the computation is given below[1].

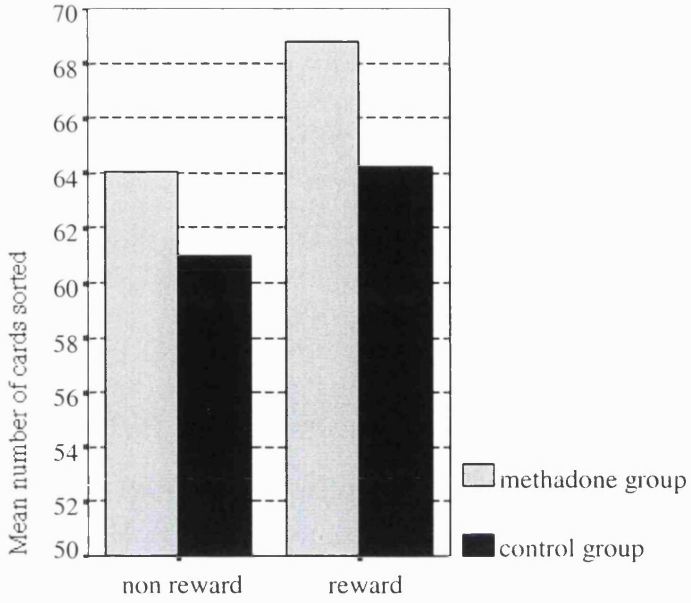
[1] The reward responsivity measure (REWRESP) was originally calculated by Powell, Al-Adawi & Greenwood (1996) by subtracting the average of the scores for T2 and T4 from the score for T3 (T3- [(T2+T4)/2]. In Al-Adawi and Powell (1997), the comparison of reward and non-reward conditions was made by looking at times on trials 2 and 3 only. Al-Adawi and Powell (1997) found that when T2 and T4 were both used to compute reward responsivity score (T3-[T2+T4)], the result was perfectly correlated with the reward responsivity score derived from just using T2 alone (T3-T2).

Table 7. Mean (standard deviations) number of cards sorted on the CARROT trials (T1, T2 & T3) by methadone and control groups.

condition	mean (*s.d.*)	
	methadone	control
Non-reward (T2)	64.06 (*7.60*)	61.00 (*3.44*)
Reward (T3)	68.75 (*7.98*)	64.21 (*3.93*)
Non-reward (T4)	69.31 (*9.25*)	65.00 (*6.36*)

A repeated-measures ANOVA with reward condition (T2, T3) as the within-subjects factor and group (methadone, control) as the between-subjects factor was performed on transformed data (square-root transformation). There was no differential group sensitivity to reward as revealed by the non-significant 2-way interaction of group x reward condition ($F(1,28)=.30$; n.s.) which did not change when age, years of education and depression score were controlled for as covariates. There was a significant main effect of reward condition ($F(1,28)=10.11$, $p=.004$) which was non-significant after age, years of education and depression score were controlled for as covariates. There was a trend towards a group main effect ($F(1,28)=3.88$, $p=.059$), which reached significance when depression scores were entered as a covariate ($F(1,27)=7.87$, $p=.009$) (age and years of education covariates did not have a significant effect). The mean number of cards sorted was higher in the methadone group than the control group across both conditions (see Table 7.). Figure 4. shows the mean number of cards sorted by each group for each reward condition.

Figure 4. Mean number of cards sorted by each group (methadone and control) across non-reward and reward conditions.



3.5.5. Verbal fluency

A significant difference was found between groups on verbal fluency ($F(1,28)=11.06$, $p=.002$) which remained after age, years of education and depression score were controlled for as covariates ($F(1,25)=8.22$, $p=.008$). The mean number of words produced was lower in the methadone group (36.75±10.40) than the control group (50.07±11.55). A significant group difference in fluency score also remained after the influence of premorbid intelligence (NART-2) was controlled for as a covariate ($F(1,27)=8.22$, $p=.008$).

3.5.6. Hayling test

3.5.6.i. Hayling section 1: response initiation

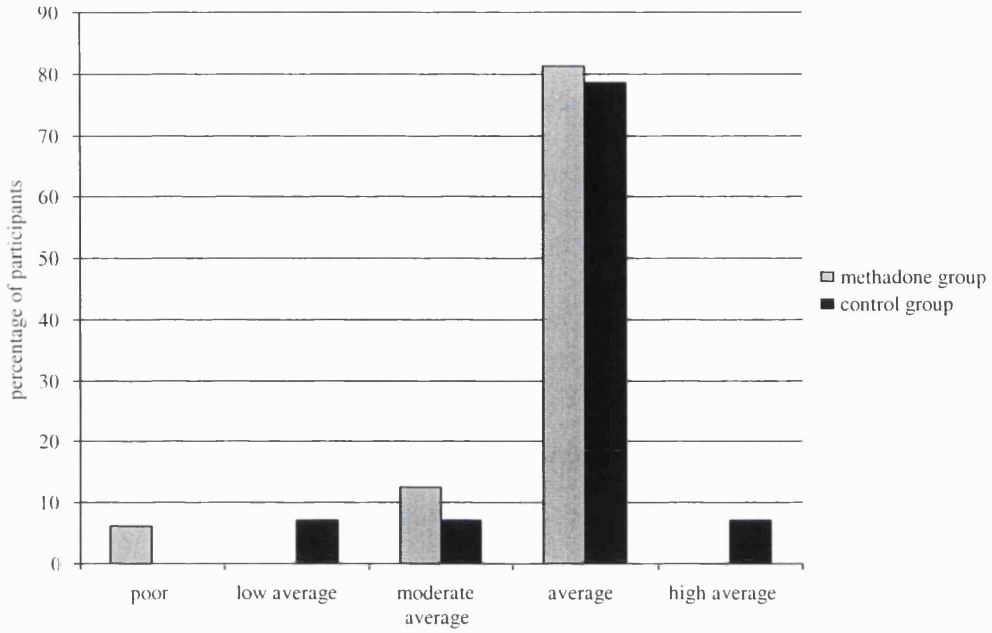
A square-root transformation was performed on the measure of mean response times (above 1 second) on section 1 of the Hayling test. There was no significant difference between groups (see Table 8.). Controlling for age, years of education and depression score did not change the pattern of results.

Table 8. Means (standard deviations) of times and errors on Hayling section 1 and 2 by methadone and control groups (before controlling for age, years of education and depression score).

	mean (*s.d.*)		*F*	*p*
	methadone	control		
Hay. 1 time (seconds)	6.50 (*6.32*)	5.29 (*5.47*)	F(1,28)=.70	*ns*
Hay. 2 time (seconds)	30.75 (*25.93*)	16.43 (15.38)	F(1,28)=3.92	*p*=.058
Hay. 2 category a errors	1.25 (*1.24*)	0.57 (*.65*)	F(1,28)=3.39	*p*=.076
Hay. 2 category b errors	2.25 (*2.32*)	0.57 (*.94*)	F(1,28)=6.37	*p*=.018

The distribution of scaled scores (presented with Burgess & Shallice's (1996) classification labels) for each group is shown in Figure 5. Most participants in both groups (81% and 79%) scored in the 'average' range. The methadone groups' scaled scores ranged from 'poor' to 'average' and the control groups' ranged from 'low average' to 'high average'.

Figure 5. Scaled scores of response time on Hayling section 1 by methadone and control groups.

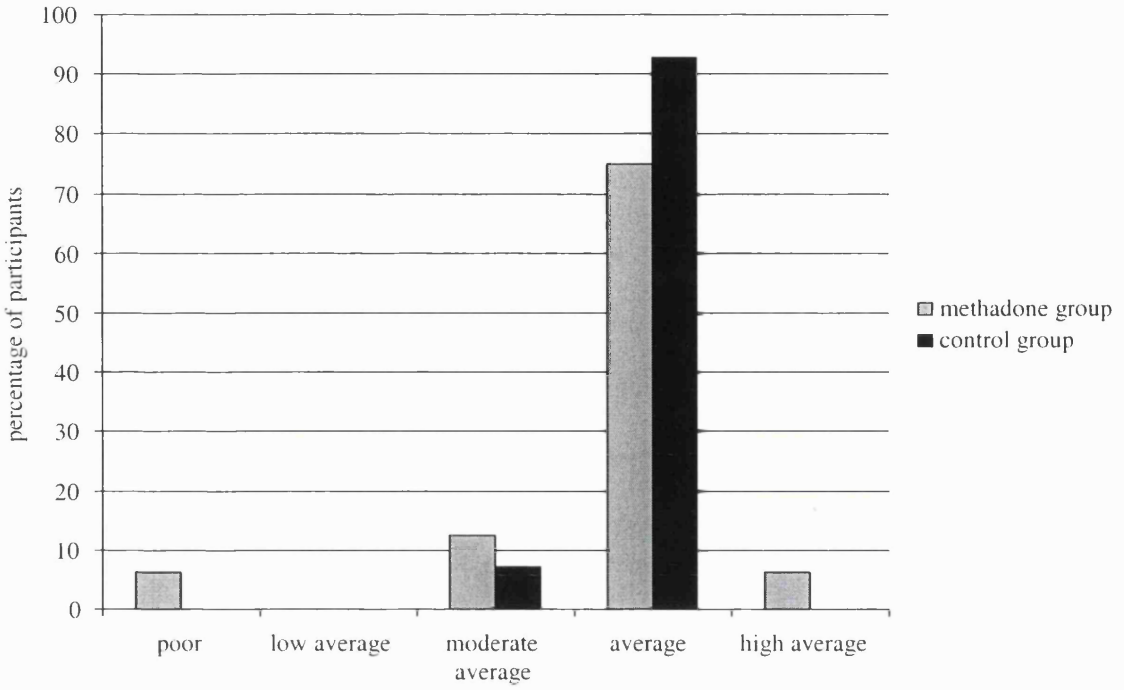


3.5.6.ii. Hayling section 2: response inhibition

3.5.6.ii.a. Response time

The mean response times in Hayling section 2 were higher in the methadone group than the control group (see Table 8.). A non-significant trend was found between groups ($F(1,28)=3.92$, $p=.058$), which no longer approached significance once the influence of covariates was controlled for. The distribution of scaled scores (presented with classification labels) for each group is shown in Figure 6. Most of the control group (93%) scored in the average range. A substantial proportion of the methadone group also scored in the methadone average range (75%), although the methadone group had a wider range of scores (poor to high average).

Figure 6. Scaled scores of response time on Hayling section 2 by methadone and control groups.



3.5.6.ii.b. Hayling 2 errors

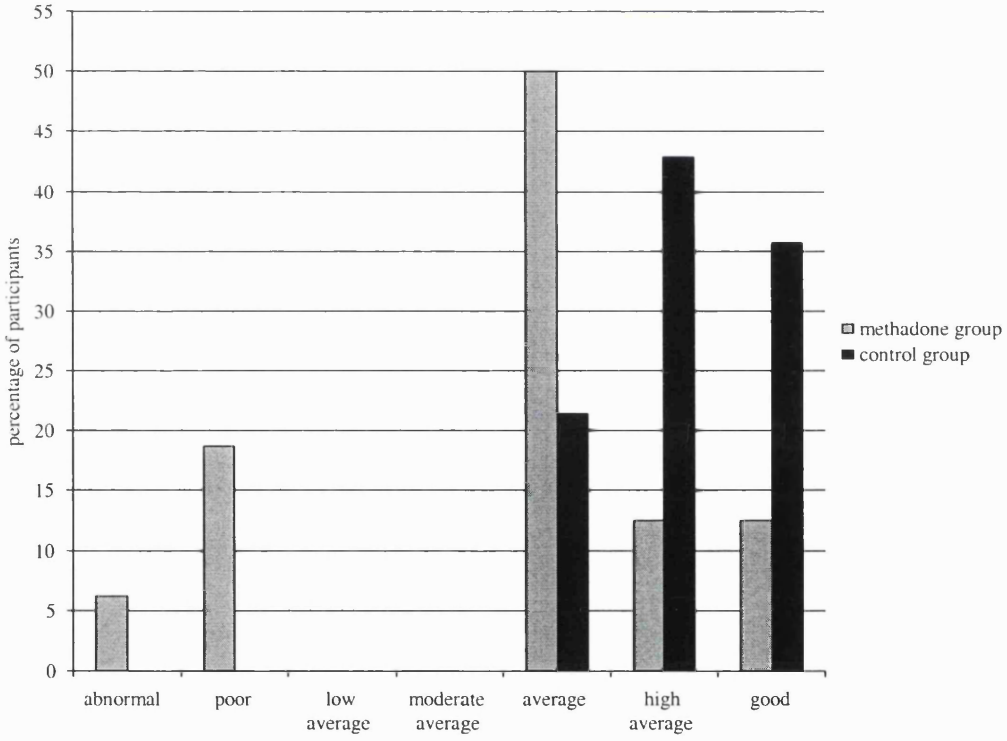
Category a errors: A square-root transformation was performed on the category a errors variable. The mean number of category a errors made on the Hayling section 2 appeared higher in the methadone group than the control group (see Table 8.). This trend toward a group difference disappeared (p=.076) once the influence of covariates was controlled for.

Category b errors: A square-root transformation was performed on the category b errors variable. The mean number of category b errors made by the methadone group was higher than the control group. A significant difference was found between groups in the number of category b errors ($F(1,28)=6.37$, p=.018), which did not remain after age,

years of education and depression score were controlled for as covariates ($F(1,25)=1.45$, ns).

Scaled scores were derived for the total number of errors made on Hayling section 2 (category a + category b). The distribution of scaled scores (presented with classification labels) for each group is shown in Figure 7. The control groups' scaled scores were distributed across the higher classifications (average to good). There was a wider range in the methadone groups' scaled scores (abnormal to good).

Figure 7. Scaled scores of errors on Hayling section 2 by methadone and control groups.



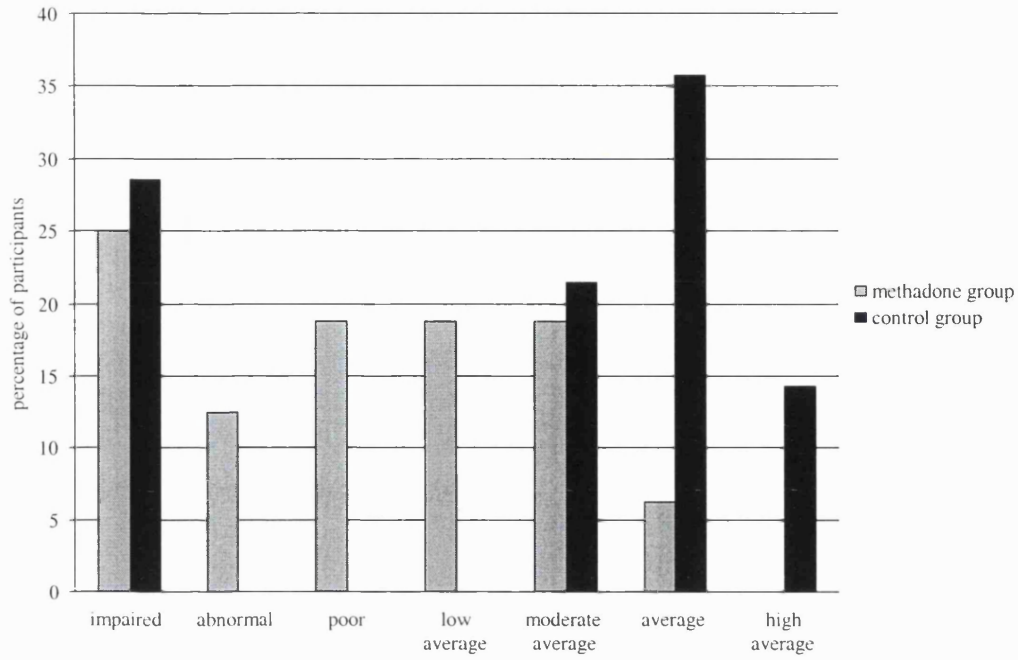
3.5.6.ii.c. Additional thinking time

Burgess and Shallice (1996) derived a measure of 'additional thinking time' associated with the second part of the Hayling compared to the first. This was calculated by subtracting response time on the initiation section from response time on the inhibition section for each participant. There was a trend of longer additional thinking times in the methadone group ($F(1,28)=3.01$, $p=.094$) although the trend disappeared once the influence of age, years of education and depression score was controlled for as covariates.

3.11. Brixton test

Although, the methadone group made more errors on the Brixton test (mean=25.5±6.74) than the control group (mean=21.57±9.32), the group difference was non-significant ($F(1,28)=1.78$, $p=.193$). The distribution of scaled scores (presented with classification labels) for each group is shown in Figure 8. A substantial proportion of participants in both groups (25% and 28%) scored within the impaired range. The methadone group had a wider range in scores (impaired to average), whereas the control groups' scores fell into a bimodal-type distribution.

Figure 8. Scaled scores of errors on Brixton test by methadone and control groups.



3.12. Dysexecutive syndrome questionnaire (DEX)

3.12.1 Comparisons of self-ratings on DEX by methadone and control groups

Five factor scores were derived from the DEX by Burgess et al. (1998) and were related to classifications of inhibition, intentionality, executive memory, positive and negative affect respectively. In the current study, a factor score was derived for each participant from their self-ratings on items on the DEX according to the method described by Burgess et al. (1998). Group means for each factor are presented in Table 9. and are represented graphically in Figure 9.

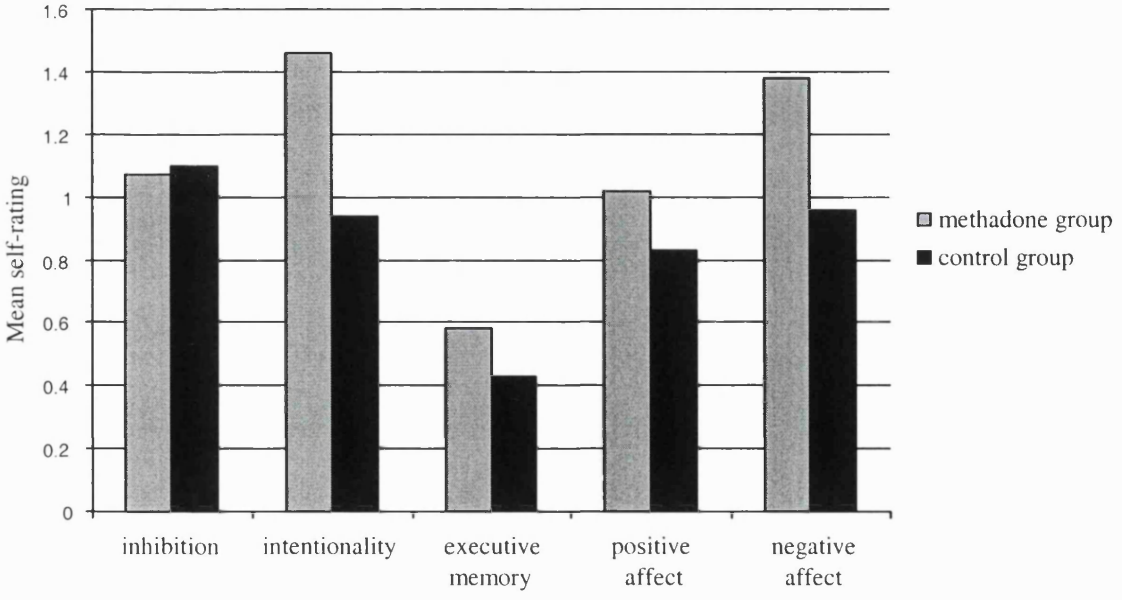
A square-root transformation was performed on each of the five factors. A Profile Analysis (formally a repeated-measures ANOVA) was conducted with factor as a within-subjects variable and group as a between-subjects variable. The group x factor

interaction was non-significant (F(1,28)=2.79, ns). There was no significant difference in mean ratings across factors (F(1,28)=1.36, ns), or between groups (F(1,28)=1.63, ns). However, when age, years of education and depression score were controlled for as covariates a different pattern emerged: the factor effect approached significance (F(1,25)=3.98, p=.057) and a trend emerged in the group x factor interaction (F(1,25)=3.21, p=.085). The effect of group remained non-significant (F(1,25)=.002, ns).

Table 9. Means (standard deviations) of factor scores on the self-rated DEX by methadone and control groups.

	mean (*s.d.*)	
	methadone	control
Factor 1: inhibition	1.07 (*.72*)	1.10 (*.56*)
Factor 2: intentionality	1.46 (*.96*)	.94 (*.52*)
Factor 3: executive memory	.58 (*.59*)	.43 (*.42*)
Factor 4: positive affect	1.02 (*.61*)	.83 (*.60*)
Factor 5: negative affect	1.38 (*.89*)	1.18 (*.86*)

Figure 9. Mean self-rated, DEX factor scores by methadone and control groups.



3.12.2 Comparisons of self-ratings and other-ratings on DEX in methadone group

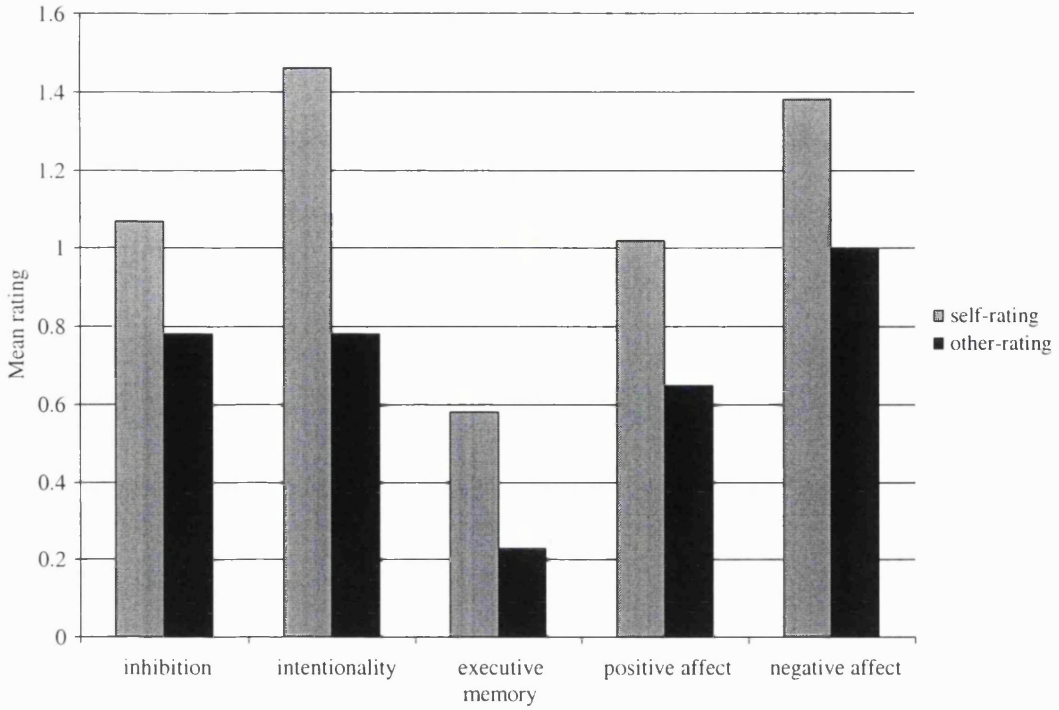
For the methadone group only, self-ratings by participants were compared to ratings by participants' keyworkers ('other-ratings') on the five factor scores. Square–root transformations were performed on all the variables and data analysed by related-samples t-tests (see Table 10.).

Results indicated significant differences between self and other ratings on the factors related to executive memory (t(15)=3.38, p=.004) and positive affect (t(15)=2.14, p=.05). The difference between self and other ratings of inhibition approached significance (t(15)=2.03, p=.061). Self-ratings by participants were higher than other-ratings across all factors (see means in Table 3.9). Mean factor scores for self-ratings and other-ratings are represented graphically in Figure 10.

Table 10. Means (standard deviation) of self-ratings and other-ratings on DEX factor scores (methadone group).

	mean (*s.d.*)		*t*	*p*
	Self-rating	Other-rating		
Factor 1: inhibition	1.07 (.72)	.78 (.57)	t(15)=2.03	*p*=.061
Factor 2: intentionality	1.46 (.96)	1.26 (1.01)	t(15)=.97	*ns*
Factor 3: executive memory	.58 (.59)	.23 (.36)	t(15)=3.38	*p*=.004
Factor 4: positive affect	1.02 (.61)	.65 (.70)	t(15)=2.14	*p*=.05
Factor 5: negative affect	1.38 (.89)	1.00 (.97)	t(15)=1.80	*ns*

Figure 10. Mean self-ratings and other-ratings on DEX factor scores (methadone group).



3.13 Exploratory correlational analyses

Several exploratory correlational analyses were conducted to gain a greater understanding of the relationships between specific variables. In particular, the relationship between two measures hypothesised to measure inhibition were explored: Hayling inhibition (response time) and fluency (significant inter-correlations are shown in Table 11.). Likewise, the association between Hayling inhibition, fluency, premorbid intelligence and current non-verbal reasoning was also explored (shown in Table 11.). A significant negative correlation was found between Hayling inhibition section response time and fluency score. Premorbid IQ was found to correlate significantly with fluency also.

Table 11. Inter-correlations between Hayling inhibition response time, premorbid IQ, current non-verbal reasoning and verbal fluency.

	N=30	1	2	3	4
1	Hayling Inhibition section *Response time*	—	ns	ns	-.40*
2	Premorbid IQ *NART-2*		—	ns	.38*
3	Current non-verbal reasoning *Matrix Reasoning*			—	ns
4	Verbal Fluency				—

** $p<0.01$ * $p<0.05$

The relationship was also explored between Hayling inhibition measures (response time, total errors, category a errors) and DEX question items related to response suppression and impulsivity separately for the methadone and control groups (significant inter-correlations are shown in Table 12. and Table 13.). Category a errors were found to correlate significantly with self-ratings of impulsivity problems in the methadone group,

but not in the control group. Self-ratings of response suppression correlated significantly with self-ratings of impulsivity in the methadone group, but not in the control group.

Table 12. Inter-correlations between Hayling inhibition (response time, total errors, category a errors) and DEX items (response suppression, impulsivity) for methadone group.

	Methadone group, N=16				
		1	2	3	4	5
1	Hayling Initiation *Response time*	—	ns	ns	ns	ns
2	Hayling Inhibition *total errors*		—	.66**	ns	ns
3	Hayling Inhibition *Category a errors*			—	ns	.55*
4	DEX item *Response Suppression*				—	.84**
5	DEX item *Impulsivity*					—

** $p<0.01$ * $p<0.05$

Table 13. Inter-correlations between Hayling inhibition (response time, total errors, category a errors) and DEX items (response suppression, impulsivity) for control group.

	Control group, N=14				
		1	2	3	4	5
1	Hayling Initiation *Response time*	—	ns	ns	ns	ns
2	Hayling Inhibition *total errors*		—	.60*	ns	ns
3	Hayling Inhibition *Category a errors*			—	ns	ns
4	DEX item *Response Suppression*				—	ns
5	DEX item *Impulsivity*					—

** $p<0.01$ * $p<0.05$

3.14. Summary of results

The main findings will be summarised briefly. Groups did not differ significantly in terms of gender, ethnicity, premorbid IQ and current non-verbal reasoning. Results of urine screening indicated that most of the methadone-maintained participants were engaged in polysubstance use. There was wide variation between methadone-maintained patients in terms of their current methadone dose and self-reported substance use history.

The main findings of the study were that the methadone group were impaired on the Hotel task compared with the control group, a finding which was robust to covariance of age, years of education and depression score. The methadone group exhibited reduced verbal fluency and lower digit-symbol coding scores compared with the control group also. Findings on the Hayling sentence completion test were less clear, with apparent group differences on the inhibition section being non-significant when age, years of education and depression score were covaried. Findings on the CARROT test revealed that there was no group effect of differential sensitivity to reward: the methadone group took longer to sort cards on the baseline trial but increased their sorting rate in line with the control group on subsequent trials. No group difference was found on the Brixton rule attainment test.

Finally, no group differences were found on the five factors of self-reported executive problems on the DEX. Keyworkers rated their methadone-maintained clients as having significantly fewer problems with executive memory and positive affect than the clients' own self-ratings. Self-ratings of impulsivity on the DEX correlated significantly with errors on the inhibition section of the Hayling test in the methadone group only.

CHAPTER 4

Discussion

In this chapter, a preliminary critique of the appropriateness of control group in the current study is considered a prerequisite to understanding any observed differences between the groups on neuropsychological measures. The neuropsychological results will then be reviewed and critiqued with reference to extant literature. Following this, the perceived strengths and limitations of the methodology employed in the current study will be discussed. An outline of the clinical and everyday implications of the current findings will follow and it will focus particularly on the role of executive deficits in the process of recovery from addiction. Ideas for future research will then be considered followed by the major conclusions of the current study.

4.1. Appropriateness of the control group

The groups were well matched in terms of premorbid IQ, current non-verbal reasoning ability and demographic factors such as gender and ethnicity. However, interpretation of the current findings is constrained by the finding that the groups also differed in several ways. The methadone group was significantly older, had significantly fewer years of education and had higher depression and anxiety scores on the HADS. The influence of these factors was statistically controlled using ANCOVA's, however, as Grant et al. (2000) have suggested, it is more prudent to reduce the variation associated with these factors by including them explicitly in the design of the study. Analyses revealed that these three variables influenced performance on several neuropsychological measures.

The most interesting findings of this study emerged on the Hotel test, which assessed multi-tasking and strategy application behaviour. The Hotel test findings are discussed below, followed by a discussion of findings on the other tasks employed in the study.

4.2. Multi-tasking and strategy application

It was hypothesised that the methadone group would be impaired on an "ecologically-valid" task of planning, decision-making and multi-tasking skills – the Hotel test. Results supported the hypothesis; the methadone group exhibited impaired performances relative to matched controls. Good planning on the task requires the participant to initially formulate an efficient strategy, which in this case is related to time allocation: the participant must decide to allocate an optimal amount of time to each task (300 seconds). Good performance during the task, is defined as performance which meets the task requirements issued in the instructions (see Method section), and is therefore typified by spending 300 seconds on each subtask, by attempting all of the subtasks, checking the clock frequently and remembering to press the garage buttons at the stated times. In the current study, significant group differences were found between the methadone and control groups on several measures: the methadone group deviated significantly more from the optimal time allocation; they checked the clock significantly less; they deviated significantly more from the stated times when they pressed the garage buttons (when age was covaried out). The methadone group also attempted fewer tasks than the control group, although this difference was non-significant. Importantly, the findings were not explicable in terms of individual differences in intelligence, as neither premorbid IQ nor current non-verbal reasoning correlated with any of the Hotel test

measures. Similarly, these findings were robust to covariance of depression score, age and years of education.

Problems in applying an efficient strategy during task performance has been noted widely in frontal lobe research (Eslinger & Damasio, 1985; Shallice & Burgess, 1991; Duncan, Burgess & Emslie, 1995) and may provide a model of the poorer multi-tasking abilities of substance users. Evidently, the methadone participants did not perform in a way that suggested that they used as an efficient strategy as the controls. It is unknown whether this represented methadone participants' failure to generate an efficient strategy at the outset or, instead, whether it reflected on-line failure of strategy application. Nevertheless, although the task requirements (Hotel test) and rule requirements (Six Elements test) were not presented as having explicit penalties for non-compliance, it is fair to say that adherence to task requirements comprised a goal in itself and in this respect the goal was not fully achieved by the substance users. The Hotel test was originally inspired by the Six Element test (Shallice and Burgess, 1991), which was described as a 'multiple sub-goal scheduling task' (p.728) and the fundamental component of successful performance on the Six Elements task was hypothesised to be the ability to 'create and activate delayed intentions'. Moreover, a later study which explored relationships between performance on a variety of neuropsychological tests and DEX ratings (Burgess et al, 1996a) found that of all the tests administered, only the Six Elements test was significantly related to the DEX intentionality factor. The concept of 'bridge processes' was used to describe intentional, goal-oriented processes that link together motivation and special-purpose memory systems and was sub-divided into three component processes: 1) plan formulation or modification; 2) marker creation or

triggering; 3) evaluation and goal articulation. Frontal lobe patients were found to be particularly prone to errors in marker creation and triggering (Shallice & Burgess, 1991). Similarities between the Shallice & Burgess (1991) account of "marker errors" and Damasio's "somatic marker hypothesis" have been noted (see Burgess, Veitch, Costello & Shallice, 2000), which raises the question of whether 'marker errors' in substance users account for their poor performance on both the Hotel test and the gambling task (Bechara et al., 2001). Burgess et al. (2000) noted that these complementary explanations are actually seeking to explain different aspects of the same deficit in frontal patients, whereby the individual fails to respond to a signal or cue for action. Bechara, Damasio and colleagues have developed a more rarefied view of these deficits in substance use, which specifies a potential anatomical substrate of hypothesised failures of somatic marker processes in chronic substance users.

The question of how to circumvent difficulties in executive processes, particularly those related to the activation of prior intentions and goals has been a recent focus of neuropsychological rehabilitation research. The tendency to neglect the task requirements - the overall goals - when engaged in a task was described by Manly et al. (2002) as a problem of *"a marker or representation from the higher level goal having difficulty in competing for expression"* (p.279). Manly et al. (2002) made an interesting point related to findings in the vigilance literature that have demonstrated that exposing individuals to unpredictable noise, changes in temperature and vibrations can improve the ability to detect infrequent perceptual stimuli. In the Hotel test study (Manly et al., 2002) it was found that an infrequent tone improved brain-injured patients' ability comply with the Hotel task requirements of attempting all of the subtasks and optimally

allocating their time to each subtask. The authors concluded that the tone acted to draw attention away from the current subtask and *"provided a window in which evaluation of actions against the goal is more likely to occur"* (p.280). They postulated that, ultimately the support of one aspect of the executive function in this method *"may give other aspects related to problem solving and organisation a better chance of expression"* (Manly et al, 2002: p.280). Substance use research, as yet, does not appear to have taken up ideas from neuropsychological rehabilitation, although they may be of value in reducing the impact of substance-related cognitive deficits.

A pertinent question relates to the extent to which the observed deficits on the Hotel task exclusively reflect executive impairments per se. As Burgess & Shallice (1996b) have noted, complex tasks that seek to tap executive processes can also be affected by impairments on non-executive processing resources. A purely motivational explanation of the methadone groups' poorer performance is not supported by observations that they expended substantial effort in their performances and the related finding that the methadone participants appeared more motivated than controls on another task (CARROT). However, it is possible that motivational decrements occurred secondary to the effects of reduced saliency of task requirements. If the task requirements were less perceptually salient to the methadone participants, then they would not motivate and guide performance to the same degree as occurred with controls. This possibility fits with Goldstein & Volkow's (2002) "I-RISA" model of addiction that posits impaired saliency attribution of non-drug related stimuli as central to cognitive deficits of substance users.

The underlying skills tapped by the Hotel test have been described as highly predictive of real-life difficulties in organisation and planning. Previously, Manly et al. (2002) demonstrated that a group of brain-injured patients were significantly impaired compared to matched-controls on almost every measure on the Hotel test (with the exception of number of clock checks). All of the patients scored in the 'average' range on current IQ (WAIS-II) and although they exhibited dysexecutive impairments in everyday skills, only 30% scored in the 'abnormal-impaired' range on an analogous multi-tasking test (Six Elements test of the BADS). It is proposed that, despite the same underlying format, the Hotel test has more ecological face validity than the Six Elements test and, in face of Manly et al.'s (2002) findings, the hotel test also appears to have greater sensitivity to real-world organisational deficits. Methadone participants' poorer Hotel test performance may represent a circumscribed version of the dysexecutive syndrome reported in Manly et al.'s (2002) study; quantitatively the methadone groups' scores in the current study fell between the scores of frontal and control groups in the Manly et al. (2002) study.

4.3. Reward Responsivity on the CARROT

Psychomotor processing speed

The methadone group took significantly longer than the control group to sort 60 cards in the baseline condition of the CARROT – a finding that was robust to the effects of age, years of education and depression score. Powell et al. (1996) proposed that speed of card sorting mostly taps psychomotor processing skills that are arguably similar to those tapped by the Digit-symbol coding test (DCST). Slowed baseline sorting speed in the

methadone group concurs with the finding that the methadone group were significantly slower at coding symbols on the DCST also. Mintzer & Stitzer (2002) noted that impaired psychomotor speed is a highly reliable finding in opiate users (see Darke et al, 2000, Specka, et al., 2000).

The influence of differences in sorting speed between participants was removed, however, by the experimental manipulation of calibrating each participants' time available on subsequent trials according to their earlier baseline speed. It was hypothesised that the methadone group would not show the normal response of increasing their sorting speed when offered a small financial incentive (approximately £1). It was predicted that the control group would show a differential sensitivity to reward evinced by sorting more cards in the time available. This hypothesis was not supported by the results. The groups did not differ in their reactions to the reward condition as both groups sorted more cards when there was a financial incentive. Therefore, the current study found no evidence that opiate users were less motivated by financial incentive than healthy controls. It would be pertinent to formally assess opiate users' clinical motivation also, given the results are not suggestive of impaired responsivity to reward.

However, the use of financial incentive as a non-drug reward in the current study may be problematic: monetary stimuli may represent a highly salient reward in substance users, given that money and drug acquisition are arguably closely linked in users' repertoire of drug-related behaviours. It would have been useful to compare differential responsivity to different categories of stimuli that vary in relation to their proximity to drug taking.

Methadone participants sorted more cards in both the reward and non-reward conditions of the CARROT and this difference was significant when depression scores were covaried. The higher sorting rates in the methadone group appear inconsistent with their slower initial baseline times. The fact that the methadone group initially took longer to sort 60 cards meant that they were allocated longer times to sort cards on subsequent trials. However, it is possible that the methadone group benefited more from practice over the trials (there was a practice effect in both groups) and subsequently were able to sort more cards because they had more available time.

In the current study, it was unknown whether the methadone group were in a state of early withdrawal or whether the receipt of their daily methadone dose acted in a similar way to the effects of smoking one cigarette did in the Al-Adawi and Powell (1997) study. The authors reported reward responsivity impairments in recently abstinent smokers, which disappeared once one cigarette was smoked. It was hypothesised that when smokers were nicotine-deprived their *"endogenous dopaminergic activity was downregulated, which rendered the smokers less able to respond to incentives"* (p.1781). It was claimed, however, that smoking one cigarette stimulated their dopaminergic activity, thus leading to improvements on tasks measuring responsiveness to incentives. In the current study, the methadone group had received an acute dose of methadone prior to performing the task, although it is unlikely that individuals would have experienced the pharmacological effects because of the recency of the dose. It is possible that acute administration of methadone produced a psychological effect that enhanced performance of the task, thus ameliorating any pre-existing reward

responsivity deficit. Future research is required to assess reward responsivity could pre and post methadone administration to explore this possibility.

4.4. Response initiation and inhibition

4.4.1. The Hayling test

Executive functions related to response initiation and inhibition were assessed in the current study using the Hayling sentence completion test. It was hypothesised that functional changes in activation of orbitofrontal and ventromedial cortical areas in chronic opiate users, would lead to deficits on tasks purported to tap inhibitory control subserved by these areas.

The first part of the Hayling test measures response initiation, by requiring the participant to complete a sentence with an automatic response, which is a word that is highly cued by the sentence context. It was hypothesised that methadone participants' response initiation abilities would be comparable to healthy, matched controls, as there was no evidence in extant literature to suggest that chronic opiate abuse is associated with impaired automatic responding. As predicted, no significant difference was found between the methadone and control groups in mean response time and most participants performed within the 'average' range. Burgess and Shallice (1996a) found that patients with frontal lobe lesions were significantly slower than controls and patients with posteriorly-located lesions. The current findings suggest that, with respect to initiation of automatic responses, the methadone group do not exhibit deficits similar to those associated with the consequences of frontal lobe injury reported by Burgess and Shallice

(1996a). Indeed, the methadone group mean time to respond was 15 seconds less than the frontal lesion group mean in the Burgess and Shallice (1996a) study. However, the finding that frontal patients showed longer response times was not replicated in a study by Andrés and van der Linden (2001) who found no evidence that frontal patients differed from controls on the initiation section. The frontal group mean (in the Andrés & Van der Linden, 2001) was within 5 seconds of the methadone mean in the current study. A lack of consistency in finding a 'frontal deficit' on this measure suggests that, speculations on the functional-anatomical intactness of the methadone group would be inappropriate.

The second part of the Hayling is purported to measure response inhibition, defined as the 'inability to suppress the most salient response' (Burgess & Shallice, 1996a: p.263). Participants had to inhibit a well-learned response, which was highly cued by the sentence context. Both groups took longer on the inhibition section than the initiation part. There was a trend towards methadone participants taking slightly longer than controls to give a response, but the difference was non-significant. Most participants performed in the 'average' range, although there was greater variability in the methadone participants' performances.

Burgess and Shallice (1996a) derived a measure of 'additional thinking time' associated with the second part of the Hayling compared to the first, because they hypothesised that inhibition performance was partly influenced by the ability to initiate a response. Therefore, they calculated the difference in response time between initiation and inhibition sections for each participant and found a significant frontal-control difference.

There was a trend, in the current study, of longer additional thinking times in the methadone group, although the trend disappeared once the influence of age, years of education and depression score were covaried. It seems that the methadone participants tended to require longer times when asked to inhibit automatic responses, but this tendency was related to more general variance between the groups.

An error in the inhibition section was defined as the inability to inhibit automatic responses that were semantically related to the sentence and were divided into two subtypes; category a errors were defined as straightforward, automatic, completions of the sentence, whereas category b errors were defined as being only semantically-related. The current study found the methadone group made significantly more category b errors and tended to make more category a errors too, compared to controls. However, these error scores were comorbid with age, years of education and depression score, as the differences were non-significant once the influence these factors were covaried out. The finding that error score was influenced by age, replicates findings by Burgess and Shallice (1996a), who also found age to be a source of covariance, although the frontal impairment in error score remained after the effects of age were accounted for in their study.

Importantly, unlike the control group, there was wide variation among methadone participants in scaled error scores. A bimodal distribution was observed in the methadone groups' error scores, whereby a sub-group (25%) performed in the 'abnormal'-'impaired' range and another sub-group (75%) performed in the 'average'-'good' range. This observation of wide inter-group heterogeneity has been observed in

other studies of neuropsychological functioning in methadone users (Davis, Liddiard & McMillan, 2002), which raises the question of whether there is a sub-set of severely cognitively impaired opiate users, whose cognitive deficits are well-represented by models of executive dysfunction in frontal patients. Unfortunately, the small sample size in the current study means that it is impossible to meaningfully analyse these inter-group variations.

Overall, the results supported the hypothesis that response initiation abilities are not impaired in the methadone group. The hypothesis that the methadone group would be impaired on the response inhibition section of the Hayling was not supported in the current study. Wide variability in the performance of methadone participants on the inhibition section was found however, and revealed that a sub-group of methadone users exists that who demonstrate severely impaired inhibitory control. This finding warrants further investigation.

4.4.2. Verbal fluency

It was hypothesised that the methadone group would show significantly reduced word fluency compared to healthy controls, as a result of reduced inhibitory control in the methadone group. This hypothesis was supported by the results, which indicated that methadone participants produced fewer words compared to controls. However, there is much debate in the literature regarding the underlying mechanisms governing word fluency abilities, some have posited fluency as mediated by initiation abilities (Ramier & Hacaen, 1970 cited in Burgess & Shallice, 1996a), whereas others take the view that it taps inhibitory processes because it requires the suppression of habitual meaning-based

word search strategies (Perret, 1974). In the current study, a significant negative correlation between fluency and the response time on the inhibition section of the Hayling was found, whereby lower fluency was associated longer response latencies on the Hayling (inhibition), which supports the view that both tasks may tap similar underlying inhibitory processes.

Qualitative differences were observed between the groups in their tendency to use organised approaches to the fluency task. Word fluency tasks have been viewed as measuring an individuals' strategy generation abilities (Estes, 1974), good strategies include using the same initial stem (e.g. content, contend, contain) or deriving word from a themed category (e.g. sew, stitch, seam) (Lezak, 1995). Informal examination of the words produced by participants in the current study suggested that, methadone participants did not use strategies as often as control participants. Methadone participants showed a greater tendency to pick random words from memory, which, it is proposed, is a less efficient means of achieving the goal of the task.

Superior verbal fluency performance has been related to higher intelligence (particularly verbal intelligence), however, the group difference remained significant once the influence of premorbid intelligence and current non-verbal reasoning were covaried out.

4.5. Rule attainment

The Brixton test assesses executive abilities of rule attainment and responsivity to rule changes. The Brixton test manual (Burgess & Shallice, 1997) measures performance in terms of the total number of errors made. It was hypothesised that the methadone group

would make more errors than controls, because of executive deficits in rule attainment associated with chronic opiate use. This hypothesis was not supported by the results; there was no significant difference between the groups in the mean number of errors made. Although statistically significant differences were not found, the Brixton test appeared to pose especial difficulties for more of the methadone participants than the controls. A large percentage (75%) of methadone participants' scores fell in the 'impaired-low average' range compared to just 29% of controls. Interestingly, a proportion of both methadone and control participants performed in the 'impaired' range, a finding that suggests that a sub-group of participants had severe difficulties in rule attainment that were unrelated to chronic substance use.

It is difficult to establish the underlying cause of errors by participants scoring in the lower range on the test on the basis of standard test scoring procedures outlined in the Brixton test manual (Burgess & Shallice, 1997). In the Burgess & Shallice (1996b) study, three Brixton test performance measures were reported to be affected by frontal lesions: overall error rate, the proportion of bizarre error responses and the number of move responses when a rule has already been attained. The current study only measured overall error rate because of the lack of clear guidelines on analysis of error types in Burgess & Shallice (1996b). In the 1996b study, the authors found a very high correlation between bizarre responses and overall error rate, which they concluded was indicative that these measures tapped a similar processes. This raises the question of whether the poorer performance of some participants was linked to bizarre guessing. It is notable that during performance of the task, many participants appeared to make random guesses frequently.

Three hypotheses were offered by Burgess and Shallice (1996b) to explain the greater propensity of frontal patients to make bizarre guesses; 1) Guessing was the result of difficulties in utilising memory representations to guide current behaviour; 2) Greater difficulty in creating abstract rule sets; 3) Rules on the Brixton are perceptually less salient than rules on the WCST, instead rules are must be deduced from relations between current and previous stimuli, which is cognitively more complex. Frontal patients' deficits were attributed to be the result of them formulating odd rules and failing to check the plausibility of the formulated rule. On the basis of the current findings it is impossible to discern if this explained the poorer performance of many participants in the current study.

As discussed, the current study did not employ the system of error classification discussed in the Burgess & Shallice (1996b), instead the standard administration and scoring procedures described in the manual were followed. To gain a greater understanding of qualitative differences in performance on the Brixton test it would be instructive to conduct more detailed error analysis in future research.

4.6. Behavioural indicators of dysexecutive syndrome: DEX questionnaire

The current study examined severity ratings of dysexecutive problems in everyday life using the DEX questionnaire (Wilson et al., 1996). This examination was exploratory in nature, as this is a previously neglected area of research in substance users, which therefore made it impossible to construct empirically-based hypotheses. Differences in DEX ratings of executive problems have been found between frontal patients, controls and significant others (Burgess et al., 1998). Self-ratings by frontal lobe patients have been found to be significantly lower than significant others' ratings of patients' difficulties, which Burgess et al. (1998) interpreted as frontal patients having a lack of insight. In contrast, self-ratings by controls have been found to be significantly higher than significant others' ratings of controls' difficulties. However, frontal lobe patients rated their problems as significantly higher than controls in the Burgess et al. (1998) study, which questions whether frontal patients truly lacked insight into their difficulties.

4.6.1. Self-ratings in the methadone and control groups

If methadone participants were aware of their apparent executive difficulties, then self-ratings by the methadone group on the five factors of the DEX were expected to be higher than self-ratings by the control group, On the other hand, if methadone participants lacked awareness or insight similar to frontal lobe patients, then it was expected that their self-ratings would be equal to or lower than the control groups' self-ratings. There were no significant differences between groups in mean self-ratings on any of the five factors. However, when the influence of age, years of education and depression score were controlled for as covariates, only a trend emerged that suggested

higher self-ratings in the methadone group on specific factors. Therefore, findings did not support the notion that methadone participants were less aware of their executive problems.

4.6.2. Self-ratings and executive test performance

Although not statistically significant, on 4/5 factors (intentionality, executive memory, positive & negative affect) the methadone group rated themselves as having more executive-type behavioural difficulties in everyday life than the control group. The question was whether self-ratings accurately reflected their executive performances. Very few correlations were found between the DEX factors and performance on the executive tests. Interestingly, ratings on the DEX executive memory factor correlated with a prospective memory aspect of the Hotel test – whether participants remembered to press the hotel buttons and their deviation from the stated time.

The current study assessed response inhibition using the Hayling and fluency tests, therefore, correlations between these tests and DEX self-ratings of inhibition were explored. The methadone group were impaired relative to controls on fluency and to a lesser degree on the Hayling test (although performance was influenced by covariates), but self-ratings of inhibition problems (i.e. DEX inhibition factor) were higher in the control group. Clearly, it is reasonable to expect higher self-ratings by the methadone group, if they had awareness of their apparent reduced inhibitory control. However, it appears that the inhibition factor included a wide range of behaviours, each of which loaded onto the factor to different degrees (listed in Table 14.).

Table 14. Sub-components of DEX inhibition factor (Burgess et al., 1998)

Factor loading	DEX question	Inhibition factor behaviours
.83	**I find it difficult to stop doing things even if I know I shouldn't**	**Response suppression problems**
.77	**I act without thinking, doing the first thing that comes to mind**	**Impulsivity**
.77	I am unconcerned about how I should behave in certain situations	No concern for others' feelings
.75	I am unaware of, or unconcerned about, how others feel about my behaviour	No concern for social rules
.63	I do or say embarrassing things when in the company of others	Disinhibition
.55	I have problems understanding what other people mean unless they keep things simple and straightforward	Impaired abstract reasoning
.50	I tend to be very restless, and 'can't sit still' for any length of time	Restlessness

Burgess et al. (1998) analysed factor loadings and found high loadings for questions assessing response suppression and impulsivity. It is argued that these two questions also relate most closely to task-related inhibition problems. No correlation was found in the control group between their self-ratings on these two questions and their performance on the Hayling and fluency tests: it appears that the controls did not appraise their inhibitory control accurately. In contrast, the methadone groups' self-ratings on impulsivity correlated significantly with category a errors (automatic completions) on the Hayling test (but no correlation with any other performance measure on the Hayling or fluency). Category a errors were higher in the methadone group, thus it appears that

the methadone group made more accurate appraisals of their propensity towards impulsivity. Interestingly, self-ratings by methadone participants on these two questions correlated significantly with each other i.e. individuals who rated themselves highly on response suppression problems also rated themselves highly on impulsivity.

4.6.3. Self-other ratings in the methadone group

It was expected that if methadone participants lacked insight into their problems, then their self-ratings would be significantly lower than the ratings by their keyworkers who were involved in the methadone participants' treatment. There was a significant difference between self-other ratings on 2/5 factors (executive memory, positive affect) and a trend on the inhibition factor, whereby keyworkers' ratings were significantly lower than the participants' self-ratings. Given that self-ratings did not differ significantly between the methadone and control groups, it seems unlikely that inflated self-reporting occurred among the methadone participants. The implication of the current finding is that keyworkers perceived their methadone clients' problems in executive abilities as less severe than the clients perceived them.

Burgess et al. (1998) found that control participants rated themselves as showing a significantly greater severity of dysexecutive problems in everyday life than raters who knew them well. This fits with the findings in keyworkers and their methadone clients found in the current study. In contrast, frontal patients rated their dysexecutive problems as significantly less severe than raters who knew them well. The current study does not support the notion that methadone participants have a lack of insight into their difficulties. In contrast, the findings suggested that keyworkers rate the methadone

participants' difficulties related to executive memory, positive affect and inhibition as less severe than the methadone participants' own ratings.

It is probable that keyworkers do not perceive these difficulties because of the limited session time available to discuss issues with their clients that are not directly related to drug-use. Several keyworkers commented that they did not think they had opportunities to observe several of the executive skills referred to in the questionnaire and gave lower ratings on these questions. Nevertheless, it is proposed that differences in perception of difficulties between keyworkers and methadone clients may have treatment implications (these are discussed in section 4.8.).

4.7. Methodological Issues

4.7.1. Strengths of the design

The design of the current study addressed several weaknesses of previous research. Firstly, it has been suggested that methadone maintained patients are at a greater risk of neuropsychological problems as a result of brain damage caused by alcohol abuse, traumatic brain injury and overdose-related hypoxia (Darke et al., 2000; Davis et al., 2002). The current study attempted to reduce the influence of these factors by excluding individuals who had experienced traumatic brain injury and had a history of alcohol dependence. Indeed, Darke et al. (2000) found that alcohol dependence was a significant predictor of cognitive performance among a group of methadone-maintained patients. The influence of overdose-related pathology was impossible to exclude given that it has been estimated that a heroin user will experience a median of three life-time overdoses (Darke et al., 1996). In the current study, a crude measurement of the number of overdoses was taken and discussions indicated that none of the participants described prolonged periods of unconsciousness or an onset of memory impairment following overdose.

The time between administration of methadone and neuropsychological testing was controlled so that all methadone participants completed tests at the same time since dosing, and prior to the onset of major peak effects of methadone (peak effects occur after 3-4 hours). Mintzer and Stitzer (2002) previously suggested that time relative to methadone dosing should be a key consideration in neuropsychological research in methadone use.

Urinary analysis permitted clarification recent drug use by methadone participants at the time of testing, given that self-reported substance use is notoriously unreliable. In the current study, it became clear that most methadone participants were, in fact, polysubstance users, which suggested that the current sample was highly representative of the general opiate-using population. Therefore, this accords some validity to the generalisability of the findings of the current study to the target population in drug treatment. However, it also means that any conclusions regarding observed cognitive deficits in the current study are applicable to polysubstance users only.

It was considered important to have a control group that was comparable to the methadone group in as many ways as possible, with the obvious exception of substance-dependency. Bechara et al. (2001) previously found that employment status significantly predicted the level of cognitive performance in a group of polysubstance users, therefore the current study ensured the groups were comparable in this respect.

4.7.2. Limitations of the design

The conclusions from the current study are constrained by several factors related to limitations of the design. Firstly, the sample size was relatively small, although small numbers are characteristic of research in this field. Pronounced difficulties in research in this area have been noted, particularly uncooperativeness and unreliability (Curran, et al., 1999) – factors which impacted severely upon numbers in the current study. The small sample size means that statistical power may have been reduced and consequently reduced the effect size from optimal levels. It was difficult to establish an optimal effect

size on most of the tests employed in the current study, as they had not been used in substance-using populations before.

The heterogeneity of the methadone group constrains conclusions regarding the direct neuropsychological consequences of substance use *per se*. The methadone group were particularly heterogeneous with respect to severity and chronicity of substance use, a finding common in the area (Ornstein et al., 2000). As the severity of dependence was not systematically measured, it is possible that this was an important factor. Differences were also found with respect to number of overdoses, level of daily methadone dose, intoxification and polysubstance use, all of which may be linked to differences in cognitive abilities. In an attempt to circumvent problems related to polysubstance use and acute intoxification, cognitive abilities of inpatient substance-using populations have been studied (Curran et al., 2001). Others have assessed patients after fully withdrawing from methadone and other opioids. For example Davis et al. (2002) found that abstinent methadone users performed neuropsychological tests relatively well, which suggests that cognitive recovery may occur on cessation of use.

The finding that polysubstance use was highly prevalent in the methadone group, particularly concurrent opiate and cocaine use, has important implications for performance on neuropsychological measures: *"abuse of cocaine is associated with decrements on neurobehavioural tests measuring executive function, impulsivity, visuoperception, psychomotor speed, manual dexterity, verbal learning and memory"* (Bolla, Funderburk & Cadet, 2000: p.2285). It is possible that the cognitive deficits observed in the methadone group in the current study reflected their cocaine use as much

as, or even more than, the effects of opiate use. Clearly, however, it is impossible to isolate key variables associated with cognitive impairment on the basis of the current findings. At best, the current findings provide a snap shot of executive functioning in polysubstance users who take methadone daily.

Clearly questions of causality of cognitive impairment cannot be answered by the design of the current study: it is unknown whether observed deficits pre-dated substance use or even played an etiological role in the development of addiction. The role of long-sanding personality issues cannot be discounted, given that formal psychiatric diagnoses are not made routinely in the drug services from which methadone participants were recruited in the current study. Neuropsychological status especially executive functioning has been linked to borderline personality disorder and avoidant personality disorder (Van Reekum, Bolago, Finlayson, Garners & Links, 1996) and high rates of comorbidity between substance-dependency and antisocial personality disorder have been reported (Robins & Reiger, 1991). Therefore, it is proposed that the cognitive deficits observed in the methadone group may represent not only the direct neurological effects of polysubstance use, but also potential comorbid neurological factors associated with personality disorder.

4.8. Clinical and everyday implications

One of the major findings of the current study was that the methadone group were impaired in planning, organisation and multi-tasking (on Hotel test) compared to healthy controls. Ecologically-valid tests, such as the Hotel test, are believed to more accurately predict the types of problems the individual may have in a real-life situation compared to

standard neuropsychological tests. Accordingly, it is argued that the current findings are highly suggestive that many of the methadone participants may exhibit debilitating problems in coping with the organisational demands of both everyday life and engagement in therapy and rehabilitation. Impaired planning and organisational skills pose severe problems for an individuals' ability to manage their domestic and financial affairs and their ability to seek and maintain gainful employment.

Responsivity to incentive, at least financial incentive, was not impaired in the methadone group in the current study. Al-Adawi et al. (1998) linked reward responsivity behaviour to the individuals' receptiveness to encouragement and praise in clinical settings. Thus, the current findings tentatively imply that methadone participants may be as responsive to these clinical motivators as non-drug using populations, although further research is required to clarify these links. It is possible that financial incentives may have equal salience as drug-related incentives to substance-users, given the inextricable link between money and drug-acquisition and non-drug incentives are of lower salience. Therefore the differential salience of different incentives for substance users would be worthy of attention in future research.

The current findings support the notion that polysubstance use is associated with reduced inhibitory control in methadone users. Goldstein & Volkow (2002) identified this aspect as of central significance to the maintenance cycle of addiction and, clearly, it carries severe repercussions for users' attempts to recover from addiction. A common goal identified by methadone clients is to abstain from illicit drug use when engaged in methadone maintenance treatment. Differences in perceptions of inhibitory problems

between clients and keyworkers on the DEX were found in the current study and suggests that keyworkers may be unaware that methadone clients are significantly compromised in their ability to suppress automatic, habitual responding, particularly in response to drug-related cues. A greater awareness in clients and keyworkers alike of this potential weakness may prove helpful in the development of coping strategies for dealing with stimuli likely to elicit automatic, habitual responses e.g. drug-related cues. Darke et al.'s (2000: p.694) view concurs with this point: *'Clinic staff need to be aware of these deficits, and their likely implications for behaviour. Many behaviours considered the result of antisocial personality disorder, for instance may be in fact due to acquired cognitive impairment...such patients may have trouble thinking of adaptive solutions to everyday problems that crop up in their everyday routines. Non-compliance with clinical routines and instructions may, therefore, reflect inability rather than motivational or personality characteristics'.*

Psychotherapy requires many cognitive skills, a factor which has been acknowledged in the neurological rehabilitation field where standard cognitive-behavioural therapy has been adapted to compensate for deficits acquired due to brain-injury (see 'neuropsychotherapy' advocated by Judd, 1999). Additional repetition and provision of written material is used to compensate for memory impairments in brain-injured individuals. Executive deficits in methadone users may have particularly profound effects on the ability of a user to carry-out their agreed treatment plan, despite them being able to verbalise the plan/strategy with their drug-worker or therapist. This was observed informally on the experimental tasks, especially the Hotel test, whereby despite being able to identify the correct strategy at the end of the task, many methadone

participants were unable to actively apply the strategy. In this respect, they demonstrated qualitatively similar behaviours to frontal lobe patients (see Shallice & Burgess, 1991), who show a dissociation between generated intentions and their actions. Keyworkers rated substance users' intentionality problems on the DEX as higher than any other executive problems, which suggests that keyworkers are aware of these behaviours. A greater understanding of the underlying causes of the behavioural difficulties of intentionality i.e. that it is not purely because of a lack of motivation, may lead keyworkers to the generate different strategies with the client to cope with these problems.

Deficits in 'strategy application' (Shallice & Burgess, 1991) may have particular relevance to relapse prevention therapy, which often emphasises planned exposure to high-risk stimuli by the individual. If the individual is able to articulate a well-thought out plan, it may be assumed that it is merely a matter of motivation whether the plan is enforced or not. A lack of awareness of potential deficits in application of goals greatly increases the individuals' risk of relapse. However, it is argued that relapse strategies could be subtly altered to take account of these deficits e.g. explicit trouble-shooting of application problems with therapists, alerting techniques to remind people of their goals, environmental support of plans.

4.9. Future research

It is unknown whether executive impairments observed in the current study were attributable to acute or chronic effects of methadone and/or other illicit substances. A longitudinal research design would allow the executive functioning of users to be

studied over time possibly encompassing periods of abstinence and dependence, although such a design would be difficult given the chaotic nature of many drug users' lives. A cross-over design was originally planned for the current study, whereby comparisons were to be made of executive function prior to methadone administration and again during peak effects. Such a design would allow aspects such as reward responsivity to be studied during withdrawal and intoxication states.

The role of different incentives in motivating substance users is of clinical significance to treatment programs. Therefore, it would be expedient to assess the relative saliency of a variety of incentives to optimise treatment response. The relationship between the CARROT task and clinical motivation has been studied in brain-injured populations, but as yet, little is known of the relationship in substance users. Future research could address this issue.

The neurological rehabilitation literature has explored means of supporting, and consequently improving, aspects of brain-injured individuals' goal-oriented behaviour (Manly et al., 2002). Future research could assess whether manipulations such as the provision of environmental cues have any role in improving substance users' executive skills.

The current findings have partially supported the view that loss of inhibitory control may be related to substance use. The question remains of whether executive dysfunction contributes to the maintenance of addiction, in particular relapse. Future research could investigate the role of planning and organisation abilities in relapse prevention treatment

and identify key factors in drug lapses: are lapses linked to difficulties with inhibitory control and/or failures of strategy application?

Finally, it appears necessary to consider what level of cognitive functioning should be assumed adequate for an individual to be able to participate in widely-used psychotherapies such as cognitive-behavioural therapy. If it is accepted that chronic substance users have cognitive impairments particularly executive problems, then one must consider whether they are indeed able to complete aspects of the therapy that require planning and organisation e.g. homework tasks etc. Future investigations could explore which aspects of these therapies prove to be pitfalls for users and explore possible relationships to cognitive status.

4.10. Summary

In summary, this thesis aimed to investigate the executive abilities of methadone maintained individuals in relation to response initiation and inhibition, reward responsivity and real-world skills of planning and multi-tasking compared to matched controls. The majority of the methadone maintained group were found to be concurrently using other illicit substances, most commonly cocaine, which constrained interpretation of the cognitive consequences of chronic opiate use *per se*. Results indicated that there appeared to be a sub-set of methadone users whose performances were severely impaired, although the contributing factors to this finding were not discernible from the current data.

A main finding was that the methadone group performed significantly poorer on an "ecologically-valid" test of multi-tasking and planning compared to controls. Given that performance on this task has been associated with of problems in everyday activities of frontal patients, this finding suggests that the disorganisation that frequently characterises substance users' lives may be partially related to underlying cognitive deficits.

Group differences on other tasks (Hayling test, CARROT) were less clear and in many cases influenced by depression score, age and years of education. These findings were discussed in relation to limitations of the study. The possible role of inhibitory problems in the maintenance of addiction and the process of relapse were discussed however.

The potential clinical and everyday implications of the observed executive deficits of substance users were discussed, particularly the role of executive dysfunction in completing the tasks of rehabilitation and therapy. It was proposed that neurological rehabilitation research may provide incisive clues into methods of reducing the impact of executive deficits on substance users' everyday lives.

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Appendix I: Ethical approval letter from Camden & Islington Community Health Service Local Research Ethics Committee

Camden and Islington Community Health Service
LOCAL RESEARCH ETHICS COMMITTEE

Research & Development Unit, 3rd Floor, West Wing, St. Pancras Conference Centre
St Pancras Hospital, London NW1 0PE
tel: 020 7530 3376 fax: 020 7530 3235
e-mail: ayse.all@camdenpct.nhs.uk
Chair: *Stephanie Ellis* Administrator: *Ayse All*

21 August 2002

Professor Val Curran
Sub-Department of Clinical Psychology
University College London
Gower Street
London
WC1E 6BT

Dear Professor Curran

LREC Ref: 02/65 (please quote in all further correspondence)
Title: **The effects of chronic opiate use and daily methadone maintenance on executive function**

Thank you for your letter dated 5th July 2002 addressing the concerns raised by the Committee, I apologise the delayed response. I am pleased to inform you that after careful consideration the Local Research Ethics Committee has no ethical objections to your project proceeding. This opinion has also been communicated to the North Central London Community Research Consortium.

PLEASE NOTE THAT THIS OPINION ALONE DOES NOT ENTITLE YOU TO BEGIN RESEARCH.

Camden and Islington Community Health Service LREC considers the ethics of proposed research projects and provides advice to NHS bodies under the auspices of which the research is intended to take place. It is that NHS body which has the responsibility to decide whether or not the project should go ahead, taking into account the ethical advice of the LREC[1]. Where these procedures take place on NHS premises or using NHS patients, the researcher must obtain the agreement of local NHS management, who will need to be assured that the researcher holds an appropriate NHS contract, and that indemnity issues have been adequately addressed.

N.B. Camden and Islington Community Health Service LREC is an independent body providing advice to the North Central London Community Research Consortium. A favourable opinion from the LREC and approval from the Trust to commence research on Trust premises or patients are **NOT** one and the same. Trust approval is notified through the Research & Development Unit.

The following conditions apply to this project:

- You must write and inform the Committee of the start date of your project. The Committee (via the Local Research Ethics Committee Administrator or the Chair at the above address) must also receive notification:

  a) when the study commences;
  b) when the study is complete;
  c) if it fails to start or is abandoned;
  d) if the investigator/s change and
  e) if any amendments to the study are made.

- The Committee must receive immediate notification of any adverse or unforeseen circumstances arising out of the project.

[1] Governance Arrangements for NHS Research Ethics Committees, *July 2001 (known as GAFREC)*

Appendix I: Continued

- It is the responsibility of the investigators to ensure that all associated staff, including nursing staff, are informed of research projects and are told that they have the approval of the Ethics Committee and management approval from the body hosting the research.
- The Committee will require a copy of the report on completion of the project and may request details of the progress of the research project periodically (i.e. annually for longer projects).
- If data is to be stored on a computer in such a way as to make it possible to identify individuals, then the project must be registered under the Data Protection Act 1998. Please consult your department data protection officer for advice.
- Failure to adhere to these conditions set out above will result in the invalidation of this letter of no objection.

Please forward any additional information/amendments regarding your study to the Local Research Ethics Committee Administrator or the Chair at the above address.

Yours sincerely

Stephanie Ellis
Chair, LREC

Appendix II: Keyworker information sheets

Methadone Maintenance & Decisionmaking Research

Information for Keyworkers

- As part of the research (as discussed in the XX team meetings), I would like to recruit **16 clients** to participate.
- As keyworkers you have the best idea regarding **which clients from your caseload would be most suitable** for the study.
- If you think a client is suitable, then can you **write their name on the slip (overleaf) and put the slip in my tray (marked 'Sharin' beside Psychology trays) please.**
- **I will contact you to arrange to meet the client** (for 5 minutes to explain the study & ask if the client is interested in taking part). I can meet the client when its most convenient for them - probably at the end of one of your usual keyworking meetings with the client.
- You will not have to describe the study to clients. **You would need only to ask the client if they are willing to meet me for 5 minutes to talk to them about the study.**

Suitable Clients (criteria)

- **Opiate dependent SSA client aged 18-50yrs**
- **English as first language**
- **No history of alcohol dependency**
- **No history of major head injury**
- **No major current medical condition/illnesses e.g. epilepsy/HIV**
- **Opiates are predominant drugs of use (polydrug users are acceptable if main drug is opiate)**
- **No major psychiatric illness including psychosis**

What the client will be asked to do if they participate

- to give 1.5 hours of their time as follows: to come to X Centre for 1.5 hours
- to abstain from alcohol and other substances immediately prior to 1.5 hour testing period
- to undertake a urine test immediately prior to 1.5 hour testing period
- to take their daily methadone dose (last dose of 14 day script) at the centre at beginning of 1.5 hour testing period
- give some personal information (medical, employment, substance/alcohol use)
- to complete some paper and pencil tasks on decisionmaking

What the client will receive

- Vouchers
- Clients will be offered the option of receiving information regarding their performance

Appendix III: Methadone group information sheet

Participant Information Sheet

Research Study: Substance use and decision-making.

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

What is the purpose of the research project?

To understand what effect using drugs has on decision-making. Recently, it was found that long-term use of drugs like heroin may be linked to a person having difficulties making decisions in certain situations. This study aims to look at whether people who have used drugs like heroin differ in the kinds of decisions they make from those who have not used drugs like heroin. It is also important to see if methadone affects the decisions they make.

Why have I been chosen?

We have asked you to take part in the study as we would like people to take part who have used drugs like heroin and are now on methadone maintenance scripts.

Do I have to take part?

You do not have to take part in this study if you do not wish to. If you decide to take part, you can withdraw at any time without having to give a reason. Your decision to take part will not affect your healthcare or management in any way.

What will happen if I take part?

You will be asked to complete some paper and pencil tasks and a questionnaire. I will arrange a morning to meet you at the XX Centre. When you arrive you will be asked to do some tasks involving making decisions for 1.5 hours. After completion I will give you a voucher to cover expenses. **All information collected about you during the study is strictly confidential** and will be coded by number. Your name will not appear on any forms.

What will happen to the results of the study?

The results will be written-up as part of a thesis, which it is hoped will be published in a scientific journal. A summary of the findings will be available to all who took part.

Who is organising and funding the study?

The study is organised & funded by Camden & Islington NHS Trust & University College London.

Contact for further information

If you would like further information or have any questions, then please call me at the XX Centre (XX) and I will call you back.

Thank you for taking time to read this

date:_____

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

Appendix IV: Methadone group consent form

participant identification code:

CONSENT FORM

Confidential

Research Study: Substance use and decision-making.

Name of researcher: Sharin Garden

1. I confirm that I have read and that I understand the information sheet dated_____for the above study **YES / NO**

2. I have had an opportunity to ask questions and discuss this study **YES / NO**

3. I understand that I am free to withdraw from this study:-
at any time
without reason
without affecting my health care and management at the X Centre
YES / NO

4. I agree to take part in the above study. **YES / NO**

Name of participant	**Date**	**Signature of participant**
Researcher	**Date**	**Signature of researcher**

Appendix V: Control group information sheet

Participant Information Sheet

Research Study: Substance use and decision-making.

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

What is the purpose of the research project?

To understand what effect using drugs has on decision-making. Recently, it was found that long-term use of drugs like heroin may be linked to a person having difficulties making decisions in certain situations. This study aims to look at whether people who have used drugs like heroin differ in the kinds of decisions they make from those who have not used drugs like heroin. It is also important to see if methadone affects the decisions they make.

Why have I been chosen?

We have asked you to take part in the study as we would like to compare the results we have gained from people with drug problems to members of the general public.

Do I have to take part?

You do not have to take part in this study if you do not wish to. If you decide to take part, you can withdraw at any time without having to give a reason. Your decision to take part will not affect your management at the employment agency in any way.

What will happen if I take part?

You will be asked to complete some paper and pencil tasks and a questionnaire. I will arrange a date to meet you at University College London (UCL) on Torrington Place (off Tottenham Court Road). When you arrive at UCL you will be asked to do some tasks involving making decisions for 1.5 hours. After completion I will give you cash as reimbursement of expenses. **All information collected about you during the study is strictly confidential** and will be coded by number. Your name will not appear on any forms.

What will happen to the results of the study?

The results will be written-up as part of a thesis, which it is hoped will be published in a scientific journal. A summary of the findings will be available to all who took part.

Who is organising and funding the study?

The study is organised & funded by Camden & Islington NHS Trust & University College London.

Contact for further information

If you would like further information or have any questions, then please leave a message for me (including your telephone number) on XX and I will call you back.

Thank you for taking time to read this

date:_____

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

Appendix VI: Control group consent form

participant identification code:

CONSENT FORM

Confidential

Research Study: Substance use and decision-making.

Name of researcher: Sharin Garden

1. I confirm that I have read and that I understand the information sheet dated_____for the above study **YES / NO**

2. I have had an opportunity to ask questions and discuss this study **YES / NO**

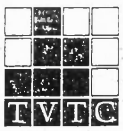
3. I understand that I am free to withdraw from this study:-
   - at any time
   - without reason
   - without affecting the management of my case at the Employment Agency

   YES / NO

4. I agree to take part in the above study. **YES / NO**

_____	_____	_____
Name of participant	**Date**	**Signature of participant**
_____	_____	_____
Researcher	**Date**	**Signature of researcher**

Appendix VII: DEX independent-rated version



BADS

Dex Questionnaire
Independent rater

Thames Valley Test Company

Subject's name _____

Date of rating _____

Rater's name _____

Relationship to subject _____

This questionnaire looks at some of the difficulties that people sometimes experience. We would like you to read the following statements, and rate them on a five-point scale according to your experience of _____ [the subject]:

1 Has problems understanding what other people mean unless they keep things simple and straightforward

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

2 Acts without thinking, doing the first thing that comes to mind

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

3 Sometimes talks about events or details that never actually happened, but s/he believes did happen

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

4 Has difficulty thinking ahead or planning for the future

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

5 Sometimes gets over-excited about things and can be a bit 'over the top' at these times

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

6 Gets events mixed up with each other, and gets confused about the correct order of events

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

7 Has difficulty realizing the extent of his/her problems and is unrealistic about the future

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

8 Seems lethargic, or unenthusiastic about things

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

9 Does or says embarrassing things when in the company of others

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

10 Really wants to do something one minute, but couldn't care less about it the next

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

11 Has difficulty showing emotion

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

12 Loses his/her temper at the slightest thing

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

13 Seems unconcerned about how s/he should behave in certain situations

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

14 Finds it hard to stop repeating saying or doing things once started

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

15 Tends to be very restless, and 'can't sit still' for any length of time

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

16 Finds it difficult to stop doing something even if s/he knows s/he shouldn't

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

17 Will say one thing, but will do something different

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

18 Finds it difficult to keep his/her mind on something, and is easily distracted

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

19 Has trouble making decisions, or deciding what s/he wants to do

☐0 ☐1 ☐2 ☐3 ☐4

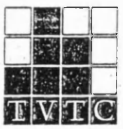
Never Occasionally Sometimes Fairly often Very often

20 Is unaware of, or unconcerned about, how others feel about his/her behaviour

☐0 ☐1 ☐2 ☐3 ☐4

Never Occasionally Sometimes Fairly often Very often

Appendix VIII: DEX self-rated version



Thames Valley Test Company

BADS

Dex Questionnaire
Self-rating

Subject's name _____

Date _____

This questionnaire looks at some of the difficulties that people sometimes experience. We would like you to read the following statements, and rate them on a five-point scale according to your own experience:

1 I have problems understanding what other people mean unless they keep things simple and straightforward

☐0 ☐1 ☐2 ☐3 ☐4
Never Occasionally Sometimes Fairly often Very often

2 I act without thinking, doing the first thing that comes to mind

☐0 ☐1 ☐2 ☐3 ☐4
Never Occasionally Sometimes Fairly often Very often

3 I sometimes talk about events or details that never actually happened, but I believe did happen

☐0 ☐1 ☐2 ☐3 ☐4
Never Occasionally Sometimes Fairly often Very often

4 I have difficulty thinking ahead or planning for the future

☐0 ☐1 ☐2 ☐3 ☐4
Never Occasionally Sometimes Fairly often Very often

5 I sometimes get over-excited about things and can be a bit 'over the top' at these times

☐0 ☐1 ☐2 ☐3 ☐4
Never Occasionally Sometimes Fairly often Very often

6 I get events mixed up with each other, and get confused about the correct order of events

☐0 ☐1 ☐2 ☐3 ☐4
Never Occasionally Sometimes Fairly often Very often

7 I have difficulty realizing the extent of my problems and am unrealistic about the future

☐0 ☐1 ☐2 ☐3 ☐4
Never Occasionally Sometimes Fairly often Very often

8 I am lethargic, or unenthusiastic about things

☐0 ☐1 ☐2 ☐3 ☐4
Never Occasionally Sometimes Fairly often Very often

9 I do or say embarrassing things when in the company of others

☐0 ☐1 ☐2 ☐3 ☐4
Never Occasionally Sometimes Fairly often Very often

10 I really want to do something one minute, but couldn't care less about it the next

☐0 ☐1 ☐2 ☐3 ☐4
Never Occasionally Sometimes Fairly often Very often

11 I have difficulty showing emotion

☐0 ☐1 ☐2 ☐3 ☐4
Never Occasionally Sometimes Fairly often Very often

12 I lose my temper at the slightest thing

☐0 ☐1 ☐2 ☐3 ☐4
Never Occasionally Sometimes Fairly often Very often

13 I am unconcerned about how I should behave in certain situations

☐0 ☐1 ☐2 ☐3 ☐4
Never Occasionally Sometimes Fairly often Very often

14 I find it hard to stop repeating saying or doing things once I've started

☐0 ☐1 ☐2 ☐3 ☐4
Never Occasionally Sometimes Fairly often Very often

15 I tend to be very restless, and 'can't sit still' for any length of time

☐0 ☐1 ☐2 ☐3 ☐4
Never Occasionally Sometimes Fairly often Very often

16 I find it difficult to stop myself from doing something even if I know I shouldn't

☐0 ☐1 ☐2 ☐3 ☐4
Never Occasionally Sometimes Fairly often Very often

17 I will say one thing, but will do something different

☐0 ☐1 ☐2 ☐3 ☐4
Never Occasionally Sometimes Fairly often Very often

18 I find it difficult to keep my mind on something, and am easily distracted

☐0 ☐1 ☐2 ☐3 ☐4
Never Occasionally Sometimes Fairly often Very often

19 I have trouble making decisions, or deciding what I want to do

☐0 ☐1 ☐2 ☐3 ☐4
Never Occasionally Sometimes Fairly often Very often

20 I am unaware of, or unconcerned about, how others feel about my behaviour

☐0 ☐1 ☐2 ☐3 ☐4
Never Occasionally Sometimes Fairly often Very often