The Neuropsychological Impact of Opiate Abuse

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Declaration of Own Work

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Abstract

**Background:** Heroin addiction is an extremely prevalent problem worldwide, and in Britain is commonly treated with methadone maintenance therapy. Previous literature has examined the neuropsychological impact of opioids such as heroin and methadone and points to a detrimental effect on neuropsychological functioning. However no attempt has been made to examine and compare the impact of these opioids on the same group of individuals. This study aims to measure the neuropsychological functioning of a group of opiate dependent males while actively using heroin and again once maintained on prescribed methadone. As previous research has been complicated by the effects of head injury and/or concurrent substance/alcohol dependence, the presence of these factors is used as exclusion criteria.

**Method:** Neuropsychological functioning was assessed in a cohort of 14 opiate dependent males while actively using heroin, using the Repeatable Battery for the Assessment of Neuropsychological Status. The same measure was repeated with the ten members of the original cohort who successfully progressed to methadone maintenance. In order to identify any neuropsychological impairment, participants' level of functioning while using heroin and while using methadone was compared to an estimate of their premorbid intellectual functioning. Quantitative statistical analyses were used to determine whether results were statistically significant.

**Results:** Participants performed significantly below the level predicted by their estimate of premorbid intellectual functioning both while using heroin and while using prescribed methadone. There was no significant difference in the participants' neuropsychological performance while using heroin and while maintained on a daily prescription of methadone.

**Discussion:** The results of the present study support previous research which has demonstrated a link between heroin and methadone use and neuropsychological impairment. Previous literature has not directly compared the neuropsychological
performance of heroin users with opioid addicts maintained on a daily methadone dose. The present study found no significant differences between the performances of the group while using heroin and once maintained on methadone. These findings have important implications for clinical practice in the field of addictions. There are a number of challenges associated with recruiting and retaining participants in the context of opioid addiction research, which are discussed in detail. The limitations of this study are explored, and future directions for research in this area are considered.

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Chapter 1: Introduction

1.1 Introducing the Research Area – A Brief History of Opioids

"Among the remedies which it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium" (Thomas Sydenham, 17th Century, in Carnwath and Smith, 2002; p138).

Opioids are derived from the dried fluid found inside the unripe seed of the opium poppy plant, or *Papaver Somniferum* (Martin et al., 2007) and have been used for centuries for their narcotic properties. Historically there are documented references to the effects of the poppy plant as long ago as 3400 BC, when the Sumerians described it as "Hul Gil" or the 'joy plant' (Booth, 1996). The Sumerians passed their art of 'poppy-culling' to the Assyrians, who in turn passed it on to the Babylonians before it finally reached the ancient Egyptians.

In the 1300s BC the Egyptian opium trade was hugely successful, and consequently opium travelled across the Mediterranean to Europe. In 460 BC Hippocrates, known as the “father of medicine” acknowledged that opium was useful in the treatment of “internal diseases, diseases of women and epidemics” (Booth, 1996). Not long after this, opium was introduced to Persia and India by Alexander the Great. From this point onwards, there are numerous historical references to the medicinal and mood-altering properties of this substance. However, in the 1300s AD, records suggest that the drug took on a more controversial role in global society. In Europe, it became a taboo following the Holy Inquisition which linked anything from the East with the devil. It finally reappeared as an acceptable medicinal resource in 1527 when Paracelsus developed techniques for the production of Laudanum, which was used for its analgesic properties.

In the 1600s opium became popular in India and Persia as a recreational drug, and Thomas Sydenham marketed ‘Sydenham’s Laudanum’ as a cure for many ailments. Over a century later, in 1803, the principal active ingredient of opium was isolated by Friedrich Sertturner. He named the resulting alkaloid (*Principium somniferum*) ‘Morphine’ after Morpheus, the Greek God of dreams (Brownstein, 1993). In the 1850s, the invention of the hypodermic needle and hollow syringe allowed for the
intravenous administration of morphine, a method which was found to be significantly faster and more intense in its effects than oral ingestion (Brownstein, 1993). Opioid abuse became increasing common in British society as morphine started to be commercially manufactured, and writers such as John Keats are known to have enjoyed the effects of the drug.

In 1874, heroin (diacetyl morphine or diamorphine) was first synthesised from morphine by the English scientist C.R. Wright, and in 1898 a cough suppressant featuring this new ingredient was launched by the Bayer Company (Booth, 1996). As heroin did not produce many of the side effects commonly associated with morphine, it soon became widely accepted as a safe and ‘non-addictive’ alternative to its predecessor. So much so, that at the start of the 20th century it was provided free of charge to recovering morphine addicts as a “step-down cure” (Booth, 1996). However, by the time the First World War began, there was no longer any question about the addictive properties of heroin, and in 1924 the American government banned the non-medical use of this substance. In 1970, heroin was also banned as a medical resource (Self, 1999).

Despite these legal reforms, other members of the opioid family are still used as highly effective and well tolerated analgesics. Medically, opioids such as morphine, meperidine, oxycodone and codeine are used as surgical anaesthetics, post-operative analgesics and in the treatment of chronic pain. In addition, opioids such as methadone and buprenorphine are widely prescribed in the treatment of heroin addiction. Unfortunately however, these are all highly addictive substances even when used as medically directed, and are frequently misused and used illicitly (i.e. without a prescription).

At a global level, opioid abuse figures are thought to have stabilised at 0.4 per cent of the population, and of these, 0.3 per cent of the population specifically abuse heroin. (United Nations Office on Drugs and Crime, 2007). Figures for Europe are higher than any other continent, at an estimated 0.7 per cent of the population. In North America, opioid abuse is thought to affect 0.5 per cent of the population. Opioids are
currently the main problem drug of abuse across the world, and account for 60 per cent of treatment demand in Asia and Europe. In 2007/2008, the British Crime Survey (Home Office, 2008) estimated that 0.1 per cent of the population (aged 16-59) in England and Wales had used heroin in the past year. The same proportion of adults admitted to having used methadone in the past year. These statistics provide just a snap-shot of the extent to which opioid dependence has become a world-wide epidemic.

Despite its long and fascinating history, it is only in recent years that we have begun to understand clearly the true nature and properties of the opioid family, and the extent to which they will affect those who use them. These effects are varied and multiple, and are known to include altered mood, behaviour and cognition. In addition, opioid abuse is associated with social exclusion, financial strain and increased rates of offending. The British Crime Survey (Home Office, 2008) stated that between 1999 and 2000, 29 per cent of all arrestees included in their research study tested positive for opioids in their urine. This study found that among heroin users, the rates of acquisitive crimes (theft, shoplifting, fraud, handling stolen goods, drug supply and prostitution) was around ten times higher than in the non-drug using population.

The health and medical consequences of opioid abuse are numerous, not to mention the risk of anoxic brain injury or death from overdose. Amongst these consequences is the increased risk of contracting blood borne viruses such as HIV and Hepatitis (Department of Health, 2007). Chronic heroin injection can also result in collapsed or scarred veins, abscesses and other soft tissue infections, bacterial infections and liver or kidney diseases (National Institute on Drug Abuse, 2008). Furthermore, indirect consequences (e.g. those which result from the poor health of the heroin user or from the additives found in street heroin) can include lung problems and arthritis.

In addition to these numerous health and social concerns, much attention of late has been directed towards the neuropsychological and neurobiological mechanisms which may suffer as a consequence of opioid use. It is these areas of research which
are of specific relevance to the present study. The progress in these areas will therefore be discussed in detail, before introducing the research aims and hypotheses.

1.2: The Neurobiological Impact of Opioid Abuse

There are four broad categories of drug within the opioid family:

- Natural opiates – these are alkaloids which are derived directly from the opium poppy and include morphine and codeine. The term opiate is often used interchangeably with the term opioid; however opiates refer only to the natural alkaloids derived from the opioid plant, and their semi-synthetic derivatives.
- Semi-synthetic opiates – these are opiates which are created from natural opiates and include diamorphine (heroin) and oxycodone.
- Fully synthetic opioids – These include methadone and pethidine.
- Endogenous opioid peptides – These occur naturally in the body and include endorphins and endomorphins. The human body also produces small amounts of morphine and codeine.

Opioids exert activity on the endogenous opioid system by binding to opioid receptors in the central nervous system and in other tissues (Mintzer and Johnson, 2007). There are three main types of opioid receptor, known as mu, kappa and delta, as well as various subtypes of receptor. Recent studies using Positron Emission Tomography (PET) have provided detailed information on the precise localisation of each of these receptors in the brain (Martin et al., 2007). The mu receptor is most plentiful in the amygdala, the periaqueductal midbrain, the striatum, the thalamus, most areas of the cortex and to a lesser degree in the cerebellum. When stimulated, these receptors are thought to have analgesic and euphoric properties as well as resulting in miosis (constriction of the pupil of the eye). The kappa receptor is associated with miosis, dysphoria, sedation and spinal anaesthesia. These receptors are most commonly found in the cerebellum, the cerebral cortex, the amygdala, the basal ganglia and the hippocampus. Finally, delta receptors are associated with analgesia and are most plentiful in the cerebral cortex and the striatum, and to a lesser degree in the amygdala and the hippocampus.
The effect that a specific opioid will have on the body depends upon which receptor it binds itself to and its particular affinity to that receptor, as well as on whether it is an agonist or an antagonist. An agonist is a drug which binds to and alters the activity of a receptor and can act in a positive or a negative way upon it, increasing or decreasing its activity respectively. An antagonist binds to a receptor without altering its activity, but instead will block or reduce agonist mediated responses. One common medical use of opioid antagonists is in the treatment of overdose, to eliminate the agonistic effects of the overdosed opioid on its specific receptors.

In addition to their action upon the opioid receptors, much interest has also been paid to the potentially damaging effects of the opioid family on other areas of the central nervous system, both in humans and in animals.

**Animal Studies:** In 1987, Tapia-Arizmendi *et al.* used light microscopy to detect structural changes in rats who received chronic morphine doses, compared to a control group of opioid-free rats. They discovered extensive morphological alterations to the hippocampus of the morphine group, with moderate alterations to the sensory motor cortex and the caudate nucleus. There is also evidence to suggest that chronic morphine administration in rats can result in the development of certain proteins in the brainstem (Ronnback *et al.*, 1983), and reduced dopamine cell size in the ventral tegmental area (Sklair-Tavron *et al.*, 1996). In addition, administration of certain opioids including morphine can result in seizures which cause damage to areas such as the limbic system (Kofke *et al.*, 1996, 1999). Furthermore Izquierdo (1983, 1990) showed that in animals, opiates inhibit the release of acetylcholine, a neurotransmitter which in humans is found in the central and peripheral nervous system. Similarly, Taguchi *et al.* (1993) found that morphine administration resulted in reduced striatal acetylcholine release in rats. These results may have significant implications for the study of human opioid abuse as acetylcholine shortage is associated with Alzheimer’s disease in humans and it is known to have an impact on memory (Chan *et al.*, 2007) and attention (Blokland, 1995).
Human Studies: A large body of research has been dedicated to discovering the ways in which opioids act upon the human brain. These have generally used neuroimaging techniques, or have carried out post-mortem investigations to identify changes in the brains of opioid dependent participants. One difficulty with interpreting the results of these studies is that many have combined “opioid” abusers into a single group, making it impossible to draw specific conclusions about the effects of different types of opioid. A thorough discussion of the current research in this area is provided by Mintzer and Johnston (2007).

A number of studies have revealed neurobiological abnormalities in opioid dependent individuals. Krystal et al. (1995) found lower brain activity in the parietal and frontal lobes of opioid users, and Danos et al. (1998) found decreased cerebral blood flow in the parietal and temporal lobes of opioid users. Similarly, Pezawas et al. (2002) showed a reduction in the cerebral blood flow of opioid users in the prefrontal cortex as well as a reversal in the lateral asymmetry of blood flow in some cortical areas when compared to non-drug using controls. This study also showed a significant correlation between increased duration of opioid abuse and decreased cerebral blood flow. However this study found no significant differences between heroin, morphine and methadone users in terms of rate of cerebral blood flow. There is also evidence to suggest that acute morphine and buprenorphine intoxication results in decreased cerebral glucose metabolism (London et al., 1990; Walsh et al., 1994).

Some studies have also examined the possibility that opioid abuse causes atrophy (a loss of neurons and their connections) in certain regions of the brain, with mixed results. For example, Strang and Gurling (1989) performed CT scans on the brains of seven heroin users. Although they found evidence of atrophy in six of the seven, there was no consistent pattern of damage within the group. Pezawas et al. (1998) also found evidence of cortical volume loss in opioid dependent participants. Furthermore, Lyoo et al. (2006) found a decrease in grey matter (but not in white matter) in the temporal, prefrontal and insular cortices of participants maintained on methadone. However a number of studies have found no evidence of atrophy in
opioid users (e.g. Amass et al., 1992). Similarly, a review by Ghodse (1981) showed no clear evidence that opioid abuse causes consistent damage to the brain.

In addition to studies examining the specific nature of the effects of opioids on the brain, several studies have attempted to discover whether the potential neurobiological changes in the brains of opioid users reduce or reverse with abstinence from this substance. Rose et al. (1996) showed increases in cerebral blood flow in the first three weeks of opioid abstinence. Conversely, Gerra et al. (1998) found evidence of reduced cerebral blood flow after four months of abstinence from opioid abuse.

A number of post-mortem studies have examined the brains of deceased opioid users in order to identify any organic damage by means of comparison with the brains of non-drug using controls. The results of these studies are varied and paint a rather inconsistent picture. Garcia-Sevilla et al. (1997) compared the brains of individuals who had died of a heroin or methadone overdose to those of drug-free controls and discovered a reduction in neurofilament protein levels in the frontal cortex of the former group. Furthermore, several studies have pointed to the existence of lesions of different areas of the brain as a direct result of opioid abuse. For example, Rounsaville et al. (1981) found evidence for deterioration in the integration of various cortical areas, and Protass (1971) reported that prior opioid abuse can result in post anoxic encephalopathy.

A study in 2001 by Kish et al. found decreased serotonin and dopamine activity in the striatum of opioid dependent participants relative to controls. Despite the fact that these reductions were slight, they may have been sufficient to result in altered impulse control (associated with serotonin) and motivational regulation (associated with dopamine), two skills which are considered to be aspects of ‘executive functioning’ (Mintzer and Johnston, 2007). The executive functions are neuropsychological skills commonly associated with the frontal lobes of the brain, and include planning, problem solving, cognitive flexibility, decision making and impulse control. Lezak (2004; p35) defined executive functions as:
"those capacities that enable a person to engage successfully in independent, purposive, self-serving behaviour".

**Neurobiological Effects of Methadone versus Heroin:** Several studies have indicated that methadone use and heroin use may have differing effects on the brain. For example, Garcia-Sevilla *et al.* (1997) found a greater decrease in neurofilament proteins in the brains of individuals who had died of a heroin overdose compared to those who had died of a methadone overdose. Galynker *et al.* (2000) compared the regional cerebral metabolic rate of abstinent heroin addicts (at least 6 months post-detoxification) and methadone maintained opioid addicts with that of drug-free controls. This study showed that cerebral metabolic rate in the anterior cingulate cortex was elevated in the abstinent group compared to the controls, but elevated to a lesser degree in the methadone maintained group. The same trend was observed in other cortical areas, although not to a significant degree. Furthermore, Herning *et al.* (2003) showed that polydrug users receiving methadone maintenance therapy have a lower blood resistance than those not receiving methadone.

Finally, a study by Ersche, Fletcher *et al.* (2006) examined regional brain activation associated with decision making ability in methadone maintenance patients as compared to heroin users and drug-free controls. Decision making is a skill associated with the executive functions of the brain. This study used PET scans to examine activation levels during task completion in four brain areas, based on previous literature implicating these areas in the encoding and representation of affective properties of feedback. The areas of the brain which were focused upon were the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), amygdala and insulate. The results of this study showed no group differences in activation levels of the ACC, amygdala and insulate areas of the brain. However, all three groups showed different OFC activation levels, with the methadone group experiencing over-activation in the left OFC compared to controls, and the heroin group showing under-activation in the right OFC compared to controls. Despite these differences in regional activation levels, decision-making ability was not significantly impaired in either of the opioid groups relative to controls. The authors suggest that as the OFC is implicated in mediating decision making and behaviour, further research is
required to clarify the precise implications of the different profiles of activation in heroin and methadone users.

**Summary of Neurobiological Impact of Opioids**
Animal studies have provided evidence for a variety of neurobiological changes following opioid administration, some of which may have implications for memory and attention in humans. Furthermore, research into the neurobiological impact of opioid intoxication in humans points to damage in a number of brain regions, most commonly of which being areas of the frontal cortex. This is a region of the brain which is generally associated with executive functioning skills. In addition, the literature suggests that methadone may have a different and potentially less harmful effect on the brain than heroin. It is important however that the human research is treated with caution, as opioid abuse is commonly comorbid with factors such as head injury and drug overdose which may also have an impact on neurobiology. These factors will be discussed in detail in section 1.3.

**1.3: The Neuropsychological Impact of Opioid Abuse**
Given the range of neurobiological changes that have been linked to opioid use, it seems likely that these changes may be expressed as neuropsychological deficits. A large number of studies have been conducted which examine the effects of opioid use on a variety of neuropsychological skills and abilities. Many of these focus specifically on the effects of prescribed methadone; however several also include heroin dependent participants or the broader category of ‘opioid users’. The progress in each of these areas will be examined in turn.

**Methadone use and Neuropsychological Functioning**
Methadone is currently the most commonly used drug in opioid substitution programmes. It is an opioid agonist that acts upon the mu-opioid receptors.

“(Methadone) can be substituted for opioids such as diamorphine (heroin), preventing the onset of withdrawal symptoms; it is itself addictive and should only be prescribed for those who are physically dependent on opioids. It is administered in a single daily dose usually as methadone oral solution 1 mg/ml. The dose is adjusted according to the degree of dependence” (BNF 56, 2008; p276).
When administered at a therapeutic level to opiate addicts, methadone produces no obvious psychotropic side-effects such as euphoria or sedation. It is well absorbed when taken orally and reaches a peak plasma concentration in the blood 2-4 hours after ingestion. In naïve users it has a plasma elimination half life of 16-24 hours, however in opioid dependent users this half life increases to 24-48 hours. For this reason, a one a day dose of methadone is thought to induce a steady state, and is therefore favoured by most professionals or clinics prescribing this type of opioid (Curran et al., 2001).

The first published study to examine the effects of chronic methadone use in humans was conducted by Isbell et al. in 1948. This study examined ‘general intelligence’ in institutionalised methadone users and concluded that methadone may have a detrimental impact on intellectual functioning. However, in 1965, Gordon et al. stated that they had not discovered a medical or psychological test capable of differentiating methadone maintenance therapy patients from normal controls (Pugliese, 1973). Gordon et al. published their findings in 1967, which reported that they had found no irregularities in the performance of methadone maintenance patients on the Wechsler Adult Intelligence Scale (WAIS, a measure of intellectual functioning). They also found no difference between methadone users and controls on mood rating scales. Despite their conclusion, their research was to herald an interest in this area which continues to this day.

In the seventies, research continued to focus on the possible effects of methadone on neuropsychological functioning. However, many of these early studies failed to clarify the issue. For example, Gordon and Lispet (1976) followed up Gordon et al.’s (1967) initial cohort approximately 112 months after their first assessment. They repeated the WAIS assessment with thirty of these participants who were still receiving prescribed methadone and found that all participants’ intellectual functioning remained in the average range. In the same year, Lombardo et al. (1976) failed to demonstrate any difference in neuropsychological functioning as measured by the WAIS between patients maintained on 50mg and 80mg of methadone. Grevert et al. (1977) examined memory function in participants prior to and three months
after commencing methadone treatment and concluded that methadone had no impact on memory. Gordon (1970) and Gorden and Appel (1972) found no deterioration in the reaction time of methadone therapy patients when compared to drug-free ex-heroin users or opiate-naïve controls, even after 24 hours of methadone abstinence. Other early studies which showed minimal impairments in methadone maintenance patients (e.g. Appel, 1982; Appel and Gordon, 1976; Rothenberg et al., 1977) have been criticised for using a limited range of assessment measures (Mintzer and Stitzer, 2002; Zacny, 1995).

Several early studies made a distinction between “working” and “non-working” methadone maintenance patients to describe their current employment status. For example, Appel (1982) reported that non-working patients made more false positive errors than working patients on a continuous performance test of working memory, and Appel and Gordon (1976) reported that non-working patients performed at a lower level than working patients on the digit symbol subtest of the WAIS. The authors of these studies suggest that “activation and arousal levels of unemployed persons may be lower than those engaged in productive activities or employment”, a statement which might now be considered to be controversial and somewhat unsubstantiated.

A number of studies specifically aimed to examine the effects of narcotics such as heroin and methadone on driving abilities. In a review of the available literature at the time, Gordon (1976) stated that there was no evidence for a detrimental effect of methadone maintenance therapy on driving skills. Similarly, Cheshers’s (1989) review on traffic violations and accidents concluded that narcotics including methadone were not a source of concern in road traffic accidents. Clearly this is a view which is no longer held, as current safe driving legislation is being addressed and altered in accordance with the idea that narcotic use in general is likely to have an adverse effect on driving abilities.

An early study which did demonstrate impaired neuropsychological functioning in methadone maintenance patients was conducted by Gritz et al. (1975). This study
compared methadone users with a control group matched for education on a range of measures, and found that the former group were impaired in the areas of perception and verbal memory. Two further early studies which also produced evidence for specific neuropsychological impairment in methadone users were conducted by Penk et al. (1981a, 1981b). These examined the performance of a group of methadone maintained ex-heroin addicts and a group of polydrug users on a measure of visual memory, in comparison to a measure of their premorbid intellectual functioning. An individual’s premorbid level of intellectual functioning is an estimate of their expected level of performance before any damage or impairment occurred (Lezak et al., 2004). Both groups were found to have visual memory scores which fell two standard deviations below their premorbid intellectual functioning level.

Despite the findings of Gritz et al. (1975) and Penk et al. (1981a, 1981b), a review by Gordon and Appel (1995; p36) concluded that:

“There should be considerable confidence that maintenance on methadone at appropriate dosage levels, as part of treatment for heroin addiction, has little if any effect on ability to function in any capacity for which the maintained person is otherwise qualified”.

However, more recent studies have in fact pointed to a wide range of possible neuropsychological deficits in methadone users.

Darke et al. (2000) compared neuropsychological performance in methadone maintained individuals with opioid-free controls matched for age, gender and education. This study examined a number of areas of neuropsychological functioning, including information processing, attention, short and long term verbal and non-verbal memory and problem solving skills. The authors report that despite being matched to the control group in terms of their premorbid level of intellectual functioning, the methadone maintenance groups’ performance was significantly poorer than the control group in all domains tested. There was no significant effect of methadone dose on performance in any of the domains. However the authors point out that the methadone maintenance group reported a significantly higher incidence of alcohol dependence and non-fatal overdose, both of which were found to be
independent predictors of poorer performance in each neuropsychological domain. The methadone maintenance group also had a significantly higher prevalence of head injury than the control group, another common cause of neuropsychological impairment. This study demonstrates the potential difficulties in identifying neuropsychological impairment which can unequivocally be attributed to opioid abuse rather than to the range of conditions which are frequently comorbid with opioid dependency. In addition, the results of this study are limited by the fact that the methadone maintenance group reported a high incidence of other substance use, and illicit substance use was not verified using urine analysis. The authors therefore suggested that the neuropsychological impairments seen in opioid users are likely to be a consequence of factors associated with drug abuse, rather than the direct effects of the drugs themselves.

In the same year, a study by Specka et al. (2000) also compared methadone maintenance patients with matched drug-free controls on a number of measures of neuropsychological functions relevant specifically to driving ability. The methadone maintained group in this study demonstrated impairments in attention and tachistoscopic perception, were faster but less accurate on a response time task, and were more accurate than controls but slower on a visual tracking test. Although this study has obvious implications in terms of an association between methadone and neuropsychological skills relative to driving, it is also weakened by the fact that participants who tested positive for other substances in their urine were not excluded.

In 2001, Curran et al. examined the neuropsychological effects of methadone in individuals who were part of an inpatient detoxification program, a setting which eliminated the risk of participants using other illicit substances in addition to their methadone. However, nine of the twenty participants were taking prescribed benzodiazepines as part of their treatment. In this double blind study, participants were either given 50 per cent of their methadone in the morning and 50 per cent in the evening, or 100 per cent of their methadone in the morning. The authors found that participants who received 100 per cent of their methadone in one dose demonstrated impaired delayed recall of a prose passage, while participants who
received only 50 per cent of their methadone in one dose showed no impairments in recall. As immediate recall was unaffected in both groups, Curran et al. concluded that methadone did not affect attention or comprehension during the presentation of the prose passage. In addition the authors point out that although a number of participants were also taking prescribed benzodiazepines which are known to affect anterograde memory, these individuals were divided between the two experimental groups. As the 50 per cent dose group showed no memory impairments it is suggested that the impairments displayed by the 100 per cent dose group could not be attributed to the effects of benzodiazepines. Given these results, the authors argue that methadone prescribed in a single dose may have implications for memory relative to methadone which is consumed in more than one daily dose. These results therefore provide evidence for a dose-related effect of methadone on neuropsychological functioning.

A study published by Davis et al. (2002) examined memory, attention, verbal fluency and verbal and non-verbal skills in a sample of patients engaged in a methadone maintenance programme. This study included a control group of opioid-abstinent ex-heroin addicts as well as a group of opioid-naive controls. The authors aimed to test the notion that the neuropsychological deficits seen in methadone users should largely be attributed to the effects of factors associated with drug abuse (Darke et al., 2000), rather than to the direct effects of opioids themselves. If this is the case, the authors hypothesised that neuropsychological deficits should persist in opioid-free ex-heroin addicts. The methadone and opioid-free ex-heroin addict groups were matched for age and drug-use history. These groups were roughly comparable in terms of reported drug related loss of consciousness, and the latter group has higher rates of past alcohol abuse than the former group (69 per cent vs. 47 per cent). The authors found significant differences in performance in only one of the domains tested. Methadone maintenance patients’ scores on the test of verbal fluency were significantly lower than those of the opioid-free ex-heroin group. For the purposes of this study, the authors identified neuropsychological impairment in participants whose scores were two or more standard deviations below the published norms for a test on at least two of the measures included. Using this definition, they found that 60
per cent of the methadone group were impaired compared to 31 per cent of the opioid free ex-heroin addicts and only 7 per cent of the drug-free controls. This result suggests that some recovery of function had occurred in the opioid-free ex-heroin users relative to the methadone maintained ex-heroin users. If this is the case, the neuropsychological impairment seen in methadone users may be due in part to the direct effects of opioids, as well as to the other factors associated with long-term drug abuse.

In 2004, Rotheram-Fuller et al. set out to compare methadone maintenance patients with drug-free controls matched for premorbid intellectual functioning on measures of decision making and cognitive flexibility. In addition, the authors divided both groups into smokers and non-smokers in order to discover whether smoking had any impact on performance of these tasks. Interestingly this study showed that the methadone maintenance patients who smoked displayed impairments in decision making relative to controls and the non-smoking methadone maintenance group. There were no significant differences between groups on the task of cognitive flexibility. These results suggest that in addition to the numerous other risk factors for neuropsychological impairment associated with substance use, smoking may be related to impairments in decision-making, and possibly to impairments in other neuropsychological domains.

Research conducted by Mintzer and Stitzer (2002), provides further evidence for the presence of impaired neuropsychological functioning as a result of methadone maintenance therapy. Their initial study (2002) compared the performance of a group of methadone maintenance participants with matched drug-free controls across a range of neuropsychological domains. Urine testing prior to assessment provided objective evidence of recent abstinence from other substances. The authors found that the methadone maintenance group showed significant impairments relative to controls in the areas of psychomotor speed, working memory, decision making and meta-memory as well as a possible impairment in inhibition control. No impairments were found in time estimation, conceptual flexibility or long-term memory.
In 2005, Mintzer et al. developed their earlier study by comparing the results of a new group of opioid free ex-heroin users on the same battery of neuropsychological tests retrospectively with their initial two groups. The new group was matched to the earlier two groups demographically, and matched to the methadone maintenance group in terms of history of drug use. The authors found that in general the new group’s scores fell between that of the methadone maintenance group and the controls on most tests, although they only performed significantly better than the methadone group on a test of cognitive flexibility, and significantly below the control group on the task of psychomotor speed. The results of this study lend further support to the notion that the impairments seen in methadone maintenance patients may be related to the direct effects of opioids rather than factors other than those associated with drug abuse (e.g. history of head injury overdose etc), as it suggests that some recovery of function may occur with detoxification from all opioids.

Verdejo et al. (2005) also compared the performance of methadone maintenance patients to a control group of abstinent ex-heroin addicts on a number of measures of neuropsychological functioning. Methadone maintenance participants were matched to the control group in terms of their age, education, employment, premorbid level of intellectual functioning and history of drug use. Both groups were assessed using measures of executive functioning, visuo-spatial attention and processing speed. The authors chose to focus particularly on the executive functioning skills of this population as they reported that this is an area of neuropsychological ability that had previously been somewhat neglected in the literature. They found that the methadone maintenance group showed impairments in analogical reasoning and working memory and slower performance on tests of processing speed, visuo-spatial attention and cognitive flexibility compared to the abstinent heroin users. As both groups were matched for history of drug use, it is possible (although unfortunately not explicitly stated) that both groups are comparable in terms of their presence of such comorbidities as history of head injury, overdose and other illicit drug use. If this is the case, this research further contradicts the notion that any neuropsychological impairments in methadone maintenance patients are likely to be a result of comorbid
conditions rather than attributable to the direct effects of opioids (in this case, methadone).

In a similar study, Prosser et al. (2006) compared methadone-maintained ex-heroine addicts with a group of ex-heroine addicts who had detoxified from methadone. Both groups were matched for drug using history. A group of healthy controls with no history of substance misuse was also included in this study. The authors hypothesised that abstinent heroin addicts should perform better than methadone maintenance patients on tests of various neuropsychological skills. However, the results of this study showed that both methadone maintenance and opiate abstinent ex-heroine addicts performed significantly worse than controls but at a similar level to one another on tests of verbal functioning, visual perception and memory, and attention/response inhibition. The only significant difference between methadone maintenance and abstinent ex-heroine addicts was on a test of visuo-spatial memory, with abstinent ex-heroine addicts performing more poorly. No effect of length or level of prior heroin use on neuropsychological functioning was found. Although this study is useful as it compares the effects of current methadone use with the possible residual effects of long-term opiate use, caution should be used in comparing the results of the two heroin addict groups with the controls. This is because both the former groups had fewer years of formal education than controls, and their scores on a test of verbal functioning were lower than the controls. As the authors explain, this measure is often used as an estimate of an individual’s premorbid level of intellectual functioning, suggesting that the two heroin groups had lower levels of premorbid intellectual functioning than the control group. If this is the case, then it would be expected that their performance on other measures of neuropsychological functioning would also be lower, consistent with their estimated premorbid level of functioning. It therefore does not make sense to compare the two ex-heroine user groups with the control group in terms of test performance in order to identify impairments in the former two groups. As the authors do not provide actual scores, it is unclear whether the two heroin addict groups’ performances are lower than would be predicted by their estimated premorbid functioning or at a similar level. This highlights the importance of matching controls to experimental participants in terms of estimated
premorbid level of functioning if meaningful between-group comparisons are to be made.

In 2006, Gruber et al. took a slightly different approach to examining the neuropsychological impact of methadone. In this study, heroin dependent participants were tested at the beginning of their methadone maintenance programme, and then again after two months. The purpose of this design was to determine whether heroin dependent individuals show improvements in neuropsychological skills over time with methadone maintenance treatment. This study found that participants showed significant improvements after two months on tests of verbal memory and learning, visuospatial memory and psychomotor speed. No differences in performance were seen on two tests which are sensitive to executive functions, examining specifically the ability to rule shift and directed attention/inhibition of impulsive responses. In addition, no differences were seen in semantic verbal fluency, although a trend towards greater verbal fluency for letter categories was noted. However, despite including a measure of premorbid intellectual functioning in their study, it is not clear whether the participants’ scores on those measures which showed no improvements were impaired at baseline, or whether these scores were at a level consistent with the participants’ premorbid intellectual functioning. If scores were impaired at baseline, the lack of improvement would suggest continuing deficits in these areas with continued methadone use. A further difficulty with interpreting the results of this study is that the participants continued to use other illicit substances, including opioids, cocaine, benzodiazepines and marijuana during the two month period. However the authors note that no effect of illicit drug use on neuropsychological test performance was observed when the group was stratified according to their urine analysis results. Despite the possible limitations, this study contributes to the literature by demonstrating improvement in neuropsychological functioning over time with methadone maintenance therapy, a finding which supports the idea that the observed impairments in opioid users are not entirely due to permanent damage caused by factors such as brain injury.
In 2007, Rapeli et al. published a study which compared a group of methadone maintained opiate addicts and a group of buprenorphine/ naloxone treated opiate addicts during the early phase of treatment, with a group of drug-free healthy controls. Buprenorphine is a partial mu-receptor agonist and kappa receptor antagonist which in combination with naloxone, an opioid antagonist, has increasingly been used as an alternative to methadone in the treatment of opiate dependency (BNF 56, 2008). The addition of naloxone prevents patients who may attempt to attenuate or alter the effect of the buprenorphine by injecting it from doing so as when this substance is injected the naloxone will cause the individual to go into opioid withdrawal. However when ingested sub-lingually (i.e. placed under the tongue) as directed, very little naloxone enters the system and withdrawal is avoided.

Each of the three groups included in this study were assessed using tests of attention, verbal memory and working memory, with the aim of identifying any differences in the neuropsychological profiles of patients receiving methadone versus patients receiving buprenorphine/ naloxone. Participants were excluded if they had any other major risk factors for neuropsychological impairment, such as DSM-IV diagnoses of psychiatric disorder(s) (other than substance misuse disorder), serious head injury, neurological disease, psychosis, HIV, epilepsy or primary neuropsychological deficit. The results of this study showed that both the methadone group and the buprenorphine/ naloxone groups performed more poorly than the control group on verbal and working memory tasks, and the methadone group also performed more poorly than controls on tasks measuring attention. However it is worth noting that the control group had slightly (although not significantly) higher average levels of verbal functioning than the other two groups, and that controls had an average of approximately three years more formal education than the methadone group and two years more than the buprenorphine/ naloxone group. This study also showed that methadone maintenance patients had an overall poorer profile of neuropsychological functioning than the buprenorphine/ naloxone and control groups. Specifically, the methadone group performed more poorly on a reaction time task aimed at measuring attention, and on a task of verbal memory. In addition, when the methadone group was split according to their daily dose size, the high dose group had significantly
slower reaction times than the low dose group. Finally, methadone patients with concurrent benzodiazepine use performed significantly below buprenorphine/naloxone patients with concurrent benzodiazepine use on tasks of reaction time and delayed verbal memory.

The results of Rapeli et al.'s study results provide further evidence for the potentially damaging neuropsychological impact of methadone. In addition this study lends support to buprenorphine/naloxone therapy for opiate dependence as a treatment with potentially fewer negative implications for neuropsychological functioning than methadone maintenance therapy. The use of the buprenorphine/naloxone group as a comparison in this study is useful as the two groups are very similar in terms of demographics and substance abuse history. This means that any differences in performance can more reliably be attributed to the effects of the specific heroin substitute being prescribed rather than to other causes associated with long-term drug use.

It is clear from the range of studies that have examined the impact of methadone on neuropsychological functioning that there is strong evidence for impairment in methadone users in a number of neuropsychological domains. There is conflicting (albeit limited) evidence regarding the possible impact of the dose of methadone on level of impairment with some research pointing to no effect of dose on performance, and some research reporting a dose related impact on the specific domains of delayed verbal memory and reaction time. Furthermore, more recent research has suggested that some recovery of functioning takes places with time in methadone maintained ex-heroin users. Finally, those studies which have compared methadone users with abstinent ex-heroin addicts and drug-free controls have indicated that abstinent ex-heroin addicts perform at a superior level to methadone users but below the level of drug-free controls. This suggests that the neuropsychological deficits observed in opioid users may be subject to at least partial recovery with total withdrawal from opioids, but that some permanent damage may occur. However, interpretation of these results must be cautious, as there are a number of possible causes of neuropsychological dysfunction at work in this population. These include the effects
of the drug itself, as well as the effects of any other illicit or prescribed substances, alcohol abuse, the effects of previous head injury, overdose, psychiatric disorders or psychological distress. Unfortunately each is prolific in the opioid dependent population. It is therefore likely that factors other than the direct effects of methadone account for at least some of the wide range of deficits observed in the research literature.

**Heroin Use and Neuropsychological Functioning**

Heroin (diamorphine/ diacetylmorphine) is a semi-synthetic opiate which is derived from morphine. It is most often used medically as an analgesic or illicitly for recreation. Illicit heroin users will often start by ‘smoking’ this substance (burning the heroin and inhaling the fumes), but many will quickly progress to intravenous use. Injecting heroin allows it to pass quickly through the blood-brain barrier where it is broken down into monoacetylmorhine and morphine. These bind to mu-opioid receptors and result in intense analgesic, euphoric and anxiolytic effects. The respiratory depressant, sedative, analgesic, emetic and euphorigenic effects of heroin reduce with increased tolerance to heroin, which means that the heroin addict must use ever increasing doses of this substance to experience the same effects and avoid withdrawal symptoms. Chronic intravenous heroin users will therefore often ingest daily dosages which could kill an individual naïve to opioids and are at risk from numerous possible fates including blood borne viruses, collapsed veins, skins abscesses and accidental overdose.

Research into the effects of heroin on neuropsychological functioning is notably scarcer than the equivalent research which examines the impact of methadone. This may be because those individuals who are either currently using heroin or are completely abstinent following prior heroin dependence are less likely to be known to health services or to be currently receiving treatment, therefore rendering them a less accessible population. However several studies have made progress in this area.

In 1975, Fields and Fullerton conducted a study to examine the neuropsychological effects of heroin. Their interest in this area was prompted by the increasing number
of males returning from the Vietnam War having developed a dependency on this substance. The authors used a battery of neuropsychological tests to examine performance in a group of heroin-dependent veterans compared with a group of drug-free veterans and a group of brain-damaged, drug-free participants. All groups were matched for age, gender and education, and the heroin dependent and drug-free veteran groups were matched for IQ. This study failed to find any significant differences between the groups on the nine subtests included in their neuropsychological battery; therefore the authors conclude that there was no evidence for the deleterious effects of heroin on cognition.

Guerra et al. (1987) examined neuropsychological functioning in heroin addicts while they were still using heroin, and again following a rapid detoxification from heroin. Detoxification took place in an in-patient unit over a 7-10 day period using decreasing doses of methadone or clonidine. At each test stage, participants were assessed using measures of perception and attention, verbal fluency, immediate recall, short term memory and long term memory. After detoxification participants also completed a test which provided an estimate of premorbid intellectual functioning. A drug-free control group matched for demographics and education was also included in this study. Both groups had comparable estimates of intellectual functioning. The results of this study showed that at the first test stage, the heroin users’ scores were significantly poorer than those of the controls on all of the measures included in the battery. Controls scored within the normal range for their level of intellectual functioning on each test. When heroin addicts were divided into heavy and mild addicts according to their level of use in the week prior to testing, no significant differences in performance were found. At the second test stage, the heroin group showed improvements in all of the areas which were assessed, such that there were no significant differences between their performance and that of the control group. However the results of this study are confounded by the fact that a number of participants in the heroin group reported concurrent use of other illicit substances or heavy alcohol use. The additional effects of these substances during the first test stage could have served to impair participant’s performance more than may have been seen if they were using heroin alone. This shortcoming further highlights
the importance of excluding participants with poly-substance misuse when conducting this type of research. Despite this criticism however, this study suggests that once free from all substances, heroin addicts’ performance may return to the level of a matched control group. This finding supports the notion that deficits seen in heroin addicts who are still using heroin or prescribed methadone are a result of the transient effects of the opioid rather than permanent effects of other factors associated with substance misuse such as a history of head injury or overdose.

In 1989, Strang and Gurling assessed seven long-term heroin addicts using a neuropsychological battery which included measures of visuo-spatial skills, visuo-perceptual skills, processing speed, verbal recognition memory, visual recognition memory and executive functioning. In addition each participant completed a measure of premorbid intelligence. Of the seven participants included in this study, three had recently stopped using heroin, and four were current heroin users. In addition to the neuropsychological assessment, the authors also performed CT scans on each of the seven participants. The results of the CT scans showed abnormalities in brains of six of the seven participants. However it is of note that most of the participants were in their sixth decade of life and some organic changes may therefore be expected. There was no consistent pattern of brain atrophy across the group. In addition, there was no consistent pattern of neuropsychological deficits, with participants showing the most significant impairments in the areas of verbal memory and processing speed. Furthermore, there was no consistent relationship between the abnormalities shown on the CT scans and participants’ neuropsychological deficits. However the absence of consistent results provided by this study is perhaps not surprising given the lack of homogeneity within the group of participants. Important factors to consider are the fact that other current or past drug dependence was not documented, the variance in drug abuse history, the advancing age of the participants and the fact that the group contained a mixture of current and ex-heroin users. Each of these factors is likely to serve to confuse the results and reduce the likelihood of obtaining a clear and consistent pattern of neuropsychological deficiency.
Ornstein et al. (2000) conducted a study which aimed to clarify the notion that there exists a distinct profile of neuropsychological impairment which is common to heroin addicts. In this study, a group of participants whose primary drug of abuse was heroin was compared to a group who primarily used amphetamine. A third group of drug-free control participants was matched to the other two groups for age and premorbid intellectual functioning. The assessment consisted of a number of subtests chosen from a computerised test battery, as well as an orally administered test of verbal fluency. The computerised battery used an interactive touch-screen computer to assess a variety of domains of neuropsychological functioning. These tests included measures of visual and visuo-spatial recognition memory, spatial working memory, attentional rule-shifting, spatial planning, and visuo-spatial strategy. This study found that relative to controls the heroin group generated fewer words (but not significantly) on the verbal fluency task, and showed no improvement following practice trials on the test of visuo-spatial strategy. In addition, impairments were found in visual and visuo-spatial recognition memory, attentional rule-shifting and spatial planning. These results point to the existence of a diverse pattern of neuropsychological impairment in heroin dependent individuals who are still using heroin.

A review by Lundqvist (2005) discussed the research evidence for neuropsychological impairments as a result of different types of drug use. This paper concluded that “There is a consensus that all drugs cause a disharmony in the neuropsychological network, causing a decrease in activity in areas responsible for short-term memory, attention and executive functioning, with the possible exception of heroin”. However, the literature described in this section paints a different picture. Although some studies have failed to find any evidence for significant neuropsychological decline associated with heroin abuse, others have shown that individuals with current heroin use display impairments in a variety of neuropsychological domains. However the evidence does not support a link between amount of heroin used and level of impairment (Guerra et al., 1987; Prosser et al., 2006) or duration of heroin use and impairment (Prosser et al., 2006). There is no research which directly compares the neuropsychological status of current heroin
users with current methadone users, therefore it is not possible to comment on the similarities or differences between the profiles of neuropsychological damage exhibited by these two groups.

Other Studies of Opioids and Neuropsychological Functioning

In addition to the literature on the effects of specific types of opioid, some studies have examined neuropsychological functioning in the more general group of ‘opioid addicts’ by combining participants with current methadone, heroin and/or other opioid use. The results of these studies are more difficult to interpret as these groups often contain individuals who abuse various different opioids, and it is therefore not possible to attribute any observed deficits to the effects of any specific type of opioid. However as many individuals in this population will use a variety of different opioids in their life time, these studies may help to examine whether there is a neuropsychological profile characteristic of this population.

An early example of this type of research was conducted by Rounsaville et al. (1982) who assessed a group of 72 “opioid addicts” upon entering treatment, using a brief neuropsychological battery. This group consisted of individuals who were still using illicit heroin, those who had recently been commenced on a prescribed methadone dose, and those who had recently been detoxified from all opioids. Many of these individuals could be classified as poly-drug users, reporting regular use of other substances including amphetamines, cocaine, sedatives, cannabis and alcohol. The group varied widely in terms of the length and nature of their drug abuse. The authors found that although the opioid group’s intellectual functioning scores fell in the normal range, their performance in a number of areas of neuropsychological functioning fell in to the ‘mildly impaired range’. These included tasks of visuospatial function, cognitive flexibility and new associative learning. Sixty-five participants in the opioid group complied with urine screening at the time of assessment, the results of which showed current use of other illicit substances (benzodiazepines and cocaine) in only two of these participants. Sixty-nine percent of those whose urine was tested showed current opioid use. When the opioid group
were compared to a control group of drug-free participants matched for socio-demographic variables, the former did not perform significantly below the latter group on any of the measures included.

Six months after the initial assessment, 59 individuals from the original opioid group were tested again, and overall improvements were found on a task of verbal fluency, as well as on the task of new associative learning on which impairments were previously seen. A significant difference in performance between those testing positive and negative for opioids at this stage was found for only one task which measured grip strength. The authors noted that the improvements observed at six months could not be attributed to the effects of detoxification from opioids as more than half of the sample provided urine samples which tested positive for opioids. Instead it is suggested that these improvements are related to an overall change in clinical status of this group when compared to their initial presentation. Although this study failed to find any significant differences between opioid users and drug-free controls, it did show that following a period of relative stability in treatment improvements were seen in some areas of functioning. This suggests that on entering treatment opioid addicts were performing at a level below their actual optimal ability on several indices of neuropsychological functioning. It may therefore be more useful for research in this area to focus on comparing the current performance of opioid addicts to a measure of their likely potential or 'premorbid' level of intellectual functioning, rather than comparing their performance to that of drug-free control groups.

A more recent study by Ersche et al. (2006) compared a group of “opioid” addicts with a group of amphetamine addicts across a number of neuropsychological domains. The opioid addict group consisted largely of methadone maintenance patients and current illicit heroin users, as well as participants receiving prescribed buprenorphine, dihydrocodeine, diamorphine and morphine sulphate. Urine analysis showed recent use of other substances in around half of the opioid group. Control groups included drug-free controls, drug-free ex-opioid users and drug-free ex-amphetamine users. All participants were assessed using two measures of executive
functioning (planning and attentional set-shift tests) and two measures of visual memory. On the planning task, both the current and former drug users performed significantly worse than the drug-free controls. Amphetamine users’ performance was poorer than opioid users and there was no difference between current and former drug users. Performance on the attentional set-shift task was comparable for all groups. On both the tests of visual memory, current and former drug users performed at a level that was significantly poorer than controls.

The results of this study contradict those of a number of previous and subsequent studies as it fails to find any difference between current and former opioid users. These results therefore support the notion that the neuropsychological deficits observed in chronic opioid users are not a direct result of the opioid itself, but rather are a consequence of the factors associated with long-term drug abuse (Darke et al., 2000). This is in contrast with more recent evidence which has provided evidence for impairments in current opioid users above and beyond those observed in abstinent ex-opioid addicts (e.g. Davis et al., 2002; Mintzer and Stitzer, 2005; Verdejo et al., 2005). However there are a number of limitations to this study, the most obvious of these being the heterogeneous nature of the opioid group in terms of the type of opioid used, whether opioid use was illicit or prescribed opioid, and whether other illicit drug were used concurrently. In addition, the former amphetamine and opioid users were combined into one group for means of comparison, with some reporting a history of previous amphetamine use or previous opioid use and others reporting a history of both amphetamine and opioid use. Given these limitation, the results of this study should be treated with caution.

Neuropsychological Functioning in Abstinent Former Heroin Addicts

In order to complete a review of the neuropsychological impact of opioids, one final area of research must be considered. These are the studies which examine the neuropsychological abilities of abstinent ex-opiate users. A number of the studies of methadone use and neuropsychological functioning which have been discussed include a control group of abstinent ex-heroin users (Davis et al., 2002; Mintzer et al., 2005; Prosser et al., 2006; Verdejo et al., 2005), and these have generally
indicated that this group may be impaired in some areas relative to controls with no history of opiate use, but may be less impaired than current methadone users. Several further studies which focus solely on abstinent ex-heroine users contribute to the research in this area.

A study by Gerra et al. (1998) compared a group of ex-heroine addicts who had been abstinent for four months with a group of drug-free controls using subtests from the Wechsler Adult Intelligence Scale and found no significant differences in performance. An interesting additional finding from this research was that a subgroup of the abstinent ex-opiate users who had been diagnosed with antisocial personality disorder did perform significantly worse than the control group. This result suggests that comorbid personality disorder may be a risk factor for neuropsychological impairment in opioid users.

Wernstein and Schaffer (1993) suggested that over time, substance misuse could lead to damage in seven key areas of functioning which include: problems with spontaneity, mental or behavioural shifting problems, impaired attention, impulsivity, a lack of insight, impaired abstract reasoning and a lack of social awareness. Pau et al. (2002) conducted a study which aimed to examine whether impairments in these areas were evident in abstinent ex-heroine users. They arranged these seven areas to fit into three domains of executive functioning, namely attention, impulse control, and mental flexibility/abstract reasoning. The ex-heroine dependent group included in this study consisted of individuals who formerly met the criteria for opioid use disorder (DSM-IV) and who did not have a history of psychiatric or physical conditions which may affect neuropsychological functioning. Participants in this group had a mean of 4.68 years of heroin use and had been abstinent from heroin for a mean of 13.7 months. A control group of drug-free individuals with no history of physical or psychiatric disorder was also included. This group was on average four years younger than the heroin group with an average of approximately two more years of formal education. All participants were assessed using a battery of neuropsychological tests which were sensitive to deficits in the three domains of executive functioning of interest. The authors found that when compared to the
control group, the heroin group showed a significantly poorer performance on a test of impulsivity control, but performed at a similar level on tests of attention and mental flexibility/abstract reasoning. The authors raise the interesting point that any impairment in impulsivity control in heroin addicts may either be a consequence of long-term heroin use, or a predisposing factor to using heroin. It is important to note however that the control group were both younger and more educated than the heroin group, and that these differences rather than direct effects of heroin may account for the differences in performance on tests of impulse control. Finally, the authors suggest that the lack of significant differences in the other areas assessed may imply that the average of 4.68 years of heroin use within the heroin group may not be sufficient to cause serious impairments in executive functioning.

In 2006, Rapeli et al. examined the neuropsychological functioning of a group of heroin addicts while in the first two weeks of opioid withdrawal. All members of this group were resident at a drug detoxification unit. The study also included a control group consisting of drug-free participants matched for age, gender and verbal functioning, however the control group had more years of formal education than the opioid dependent group. Both groups were assessed using measures of fluid intelligence, working memory, verbal memory and executive functioning. The authors found that the opioid withdrawal group performed significantly below the controls on measures of all domains except for verbal memory. However they also found that in the opioid withdrawal group, performance on tests of fluid intelligence and working memory improved with time over the two week period, suggesting that impairments in these areas may be transient and subject to recovery. No improvement in executive functioning was observed. The authors describe the variety of neural dysregulations that occur during early abstinence from opioids and suggest that these may be responsible for some of the impairments seen during this period. These dysregulations includes sudden reduction in mu opiate receptor activity, elevated levels of gamma aminobutyric acid, and release of dynorphin in the limbic system and striatum. In addition, in the medial prefrontal cortex there is a marked increase in levels of dopamine, serotonin and noradrenalin. As withdrawal continues and these abnormalities resolve, the authors suggest that many of the
observed neuropsychological functions follow suit, resulting in improvements in these abilities.

A recent study by Verdejo-Garcia et al. (2007) continued to focus on the effects of substance misuse on executive functions. Specifically, this study set out to examine inhibition control and decision making in abstinent polysubstance users whose primary addiction was heroin and in those whose primary addiction was cocaine. A third group of healthy, drug-free controls was also included in the study. All participants in the heroin and cocaine groups had been abstinent for a minimum of 15 days and none of the participants in any of the three groups had a history of mood disorder, head injury or neurological disorder. The results of this study showed that the heroin polysubstance users did not display any impairment in motor response inhibition relative to controls (unlike cocaine poly-substance users). However both heroin and cocaine polysubstance users demonstrated impairments in decision making.

The results of this study therefore lend further support to the idea that long term heroin use may result in deficits in at least some areas of executive functioning. However, because the participants included in this study are polysubstance users, it is difficult to attribute the neuropsychological impairments which were highlighted to the effects of one substance alone. It is a reality that many heroin users will concurrently use a number of other substances either consistently or occasionally. This may be for a number of reasons, such as an inability to afford or obtain their drug of choice, an attempt to attenuate or alter the effect of one drug with the use of another, or because of co-existing dependencies. This prevalence of polysubstance misuse can make it difficult to identify a group of “pure” heroin users for the purposes of research. However it could be argued that including poly-substance users in this type of research will provide results which can be more easily generalised to the drug using population.

Although the research in this area is limited, it seems to point to a general improvement in at least some areas of neuropsychological functioning following
abstinence from heroin use. This suggests that some of the deficits observed in active opioid users are transient side-effects of the drug itself, and that the residual impairments may either be a permanent and direct result of chronic opioid abuse or factors associated with opioid abuse, or may continue to resolve with sustained abstinence.

1.4 Summarising the Literature
Table 1 summarises the evidence presented in this review for an association between opioid misuse and neuropsychological deterioration. The coding system used in table 1 indicates the sample size range in which each study fell. This coding system demonstrates that just over half (11) of the 19 papers included in this table have a sample size of 25 or under, with less than half (8) exceeding a sample size of 25. It is therefore clear that much of the research in this area has been based on relatively small samples of the opioid using population. Some of the challenges associated with recruitment and retention to research projects within the field of opioid addiction and neuropsychology are discussed in chapter five.

In particular, table 1 illustrates that there is compelling evidence for the presence of impaired memory, attention and executive functions in the opioid using population. However where some areas remain blank, this does not necessarily mean that no impairment in this area has been found, but may instead reflect the fact that no research in to this particular domain in methadone/heroin users has been completed. It is also important to note that in addition to the studies included in table 1, a number of the studies reviewed failed to find any association between opioid abuse and neuropsychological impairment. This introduces the competing possibilities that either those effects that were observed in the studies included in table 1 were due to factors other than opioid abuse, or that the absence of effects found in the other studies were due to methodological shortcomings which have been discussed in this chapter, such as an inappropriate test measures or using a comparison group who are not sufficiently matched for demographic information. The present study aims to build on and contribute to the existing literature in this area (see chapter two).
<table>
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<tr>
<th>Neuropsychological domain</th>
<th>Methadone abuse</th>
<th>Heroin abuse</th>
<th>Abstinent ex-heroin addicts</th>
<th>Opioid abuse</th>
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<td>Ornstein et al., 2000</td>
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<td>Ersche et al., 2006</td>
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<td>Strang and Gurling, 1989</td>
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<td>Working memory</td>
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<tr>
<td>Attention</td>
<td>Darke et al., 2000; Specka et al., 2002; Prosser et al., 2006; Rapeli et al., 2007</td>
<td>Guerra et al., 1987</td>
<td>Prosser et al., 2006</td>
<td></td>
</tr>
<tr>
<td>Executive Functions</td>
<td>Darke et al., 2000 (30) (Problem solving skills); Mintzer and Stitzer, 2002 (18) (Decision Making); Rotheram-Fuller et al., 2004 (18) (Decision making); Verdejo et al., 2005 (18) (Analogical reasoning); Prosser et al., 2006 (29) (response inhibition); Davis et al., 2002 (Verbal fluency)</td>
<td>Ornstein et al., 2000 (Visuo-spatial strategy); Ornstein et al., 2000 (Attentional rule-shift, spatial planning, verbal fluency); Guerra et al., 1987 (verbal fluency)</td>
<td>Pau et al., 2002 (Impulse control); Rapeli et al., 2006; Verdejo-Garcia et al., 2007 (Decision making); Prosser et al., 2006 (response inhibition)</td>
<td>Ersche et al., 2006(Planning)</td>
</tr>
<tr>
<td>Information processing speed</td>
<td>Darke et al., 2000</td>
<td>Strang and Gurling, 1989</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychomotor speed</td>
<td>Mintzer and Stitzer, 2002</td>
<td></td>
<td>Mintzer et al., 2005</td>
<td></td>
</tr>
<tr>
<td>Perception</td>
<td>Gritz et al., 1975; Prosser et al., 2006 (Visual perception); Specka et al., 2000 (Tachistoscopic perception)</td>
<td>Guerra et al., 1987</td>
<td>Prosser et al., 2006 (visual perception)</td>
<td></td>
</tr>
<tr>
<td>Verbal functioning</td>
<td>Prosser et al., 2006</td>
<td></td>
<td>Prosser et al., 2006</td>
<td></td>
</tr>
<tr>
<td>Fluid intelligence</td>
<td></td>
<td></td>
<td>Rapeli et al., 2006</td>
<td></td>
</tr>
</tbody>
</table>

(Key: Red = 0 - 10 subjects Blue = 11-25 subjects Purple = 26-50 subjects Green = >50 subjects Black = unknown)

Table 1: Summary of previous research regarding opioid use and neuropsychological functioning.
Chapter 2: The Present Study

2.1 Theoretical Rationale for the Present Study

It is clear from the range of studies which have been completed in this area that opioid misuse is associated with a range of neurobiological and neuropsychological changes. Although no clear profile of opioid-related neurobiological and neuropsychological damage has been identified, it is likely that there is a relationship between the two areas. Research into the neuropsychological impact of both heroin and methadone point to the existence of impairments in a variety of domains of functioning. Despite this compelling evidence for the detrimental effects of heroin and methadone on neuropsychological functioning, to date there has been no research which directly compares the effects of heroin and methadone in order to determine whether each substance results in a comparable level and profile of neuropsychological damage. There is however limited evidence that methadone results in a different and possibly less damaging profile of neurobiological change than heroin. It is possible that these differing effects on neurobiology are translated into less neuropsychological damage as a result of methadone compared to heroin.

In light of the previous research in the area of opioid use and neuropsychology, the present study set out to expand on the current knowledge base by comparing the level of neuropsychological functioning of opiate dependent males while using illicit heroin and again while using prescribed methadone. By using this type of within-participants, repeated-measures design, this study aimed to compare directly the effects of heroin and methadone on neuropsychological functioning, an endeavour which has not previously been undertaken in the research literature.

2.2 Hypotheses

Based on the relevant research literature, the present study aimed to consider the following primary hypotheses:

1. Current heroin use will result in impaired neuropsychological functioning.
2. Current methadone use will result in impaired neuropsychological functioning.
In addition, the following secondary hypothesis was considered:

3. Current methadone use will result in less impairment than current heroin use.

It has been suggested (Darke et al., 2000) that any changes in neuropsychological functioning in opioid users may be attributable to factors which are associated with heavy drug use, rather than to the direct effects of the drug(s). These factors include head injury, overdose, psychiatric conditions or psychological difficulties, alcohol dependence and current or past dependence on other substances. In order to clarify the current picture, the present study attempted to identify a group of opioid dependent individuals without current or past presence of significant head injury or concurrent alcohol or substance dependence, as is described in chapter three. In addition, each participant was screened to identify a history of overdose and a current presence of psychiatric/psychological comorbidities.

2.3 Setting for the Study

Fife NHS Addictions Service was set up in 2002 to offer help and support to adults aged 16 and over with alcohol or substance dependency. At present, the most common treatment for diamorphine (heroin) dependency offered by Fife NHS Addictions Service is the prescription of substitute opioids at a level which will prevent the patient from experiencing significant physical symptoms of opioid withdrawal. The most frequently prescribed heroin substitutes are methadone and buprenorphine.

Methadone is currently prescribed more frequently than buprenorphine both in Fife and at a national level. This is because the National Institute for Health and Clinical Excellence (NICE) guidelines (2007) state that if both substances are equally suitable choices for maintenance treatment, methadone should be selected. Therefore only individuals who received methadone maintenance treatment were included in the present study. In Fife, from January to July 2008 between 400 and 996 prescriptions per month for methadone were produced by the NHS Addictions service, compared
to between 1 and 57 prescriptions per month for suboxone (buprenorphine/naloxone) and 8 and 11 prescriptions per month for buprenorphine.

**Accessing Fife NHS Addictions Service**

At present, this service operates a number of drop-in clinics across Fife, which are run and staffed by five different voluntary agencies working in the addictions field. This structure is the result of a recent redesign of the service. Prior to this redesign drop in clinics operated principally out of one fixed location and were staffed by NHS Addictions workers.

Individuals with substance or alcohol dependency problems can access the drop-in clinics without making an appointment or being referred to the service, and are seen by a voluntary service worker for an initial ‘triage’ appointment on the same day. After this initial appointment, opioid dependent individuals who choose to participate with a methadone program are offered a further appointment which is generally within the following four weeks. The purpose of this subsequent appointment is to complete a more comprehensive assessment and to arrange a date for commencement onto the appropriate dose of methadone. This dose is calculated by administering a low initial dose of methadone to a patient who clearly demonstrates objective symptoms of opioid withdrawal, and “topping up” this dose after every subsequent hour until withdrawal symptoms are no longer evident. The amount of methadone required to eliminate withdrawal symptoms is then considered to be an appropriate starting dose for the patient. Generally the patient will be seen again the following day to determine whether their initial dose of methadone adequately relieved withdrawal symptoms for a 24-hour period, or conversely whether it resulted in sedation therefore suggesting that it was too high (NICE, 2007).

Once their correct dose of methadone is determined, patients are required to collect and consume their prescription at their local pharmacy each day. Patients are asked to provide regular urine samples to confirm that they are not using illicit opioids in addition to their prescription. If a patient provides sufficient “clean” urine samples they will be permitted to take their methadone away from the pharmacy each day,
and progress towards picking up enough methadone to last them for a week or several weeks at a time. Ultimately, patients should aim to work with the Addictions Service towards gradually reducing their methadone dose with the goal of withdrawing from methadone use completely.

This study was run in conjunction with a larger PhD project which was completed by Dr Alex Baldacchino, Consultant Psychiatrist with Fife NHS Addictions Service. This meant that all participants included in the present study also participated in Dr Baldacchino’s project, which examined neuropsychological functioning in opioid dependent males using the Cambridge Neuropsychological Test Automated Battery (CANTAB, 1994). The CANTAB is a computerised, touch-screen battery of neuropsychological tests which examines a wide variety of neuropsychological functions including memory, reaction time and executive skills. The screening questionnaire measure (Mini International Neuropsychiatric Interview, 1997) and the estimate of premorbid intellectual functioning (National Adult Reading Test, 1991) which were included in the present study (see section 3.3) were also used as part of Dr Baldacchino’s study.
Chapter 3: Methodology

3.1 Design
This was a quantitative study, using neuropsychological assessment measures as well as a structured questionnaire. It used a within-participant, repeated measures design and data were analysed using inferential statistics.

3.2 Ethical Permission
Ethical permission for the overall project was granted to Dr Baldacchino from the local Research Ethics Committee (see Appendix 1). A further ethics amendment form was submitted prior to commencing the combined studies which included the use of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), which was the only measure to be used by the present study alone (Appendix 1). Dr Baldacchino gave full permission for all relevant data from the overall project to be used as part of the present study, in line with Fife NHS Research and Development Department advice. In addition, Fife NHS Research and Development Department gave permission for the research to be conducted within the health board area. The research proposal was also submitted to Edinburgh University who gave their permission and support for the project.

The principal ethical issues which were considered prior to beginning this study were those which concerned ensuring informed consent from participants and adequate information provision to participants. In order to address these issues, participants were provided with a comprehensive information sheet prior to beginning the study which included the chief researcher’s contact detail and a description of the study aims and the nature of their involvement (Appendix 2). In addition each participant signed a consent form, a copy of which they were provided with (Appendix 3). Participants were told that they were free to withdraw from the study at any time and that this would not affect their care provision from NHS Fife Addictions Service. During the course of the study participants were provided with brief feedback about their performance and were advised that they could contact the chief researcher following completion of the study for a full appraisal of their overall performance.
A further ethical issue was that of participant confidentiality. Participants were informed that in order to ensure complete confidentiality and anonymity their information would be identified by letter and number, and that no identifiable information would be included at any stage of the study.

Following Viva examination I am aware that both the external and internal had concerns that were related to the fact that I did not solely offer the initial ethical approval application forms. As a result there were ethical procedures and approval in place prior to my involvement in this research that both examiners raised concerns about, in particular relating to the use of incentives for participation. However despite these misgivings it is my understanding that the examiners have not raised any questions about my ethical practice, standards and behaviour in the execution of this current project.

3.3 Measures
Rationale for Selection of Measures: The measures which were selected were considered appropriate for the present study for a number of reasons:

- It was necessary to select a neuropsychological test that is repeatable, as assessment stages one and two (see procedure) were expected to take place between one and four weeks apart.
- The RBANS covers a broad span of neuropsychological functions, which allows for a more comprehensive assessment of neuropsychological functioning in the target population.
- As the NART can be used to provide an estimated WAIS-R FSIQ score and the RBANS scores have been shown to be adequately correlated with the WAIS-R, it was considered appropriate to compare each participant’s performance on the NART with their performance on the RBANS.
- The evidence from the previous literature suggests that opioid abuse can result in deficits in attention, memory and executive functions. The RBANS assesses both immediate and delayed memory, as well as aspects of attention,
language (verbal fluency) and visuospatial planning known to rely on executive functioning skills.

- The RBANS can be administered in 20-30 minutes, which was advantageous in terms of reducing the demands on participant’s time and therefore potentially increasing participation rates.
- As the RBANS has a relatively low price (approx £250), it was considered a cost-effective tool for research compared to alternative test batteries (e.g. WAIS-III). This means it can more realistically be repeated by future researchers in this area.

The following screening and assessment measures were used as part of this study:

**The Mini International Neuropsychiatric Interview (M.I.N.I., Sheehan et al., 1997)**
This is a brief, structured questionnaire aimed at identifying DSM-IV and ICD-10 psychiatric disorders. It includes questionnaire items that screen for current/past presence of the following (see Appendix 4):
- Major Depressive episode
- Dysthymia
- Suicidality
- Manic/Hypomanic episode
- Panic disorder
- Agoraphobia
- Social Phobia
- Obsessive-Compulsive Disorder
- Post-Traumatic Stress Disorder
- Alcohol Dependence/abuse
- Substance Dependence/abuse
- Psychotic Disorders
- Anorexia Nervosa
- Bulimia Nervosa
If the participant positively endorsed screening items for any of these disorders, a more detailed set of questions were delivered in order to determine if a current/past diagnosis of the condition being examined was appropriate. Current opioid dependence was ascertained in all participants using the substance-use disorders section of this questionnaire.


The National Adult Reading Test is commonly used as an estimate of an individual’s premorbid level of intellectual functioning. It examines the ability to read aloud 50 English words (see appendix 5) with varying frequency and increasing difficulty. Each of the words is phonetically irregular, so cannot be pronounced correctly by applying the usual grapheme-phoneme and stress rules common to the English language. Instead, successful pronunciation depends on the participant having prior knowledge of the word. Nelson and Willison (1991) therefore proposed that scores on this test can be used to accurately predict premorbid intellectual ability as they provide an estimate of a participant’s vocabulary size. Vocabulary size has long been considered to be one of the most accurate indicators of premorbid ability (Yates, 1954). This is due to the fact that well established verbal skills are generally retained in cognitively deteriorating individuals after other neuropsychological functions such as recent memory, reasoning skills and mental arithmetic skills have declined or failed (Lezak et al., 2004).

Raw NART scores can be used to calculate an individual’s predicted Wechsler Adult Intelligence Scale - Revised (WAIS- R) Full Scale IQ (FSIQ), Verbal IQ (VIQ) and Performance IQ (PIQ) scores. Generally the average IQ in the normal population is considered to be 100, with a standard deviation of 15 (Neisser et al., 1996). An individual’s current level of intellectual functioning obtained using psychometric testing can be compared to their predicted premorbid intellectual functioning scores to determine whether significant neuropsychological decline has taken place.
Test Reliability and Validity: The reliability of a test refers to “the degree of reproducibility of the measurement” (Barker et al., 2002). In other words, if a test is reliable it should produce the same results each time it is repeated with the same participant. A number of authors (Crawford et al., 1989a; O’Carroll, 1987; Schlosser and Ivison, 1989) have shown that the NART has high inter-rater reliability (0.96-0.98) and high test-retest reliability (0.98).

The classic definition of validity is the degree to which the test accurately “measures what it is supposed to measure” (Barker et al., 2002). A study by Crawford et al. (1989a) found that the NART is a valid test of general intelligence in adults. However there is some evidence that NART validity may be reduced by the presence of severe dementia or language disorders (Nelson and Willison, 1991).

Evidence for the accuracy of the NART comes from a study by Crawford et al., (2001) which compared NART scores for a group of 77 year-old individuals (N = 179) with IQ scores obtained 66 years earlier when the participants were 11 years old. This study correlated NART scores with the original IQ scores (r = .73) to show that the former fell in to the same range as the latter.

In addition to its accuracy in predicting premorbid intellectual functioning scores, the NART was also considered an appropriate measure as it is relatively brief to administer which reduces its demands on attention and concentration. Furthermore, if a participant is unwilling to make the necessary effort to guess the pronunciation of a word this should not affect the final score as the irregular nature of each word means any attempt to phonetically decode the word will not produce the correct response. Finally, the authors suggest that it is extremely unlikely that an individual’s NART score would be significantly influenced by the effects of drugs.

The Graded Naming Test (McKenna and Warrington, 1983)

As completion of the NART requires adequate reading abilities, the Graded Naming Test was identified as an alternative measure of premorbid functioning in the event that a participant was unable to read.
The Graded Naming Test was originally developed to identify naming difficulties in brain-injured individuals. It comprises 30 individual images, of increasing difficulty which participants are asked to name (See Appendix 6). Simpler examples include a kangaroo and a scarecrow, while the more difficult pictures include a yashmak, pagoda and centaur. Scores on this test can be used to estimate an individual’s likely NART performance.

The images selected for inclusion in this test were standardised using a sample of 100 participants (72 with neurological disorders and 28 healthy controls), and were chosen because they did not produce ambiguous responses and were not considered too easy or too difficult to discriminate between participants. Each of the participants in this sample were also assessed using the NART, and the correlation between their graded naming scores and NART scores was 0.73 (p<.0001). This suggests that the two measures are comparable although not equivalent, as the correlation between the two measures resolves 53.29% of the variance between them leaving 46.71% of the variance unresolved.

As the NART was identified as the principal measure of premorbid functioning for this study, the Graded Naming Test was considered an appropriate alternative for those participants who were unable to read as it is commonly used as a measure of premorbid intellectual functioning and provides a score which can be converted into a NART equivalent.

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS, Randolph, 1998):

The RBANS is a brief battery of tests which has two parallel forms (A and B) so that it can be repeated without the results being compromised by practice effects. The whole battery is expected to take 20-30 minutes to administer. Normative scores for this test were obtained from a “stratified, nationally representative sample of 540 healthy adults” (Randolph, 1998).
The RBANS is designed to measure neuropsychological functioning across five domains (Randolph, 1998):

1. Immediate Memory: Ability to recall information immediately after its presentation.
2. Visuospatial/constructional abilities: Ability to perceive spatial relationships and to construct a spatially accurate copy of a drawing.
3. Language: Ability to respond verbally when asked to name visually presented objects or generate words.
4. Attention: Ability to retain and manipulate visually and orally presented information in short-term memory.
5. Delayed Memory: Ability to recall verbal or visual information following a delay.

Scores from all five domains can be combined to form a ‘Total score’. Each form of the test is comprised of 12 individual subtests which contribute to each of the five domains (Table 2, Randolph, 1998). Some of the materials used in the RBANS are reproduced from or based on material from the Wechsler Memory Scale - Third Edition (WMS-III, 1999).
<table>
<thead>
<tr>
<th>Domain</th>
<th>Subtest</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate Memory</td>
<td>List learning</td>
<td>10 semantically unrelated words orally presented, participant asked to recall as many as possible. Process repeated across 4 learning trials.</td>
</tr>
<tr>
<td></td>
<td>Story Memory</td>
<td>Short story, orally presented. Participant asked to recall story from memory. Same process repeated a second time.</td>
</tr>
<tr>
<td>Visuospatial/Constructional</td>
<td>Figure copy</td>
<td>Participant is shown a complex geometric figure and asked to make an exact copy while figure remains on display.</td>
</tr>
<tr>
<td></td>
<td>Line orientation</td>
<td>Participant is shown a drawing of 13 equal lines, radiating from a single point to form a half circle. Lines are numbered 1-13. Below are two lines which match two of the lines from the display above, and participant is asked to identify which two lines they match. Ten different trials administered.</td>
</tr>
<tr>
<td>Language</td>
<td>Picture naming</td>
<td>A series of pictured objects presented, participant asked to name each. Semantic clue provided if object is obviously misperceived.</td>
</tr>
<tr>
<td></td>
<td>Semantic fluency</td>
<td>Participant is given one minute to generate as many words in a given category as possible.</td>
</tr>
<tr>
<td>Attention</td>
<td>Digit span</td>
<td>String of digits is orally presented, participant required to repeat in the same order. Length of digit string increases by one on each trial.</td>
</tr>
<tr>
<td></td>
<td>Coding</td>
<td>Participant presented with key which matches a unique geometric shape with each number from 1-9. Below the key are rows of boxes, each filled with one of the 9 geometric shapes and a blank space below each. Using the key, participant is asked to fill in the blank spaces below each shape with the correct number.</td>
</tr>
<tr>
<td>Delayed Memory</td>
<td>List recall</td>
<td>Participant is asked to recall the 10 words learnt in the list learning task after a delay (approx 15 minutes).</td>
</tr>
<tr>
<td></td>
<td>List recognition</td>
<td>Participant is read 20 words and asked to identify the 10 of these which appeared in the list learning task.</td>
</tr>
<tr>
<td></td>
<td>Story memory</td>
<td>Participant is asked to retell the story presented in the story recall task after a delay (approx 15 minutes).</td>
</tr>
<tr>
<td></td>
<td>Figure recall</td>
<td>Participant is asked to reproduce the figure copied in figure copy task after a delay (approx 15 minutes).</td>
</tr>
</tbody>
</table>

Table 2: Domains and subtests of the RBANS

Once the test is complete, raw scores for each domain can be transformed into index scores and percentile rankings, based on normative data from the participant's age range. An index score and percentile ranking for the total score can also be calculated (see appendix 7).

Test Reliability and Validity: The author reports that average reliability coefficients across all age groups for each domain and for the total score range from 0.80 to 0.94 (Randolph, 1998). In a Form A-Form A, test-retest study using 40 participants and with a test-retest interval of 33-43 weeks, Randolph (1998) found that stability coefficients ranged from 0.55 (Language) to 0.88 (Total score).
Randolph (1998) reports that the intercorrelation coefficients for each of the five domains of the RBANS range between 0.28 and 0.63, with an overall pattern which suggests that each domain is measuring a relatively distinct neuropsychological construct. The correlation between the Total Score obtained by the RBANS and the FSIQ score obtained by the WAIS-R is 0.78, confirming that they are measuring similar neuropsychological functions. Similarly high correlations are reported between specific domains of the RBANS and a variety of commonly used neuropsychological tests:

- The Immediate and Delayed memory domains of the RBANS and the Verbal Memory Index of the WMS-R (0.61 and 0.69 respectively).
- The Attention domain of the RBANS and the Attention/Concentration domain of the Wechsler Memory Scale - Revised (0.82)
- The Language domain of the RBANS and the Total Score of the Boston Naming Test (0.75).
- The Visuospatial/Constructional domain of the RBANS and the Judgement of Line Orientation Test (0.62) and the Rey Complex Figure test (0.79).

### 3.4 Procedure

There were three distinct stages of the present study (see Table 3), each of which will be described in detail.

<table>
<thead>
<tr>
<th>Stage of Study</th>
<th>Description</th>
<th>Measures Used</th>
<th>Total Duration (Approximate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recruitment stage</td>
<td>Prior to inclusion in study. Participants who meet with exclusion and inclusion criteria identified. Purpose of study and confidentiality explained and consent obtained. Questionnaire measures administered.</td>
<td>Mini International Neuropsychiatric Interview (MINI)</td>
<td>½ hour</td>
</tr>
<tr>
<td>Assessment Stage One</td>
<td>Participants still using illicit heroin. Assessed using a measure of premorbid intellectual functioning and a measure of current functioning.</td>
<td>NART/GNT RBANS</td>
<td>35 minutes</td>
</tr>
<tr>
<td>Assessment Stage Two</td>
<td>Approximately 1-4 weeks after commencement on to prescribed methadone. Assessed using a measure of current functioning.</td>
<td>RBANS</td>
<td>30 minutes</td>
</tr>
</tbody>
</table>

Table 3: The stages of the present study
The Recruitment Stage

Prior to commencing this study, information leaflets were distributed to Fife NHS Addictions Service staff advising them of the nature of the study and explaining who would be eligible to take part. This information included details of the main inclusion criteria for the study. In addition, poster versions of the leaflet were put up in the Addictions outpatient clinic to inform clients of the purpose of the study. The following inclusion criteria were detailed in this leaflet:

- Male: Only male participants were included in this study as there is evidence in the research literature for gender differences in certain aspects of neuropsychological functioning that may have confounded the results of this study. For example, men have been found to perform better women on tests of reaction time (Bleecker et al., 1987) spatial reasoning (Resnick, 1993) and decision making (Bolla et al., 2004; Reavis and Overman; 2001), whereas women performed better on tests of verbal fluency (Bolla et al., 1998), hand-eye coordination (Agnew et al., 1988) and verbal memory (Ragland et al., 2000).
- Age 18-35: This criterion was included to control for the possible effects of neuropsychological decline with age. Initially the age range for the study was limited to a maximum of 30 years; however this upper limit was increased to 35 in an attempt to increase participation rates.
- History of daily heroin use spanning at least one year immediately prior to recruitment: Current opioid dependence at the time of beginning the study was ascertained using the Mini International Neuropsychiatric Interview (MINI, Sheehan et al., 1997)

All staff members working in the Addictions Service or the voluntary sector were encouraged to contact the researchers as soon as they identified any potentially suitable participants. It was crucial to identify potential participants as soon as possible after their initial access appointment. This was to allow sufficient time to recruit the client, ascertain their suitability for the study, obtain their consent to
participate and complete assessment stage one (see below) prior to their commencement on to the methadone program.

All possible candidates were offered an appointment to meet with the researcher at the earliest mutually convenient time. At this appointment, the researcher began by explaining the purpose of the study. In addition, the researcher confirmed that the individual belonged to the requisite age range and obtained details of their history of heroin use. If the individual was willing to participate in the study they were asked to complete a consent form (Appendix 3) a copy of which was kept by the researcher. Details of each participant’s duration of heroin use and level of daily use were obtained at this stage.

In order to obtain as accurate results as possible, potential participants were screened at this stage to determine if there was any clear reason to suspect that they may have impairments in neuropsychological functioning which were not due to the direct effects of heroin. The following were used as exclusion criterion for the study:

- A current substance and/or alcohol dependency other than heroin: This was formally assessed during the questionnaire stage using the Mini International Neuropsychiatric Interview (MINI, Sheehan et al., 1997)
- Presence of current symptoms of psychotic illness: This was assessed during the questionnaire stage using the Mini International Neuropsychiatric Interview (MINI, Sheehan., 1997)
- A history of head injury: Participants were asked to provide details of any significant head injuries (those resulting in a loss of consciousness or hospitalisation). Participants who reported an injury to the head which did not result in a loss of consciousness and/or hospitalisation were not excluded.

In addition, details of the following were obtained at the questionnaire stage but were not used as exclusion criteria for the present study:
• A current or recent diagnosis of psychiatric illness other than current psychosis: This was formally assessed using the MINI.
• A history of drug overdose: Participants were asked to provide details of any accidental or intentional overdose of heroin or any other substance.

In an effort to improve recruitment rates to the study, participants were offered two incentives to take part. The first was a financial incentive of £5 per appointment, resulting in a total of £15, which participants received on completion of their final appointment. This sum was considered sufficient to cover travel expenses. As a second incentive it was also possible to offer participants a date for initial methadone commencement within 1-3 weeks of their recruitment, rather than the typical waiting time of 4-6 weeks.

Assessment Stages One and Two
Following the recruitment stage, all participants who were considered to be eligible for inclusion in this study were invited to attend two further assessment appointments, which would ideally take place in the subsequent 1-2 month period.

Assessment stage one took place while participants were still using and dependent on illicit heroin. At this stage, participants completed the National Adult Reading Test (NART). Two participants who were unable to read sufficiently to complete this test were assessed instead using the Graded Naming Test (GNT), which can be used to estimate a predicted NART equivalent score. Participants also completed the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), a battery of tests which assessed their current functioning in five neuropsychological domains.

After completing stage one, those participants who successfully complied with commencement on to prescribed methadone were asked to complete a follow-up stage of assessment.
Assessment stage two took place approximately 1-4 weeks after successful commencement on to a prescribed dose of methadone, at a time that participants were considered to have stabilised on a maintained level of daily methadone. Details of each participant’s current methadone dose were recorded. At this stage, participants were assessed using the alternate form of the RBANS.

Assessment appointments took place in hospital outpatient clinics or GP surgeries, and home visits were not offered. Every effort was made to offer appointments in locations which were as close as possible to the participant’s home in order to reduce travelling time and expense and therefore improve retention.

### 3.5 Participants

A total of 14 male participants aged 18-35 were included in the study. Of these, ten completed each stage of the study, and four completed assessment stage one but dropped out of treatment prior to completing assessment stage two. According to Cohen (1992), based on an alpha level (probability level that a test will be statistically significant) of 0.05 and a recommended statistical power (ability of a test to detect an effect of this alpha level) of 0.8, 28 participants would ideally be required to detect a large effect size. Given the strong evidence in the literature for an association between opioid abuse and neuropsychological impairment it was considered reasonable to expect a large effect size in the present study. However, it was unfortunately not possible to identify a sample of more than 14 participants. The reasons for and implications of this sample size will be discussed further in chapter five.

None of the participants reported concurrent substance dependence or concurrent alcohol dependence as assessed by the MINI (other than opioid use). None of the participants reported a history of head injury resulting in loss of consciousness and/or hospitalisation. Three participants reported a history of heroin overdose, and one of these required hospital treatment for past overdose. Of these three, one also reported current comorbid psychiatric diagnoses as assessed by the MINI (Major Depressive Episode – current/recurrent).
3.6 Data Analysis
The following data were analysed by the researcher using the Statistical Package for Social Science (SPSS, Version 14):

- Premorbid intellectual functioning scores
- RBANS Total scores at assessment stage one
- RBANS domain scores at assessment stage one
- RBANS Total scores at assessment stage two
- RBANS domain scores at assessment stage two

All data were examined by the researcher for any omissions or errors. The main analyses were paired samples t-tests.
Chapter 4: Results

4.1 Descriptive Data

Demographic Information (see Table 4): Fourteen participants took part in this study, of which ten completed both assessment stages. The four remaining participants completed assessment stage one only. Of these four, three participants dropped out of treatment prior to completing assessment stage two, and one participant died prior to completing assessment stage two. The mean age of the group was 26.8 (range: 22-32). The mean level of heroin use at assessment stage one was 0.59g (range: 0.3g-1.0g), and participants had been using heroin for a mean of 5.1 years (range: 1 year – 10 years). At assessment stage two the mean methadone dose was 53mg (range: 15mg-80mg). One of the participants had a comorbid diagnosis of Major Depressive Episode (current/recurrent) as assessed by the MINI and three participants reported at a history of one or more opioid overdoses.

All fourteen participants described their ethnicity as ‘Scottish’. Seven of the participants lived in their own (rented) accommodation, while five lived in a relative’s or partner’s accommodation and two resided in homeless accommodation. Five of the participants described themselves as in a relationship, while the remaining nine described their relationship status as ‘single’. Only one of the participants reported any offending behaviour or criminal charges within the past month (theft). All of the participants reported that they were not HIV positive.

Participants’ premorbid estimate of intellectual functioning scores ranged from 80 – 117 with a mean score of 99.36. Figure 1 is a line graph which shows each participant’s premorbid estimate of intellectual functioning score (as measured by the NART/GNT) and their Total RBANS performance at assessment stage one and assessment stage two (if completed). In the general population the average level of intellectual functioning, or ‘Intelligence Quotient’, is conventionally considered to be 100, with a standard deviation of 15 (Neisser et al., 1996). Figure 1 shows that the participant’s premorbid intellectual functioning is normally distributed around this range, fulfilling criteria for parametric statistics (Greene & D’Oliveira, 1982).
<table>
<thead>
<tr>
<th>ID</th>
<th>Age at testing</th>
<th>Premorbid score</th>
<th>Daily heroin use at stage 1 (grams)</th>
<th>Duration of heroin use (years)</th>
<th>Daily methadone dose at stage 2 (ml)</th>
<th>Comorbid MINI Diagnosis?</th>
<th>Overdoses</th>
<th>Ethnicity</th>
<th>Living arrangement</th>
<th>Relationship status</th>
<th>Offences in last month</th>
<th>HIV positive?</th>
</tr>
</thead>
<tbody>
<tr>
<td>A001</td>
<td>28</td>
<td>112</td>
<td>1g IV</td>
<td>8</td>
<td>70ml</td>
<td>No</td>
<td>0</td>
<td>Scottish</td>
<td>Own Home-Rented</td>
<td>Single</td>
<td>0</td>
<td>No</td>
</tr>
<tr>
<td>A002</td>
<td>26</td>
<td>86</td>
<td>0.6-0.8g IV</td>
<td>9</td>
<td>80ml</td>
<td>No</td>
<td>0</td>
<td>Scottish</td>
<td>Relative's Home</td>
<td>Single</td>
<td>0</td>
<td>No</td>
</tr>
<tr>
<td>A003</td>
<td>24</td>
<td>102</td>
<td>0.5g IV</td>
<td>6</td>
<td>N/A</td>
<td>No</td>
<td>0</td>
<td>Scottish</td>
<td>Relative’s Home</td>
<td>Single</td>
<td>0</td>
<td>No</td>
</tr>
<tr>
<td>A004</td>
<td>26</td>
<td>110</td>
<td>0.8g smoked</td>
<td>2-3</td>
<td>55ml</td>
<td>No</td>
<td>0</td>
<td>Scottish</td>
<td>Own Home-Rented</td>
<td>Single</td>
<td>1 (theft)</td>
<td>No</td>
</tr>
<tr>
<td>A005</td>
<td>25</td>
<td>112</td>
<td>0.4g IV</td>
<td>1</td>
<td>30ml</td>
<td>No</td>
<td>0</td>
<td>Scottish</td>
<td>Own Home-Rented</td>
<td>In a Relationship</td>
<td>0</td>
<td>No</td>
</tr>
<tr>
<td>A006</td>
<td>29</td>
<td>86</td>
<td>0.2-0.3g smoked</td>
<td>9</td>
<td>60ml</td>
<td>No</td>
<td>0</td>
<td>Scottish</td>
<td>Own Home-Rented</td>
<td>In a Relationship</td>
<td>0</td>
<td>No</td>
</tr>
<tr>
<td>A007</td>
<td>22</td>
<td>108</td>
<td>0.6g IV</td>
<td>&gt;1</td>
<td>N/A</td>
<td>No</td>
<td>0</td>
<td>Scottish</td>
<td>Relative’s Home</td>
<td>Single</td>
<td>0</td>
<td>No</td>
</tr>
<tr>
<td>A008</td>
<td>26</td>
<td>86</td>
<td>1g IV</td>
<td>10</td>
<td>60ml</td>
<td>No</td>
<td>1 (NH)</td>
<td>Scottish</td>
<td>Homeless</td>
<td>Single</td>
<td>0</td>
<td>No</td>
</tr>
<tr>
<td>A009</td>
<td>27</td>
<td>84</td>
<td>0.4g smoked</td>
<td>3</td>
<td>50ml</td>
<td>No</td>
<td>0</td>
<td>Scottish</td>
<td>Own Home-Rented</td>
<td>In a relationship</td>
<td>0</td>
<td>No</td>
</tr>
<tr>
<td>A010</td>
<td>28</td>
<td>110</td>
<td>0.2-0.3g IV</td>
<td>2.5</td>
<td>15ml</td>
<td>No</td>
<td>0</td>
<td>Scottish</td>
<td>Own Home-Rented</td>
<td>Single</td>
<td>0</td>
<td>No</td>
</tr>
<tr>
<td>A011</td>
<td>28</td>
<td>117</td>
<td>0.4g IV</td>
<td>1.5</td>
<td>60ml</td>
<td>No</td>
<td>0</td>
<td>Scottish</td>
<td>Relative’s Home</td>
<td>In a relationship</td>
<td>0</td>
<td>No</td>
</tr>
<tr>
<td>A012</td>
<td>25</td>
<td>80</td>
<td>1g IV</td>
<td>8</td>
<td>50ml</td>
<td>No</td>
<td>3 (TN)</td>
<td>Scottish</td>
<td>Relative or Partner’s Home</td>
<td>In a relationship</td>
<td>0</td>
<td>No</td>
</tr>
<tr>
<td>A013</td>
<td>29</td>
<td>100</td>
<td>0.4g IV</td>
<td>1</td>
<td>N/A</td>
<td>MDE – C/R</td>
<td>1 (NH)</td>
<td>Scottish</td>
<td>Own Home-Rented</td>
<td>Single</td>
<td>0</td>
<td>No</td>
</tr>
<tr>
<td>A014</td>
<td>32</td>
<td>98</td>
<td>0.4g IV</td>
<td>5</td>
<td>N/A</td>
<td>No</td>
<td>0</td>
<td>Scottish</td>
<td>Homeless</td>
<td>Single</td>
<td>0</td>
<td>No</td>
</tr>
</tbody>
</table>

Key: NH = Not hospitalised  TN = Treatment needed  MDE – C/R = Major Depressive Episode – Current/Recurrent

Table 4: Demographic information for each participant
4.2. Hypothesis 1: Current Heroin Use Will Result in Impaired Neuropsychological Functioning.

Table 5: Mean Premorbid score and RBANS performance at Assessment stage one.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean</th>
<th>Standard Deviation</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premorbid</td>
<td>14</td>
<td>99.36</td>
<td>12.67</td>
<td>80-117</td>
</tr>
<tr>
<td>RBANS Total</td>
<td>14</td>
<td>80.93</td>
<td>15.16</td>
<td>51-103</td>
</tr>
<tr>
<td>RBANS Attention</td>
<td>14</td>
<td>84.43</td>
<td>17.58</td>
<td>43-115</td>
</tr>
<tr>
<td>RBANS Imm Mem</td>
<td>14</td>
<td>81.64</td>
<td>15.51</td>
<td>53-103</td>
</tr>
<tr>
<td>RBANS Del Mem</td>
<td>14</td>
<td>81.36</td>
<td>20.25</td>
<td>48-101</td>
</tr>
<tr>
<td>RBANS Language</td>
<td>14</td>
<td>84.71</td>
<td>7.90</td>
<td>74-96</td>
</tr>
<tr>
<td>RBANS Visuosp/Con</td>
<td>14</td>
<td>94.07</td>
<td>17.18</td>
<td>66-121</td>
</tr>
</tbody>
</table>

Table 5 shows participants’ mean premorbid intellectual functioning score and mean stage one RBANS performance. In order to examine hypothesis 1, a paired samples t-test was used to compare participants’ premorbid intellectual functioning level (i.e. NART/GNT score) with their total RBANS score at assessment stage one. This t-test is based on the assumption that RBANS and premorbid scores are reasonably correlated, as described in chapter three. Figure 2 shows each participant’s premorbid score and their Total RBANS score at stage one.
Figure 2: Participants’ Premorbid scores and stage one Total RBANS scores

The results of this comparison showed that performance at assessment stage one was significantly poorer than the level predicted by the participants’ premorbid scores ($t(13) = 3.722, p<.05$).

Paired samples t-tests were used to compare the participants’ performance in each of the five domains at assessment stage one with their premorbid scores. The results of these comparisons showed a significant difference between premorbid scores and performance in the domains of Attention ($t(13) = 3.311, p<.05$), Immediate Memory ($t(13) = 3.709, p<.05$), Delayed Memory ($t(13) = 2.792, p<.05$), and Language ($t(13) = 3.539, p<.05$), and no significant difference between premorbid scores and Visuospatial/constructional skills ($t(13) = 0.903, p>.05$).
4.3. Hypothesis 2: Current Methadone Use Will Result in Impaired Neuropsychological Functioning.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean</th>
<th>Standard Deviation</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premorbid</td>
<td>10</td>
<td>98.30</td>
<td>14.87</td>
<td>80-117</td>
</tr>
<tr>
<td>RBANS Total</td>
<td>10</td>
<td>82.20</td>
<td>12.42</td>
<td>55-103</td>
</tr>
<tr>
<td>RBANS Attention</td>
<td>10</td>
<td>86.50</td>
<td>20.16</td>
<td>43-106</td>
</tr>
<tr>
<td>RBANS Imm Mem</td>
<td>10</td>
<td>81.90</td>
<td>11.64</td>
<td>61-100</td>
</tr>
<tr>
<td>RBANS Del Mem</td>
<td>10</td>
<td>82.00</td>
<td>20.27</td>
<td>56-109</td>
</tr>
<tr>
<td>RBANS Language</td>
<td>10</td>
<td>82.80</td>
<td>4.18</td>
<td>78-89</td>
</tr>
<tr>
<td>RBANS Visuos/Con</td>
<td>10</td>
<td>99.60</td>
<td>14.70</td>
<td>78-121</td>
</tr>
</tbody>
</table>

Table 6: Mean Premorbid score and RBANS performance at assessment stage two.

Table 6 shows the mean premorbid scores as well as the mean stage two RBANS performance for the ten participants who completed stage two. In order to examine this hypothesis, a paired samples t-test was used to compare these participants’ premorbid scores with their stage two Total RBANS score. Figure 3 shows each of the ten remaining participants’ premorbid scores and their Total RBANS scores at this stage.

Figure 3: Participant’s premorbid scores and stage two Total RBANS scores
The results of this comparison showed that performance at assessment stage two was significantly poorer than the level predicted by the participants’ premorbid intellectual functioning scores \((t(9) = 3.625, p<.05)\).

Paired samples t-tests were used to compare the participants’ performance in each of the five RBANS domains at assessment stage two with their premorbid scores. The results of this comparison showed a significant difference between premorbid scores and performance in the domains of Attention \((t(9) = 2.564, p<.05)\), Immediate Memory \((t(9) = 3.004, p<.05)\), and Language \((t(9) = 3.148, p<.05)\). As at stage one, there was no significant difference between premorbid scores and Visuospatial/constructional skills \((t(9) = .236, p>.05)\). In addition, there was no longer a significant difference between premorbid scores and Delayed Memory scores at assessment stage two \((t(9) = 2.245, p>.05)\).


<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean</th>
<th>Standard Deviation</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premorbid Intellectual Function Score</td>
<td>10</td>
<td>98.30</td>
<td>14.87</td>
<td>80-117</td>
</tr>
<tr>
<td>Stage 1 RBANS Total</td>
<td>10</td>
<td>80.30</td>
<td>15.65</td>
<td>51-103</td>
</tr>
<tr>
<td>Stage 2 RBANS Total</td>
<td>10</td>
<td>82.20</td>
<td>12.42</td>
<td>55-103</td>
</tr>
<tr>
<td>Stage 1 RBANS Attention</td>
<td>10</td>
<td>85.30</td>
<td>19.62</td>
<td>43-115</td>
</tr>
<tr>
<td>Stage 2 RBANS Attention</td>
<td>10</td>
<td>86.50</td>
<td>20.16</td>
<td>43-106</td>
</tr>
<tr>
<td>Stage 1 RBANS Imm Mem</td>
<td>10</td>
<td>80.50</td>
<td>16.43</td>
<td>53-103</td>
</tr>
<tr>
<td>Stage 2 RBANS Imm Mem</td>
<td>10</td>
<td>81.90</td>
<td>11.64</td>
<td>61-100</td>
</tr>
<tr>
<td>Stage 1 RBANS Del Mem</td>
<td>10</td>
<td>79.20</td>
<td>19.86</td>
<td>48-99</td>
</tr>
<tr>
<td>Stage 2 RBANS Del Mem</td>
<td>10</td>
<td>82.00</td>
<td>20.27</td>
<td>56-109</td>
</tr>
<tr>
<td>Stage 1 RBANS Language</td>
<td>10</td>
<td>86.00</td>
<td>7.18</td>
<td>74-96</td>
</tr>
<tr>
<td>Stage 2 RBANS Language</td>
<td>10</td>
<td>82.80</td>
<td>4.18</td>
<td>78-89</td>
</tr>
<tr>
<td>Stage 1 RBANS Visuosp/Con</td>
<td>10</td>
<td>92.40</td>
<td>19.05</td>
<td>66-121</td>
</tr>
<tr>
<td>Stage 2 RBANS Visuosp/Con</td>
<td>10</td>
<td>99.60</td>
<td>14.70</td>
<td>78-121</td>
</tr>
</tbody>
</table>

Table 7: Mean Premorbid score and stage one/stage two RBANS scores for participants who completed both stages
Table 7 shows the mean premorbid intellectual functioning score and the mean stage one and stage two RBANS performance for the 10 participants who completed both assessment stages. A paired samples t-test was used to compare Total RBANS scores at assessment stage one and assessment stage two for these 10 participants. Figure 4 shows each of the 10 remaining participants' total RBANS performance at each assessment stage.

![Figure 4: Participant’s Total RBANS scores at stage one and stage two.](image)

The results of this comparison showed that there was no significant difference between participants’ total RBANS scores at the two assessment stages ($t(9) = .772, p>.05$)

Further paired sample t-tests showed that the differences in performance in each domain at stages one and two were not significant (Attention ($t(9) = .377, p>.05$), Immediate Memory ($t(9) = .530, p>.05$), Delayed Memory ($t(9) = .615, p>.05$), Language ($t(9) = 1.571, p>.05$), Visuospatial/constructional skills ($t(9) = 1.863, p>.05$))
4.8 Additional Analysis:
As three participants reported a past history of heroin overdose and one of these three also reached diagnostic criteria for a current psychiatric comorbidity, the paired samples t-tests performed when examining hypotheses one, two and three were repeated with these participants excluded. This meant that 11 participants remained in assessment stage one and 8 in assessment stage two. The exclusion of these participants made no difference to the overall results. A significant difference remained between the groups’ premorbid scores and their Total RBANS scores at assessment stage one (t (10) = 2.985, p<.05) and assessment stage two (t (7) = 2.863, p<.05). Furthermore, there was no significant difference in the group’s Total RBANS scores at stage one and stage two (t (7) = .694, p<.05).

4.9 Results Summary
The results of the statistical analyses performed on the data found support for the hypotheses that current heroin use and current methadone use result in a significant impairment in neuropsychological functioning. However, no support was found for the hypothesis that current methadone use will result in less impairment than current heroin use. These results were not altered by excluding the three participants who reported a history of overdose/current psychiatric comorbidity. The interpretation and implications of these results will be discussed in detail in chapter five.
Chapter 5: Discussion

5.1 Summary of Research

Opioid addiction has been a worldwide issue for centuries and is showing no signs of reducing or disappearing. The opioid market provides money and livelihoods for many people worldwide, whilst simultaneously robbing millions more of their health, jobs, families and even their lives. In Western society the most common treatment for opiate addiction is the prescription of substitute opioids such as methadone, with the goal of reducing and finally withdrawing this prescription over time. In recent decades interest in the neurobiological and neuropsychological impact of both prescribed and illicit opioids has developed. This is an area which remains contentious, with widespread disagreement over the precise causes of the neuropsychological and neurobiological deficits or abnormalities which are undoubtedly present in the opioid-using population. The lack of clarity in this area owes largely to the range of conditions and circumstances which are frequently comorbid with a drug-using lifestyle. These include a history of overdose and head injury, concurrent alcohol misuse or substance dependencies, psychological or psychiatric illness and poor diet and health. Each of these factors may affect an individual’s neurobiology and neuropsychological skills, therefore serving to confuse the debate about the actual effects of opioids on these areas. Darke (2000) argued that the neuropsychological deficits observed in opioid users should be attributed to the effects of these comorbid factors rather than to the effects of the drug itself. However subsequent studies which have demonstrated improved functioning in abstinent ex-opiate abusers serve to contradict this notion.

The purpose of this study was to build on the previous literature by further examining the relationship between opioid abuse and neuropsychological functioning. Specifically this study set out to explore the neuropsychological impact of heroin and methadone on the same group of individuals. This is a design that has not been used in previous research, which has tended instead to compare separate groups of heroin and/or methadone users and/or controls. The advantage of this design is that it allows for a more direct comparison of the effects of heroin and
methadone, in order to determine whether these substances have a comparable or differing impact on neuropsychological functioning. In addition this study aimed to exclude participants with a history of significant head injury or with comorbid substance or alcohol dependencies in order to add clarity to the discussion regarding the precise causes of neuropsychological deficits in this group. Furthermore, details of any prior overdoses were obtained during the initial interview, and the presence of any comorbid psychiatric disorders was ascertained using a validated structured screening questionnaire (MINI). Three participants reported a history of prior overdose and of these three, one was found to meet criteria for a psychiatric diagnosis (major depressive illness – current/recurrent).

Based on the previous literature and the gaps in knowledge therein, this study therefore aimed to examine the following hypotheses:
1. Current heroin use will result in impaired neuropsychological functioning.
2. Current methadone use will result in impaired neuropsychological functioning.
3. Current methadone use will result in less impairment than current heroin use.

5.2 Discussion of Hypotheses

**Hypothesis One** stated that current heroin use would result in impaired neuropsychological functioning. At each stage of this study, impairment was identified when the participants’ performance was found to be at a level significantly below their premorbid estimate of intellectual functioning. This hypothesis was supported, as the group’s Total RBANS scores at stage one of assessment were found to be significantly below the level predicted by their premorbid estimate of intellectual functioning. Furthermore, when participants’ scores were broken down into the five domains assessed by the RBANS, the group was found to be performing significantly below their premorbid level in the areas of Attention, Immediate Memory, Delayed Memory, and Language. Performances in the area of Visuospatial/constructional skills were preserved (i.e. consistent with premorbid estimates).
These results are consistent with previous research evidence which has suggested that current heroin use will result in neuropsychological deficits in a variety of domains. Specifically, the presence of a deficit in attention is consistent with Guerra et al.’s (1987) study which demonstrated impaired memory in heroin users. Guerra et al. (1987) also showed impairments in immediate memory in this group, consistent with the results of this study. Further evidence for the impairments in verbal and visual memory demonstrated in the present study (both verbal and visual memory tasks are included in the Immediate and Delayed Memory domains of the RBANS) were reported by Ornstein et al. (2000) and Strang and Gurling (1989). The present study also found evidence for impairments in Language skills at assessment stage one. The Language domain of the RBANS includes a measure of verbal fluency, which is considered to be an element of executive functioning. Further evidence for deficits in verbal fluency have been reported by Guerra et al. (1987) and Ornstein et al. (2000). The present study found no evidence of impaired Visuospatial/constructional skills at assessment stage one. There is scarce information in the previous literature pertaining to the effects of heroin on this domain of functioning. However, Guerra et al. (1987) reported impaired perceptual skills in heroin users, which are arguably an important constituent of visuospatial/constructional functioning.

**Hypothesis Two** stated that current methadone use would result in impaired neuropsychological functioning. This hypothesis was also supported. The group’s Total RBANS scores at assessment stage two were significantly below the level predicted by their premorbid estimate of intellectual functioning. At this stage, the groups’ performance in the domains of Attention, Immediate Memory and Language were significantly below their premorbid estimate. However both Visuospatial/constructional skills and Delayed Memory skills were preserved.

These findings are consistent with previous research that has demonstrated impairments in attention (Darke et al., 2000; Prosser et al., 2006; Rapeli et al., 2007; Specka et al., 2000) verbal memory (Curran et al., 2002; Darke et al., 2000; Rapeli et al., 2007) and the verbal fluency component of the Language domain of the RBANS
(Davis et al., 2002). As discussed above, there is little information in the literature regarding the effects of opioids on visuospatial/constructional skills; however there is some evidence of impaired perception in methadone users (Gritz et al., 1975; Prosser et al., 2006 (Visual perception); Specka et al., 2000 (Tachistoscopic perception)). Finally, the results of the present study demonstrate preserved Delayed Memory functioning relative to premorbid ability estimates. The domain of Delayed Memory in the RBANS comprises three subtests of verbal memory and one subtest of visuospatial memory. Although previous research has demonstrated impairments in these areas in methadone users, Gruber et al. (2006) reported improvements in verbal memory and learning, and visuospatial memory over time with methadone maintenance therapy. As the group showed initial impairments in delayed memory at assessment stage one, this finding may indeed reflect an improvement in these components of memory by assessment stage two.

Implications of Hypotheses One and Two

It is clear from the results of the present study that the group experienced significant impairments in neuropsychological functioning while using heroin and while using methadone. There are a variety of implications and interpretations of this finding that must be considered.

Firstly, it is important to determine that this is a genuine effect and not a result of poor test validity or reliability. Two alternative explanations that must therefore by examined are that the group’s premorbid level of intellectual functioning was overestimated by the National Adult Reading Test (or the Graded Naming Test), or that their current functioning was underestimated by the RBANS. Either inaccuracy in measurement could result in the identification of a significant decline in functioning where none exists. The former explanation is unlikely as the NART is a well validated measure with high test-retest reliability (see chapter three). Although each participant’s NART assessment was carried out by one of the two researchers involved in this study, the NART has also been shown to have a high level of inter-rater reliability so this should not have unduly affected the test’s accuracy. The GNT was used with the two participants who were unable to read, and was chosen because
it yields a score which is highly correlated with the NART. The latter alternative explanation is also unlikely, as the RBANS has been shown to have high test-retest reliability and is highly correlated with the WAIS-R score, an estimated equivalent of which is provided by the NART.

Once these alternative explanations for the results of the present study are discounted and the hypothesis that current heroin and methadone use results in neuropsychological impairment is accepted, the question remains as to what the precise cause of this impairment might be. Previous literature has suggested that the impairments observed in opioid users should be attributed to factors associated with substance misuse rather than to the direct effects of the opioid in question (Darke et al., 2000). However, care was taken in the present study to control for the presence of these factors wherever possible. None of the participants reported a history of significant head injury or current alcohol or other substance dependencies, therefore these may be ruled out at this stage as possible causal factors. Three participants had a history of overdose, and of these, one had a comorbid psychiatric diagnosis (as measured by the MINI). When these three participants were excluded from the analysis, the same overall results were obtained. These factors may therefore have contributed to the overall pattern of impairment, however they are not sufficient to entirely explain this effect.

Several factors remain unexamined. Firstly, participants’ prior alcohol or substance dependencies were not assessed, and the possible presence of these may have contributed to the overall pattern of impaired neuropsychological performance. Secondly, the researchers relied upon the participants’ self reported history of head injury and medical records were not checked. It is therefore possible that past head injuries were under-reported or minimised. It is a reality that it is extremely difficult to gain an accurate history of significant head injury in this population for a number of reasons including an inability to recall injuries due to intoxication, and an unwillingness to report injuries sustained as a result of criminal acts such as an assault or a car theft. Furthermore, as medical attention is often not sought for head injuries gained under these circumstances, they are not detailed in the individual’s
medical records. Similarly, the researchers relied on self-reported concurrent alcohol and substance use and no objective measures were obtained (e.g. urine analysis). It is therefore possible that concurrent substance and alcohol use was under-reported and other dependencies were not diagnosed.

Given all of the above considerations, it is possible only to conclude the following:
The results of the present study demonstrate a significant level of neuropsychological impairment in current opioid dependent heroin and methadone users. There are three possible explanations for this result:

1. The impairment is a direct result of the action of heroin/methadone on the brain.
2. The impairment it is a result of one or more of the following: (1) Other factors which were not assessed, namely previous substance and alcohol dependencies; (2) Other factors which were assessed such as the effects of overdose (in three participants) and comorbid psychiatric disorders (in one participant); and (3) Other factors which were assumed to be absent but may have been under-reported, namely previous significant head injury and concurrent alcohol and substance dependencies.
3. The impairment is a result of a combination of all of the above factors

Previous literature in this area has shown that the neuropsychological deficits experienced by opioid abusers are reduced with opioid abstinence (Davis et al., 2002; Mintzer et al., 2005; Prosser et al., 2006; Verdejo et al., 2005). This suggests that deficits are associated at least in part with the direct effects of the opioid itself, and therefore supports the first explanation which was considered for the present results. Clearly further research in this area is essential in order to add clarity to this issue (see section 5.6).

Hypothesis Three stated that current methadone use would result in less impairment than current heroin use. This hypothesis was not supported. There was no significant difference between the groups’ Total RBANS scores at assessment stages one and two. Furthermore, there were no significant differences between the groups’
performance in the five domains of Attention, Immediate Memory, Delayed Memory, Language and Visuospatial/constructional skills at stage one and stage two.

**Implications of Hypothesis Three**

Evidence from the previous literature in this area has suggested that methadone use may result in a different and possibly less damaging profile of neurobiological (and therefore neuropsychological) change than heroin use. However the groups’ performance while using methadone was not significantly better than while using heroin. There are a number of possible interpretations and implications of these results. Firstly, although it may be the case that methadone causes less neurobiological and neuropsychological damage than heroin, the group included in the present study may be continuing to experience the residual effects of years of heroin use, as well as the effects of current methadone use. Indeed, it is extremely difficult to compare directly the effects of heroin and methadone on the brain as individuals who are maintained on prescribed methadone or using this substance illicitly do so almost exclusively in the context of previous heroin or other opioid abuse. Therefore it is not possible to separate the direct effects of methadone from the possible residual effects of the substances whose place the methadone has taken. In order to directly compare these substances in the most precise manner, it would be necessary to identify a group of methadone users who are naïve to prior opiate use, a scenario which in reality is extremely unlikely to be possible.

A second potential interpretation of these results is that the group were tested too soon after commencement on to prescribed methadone for a significant improvement in their neuropsychological functioning to be detected. In general the group were assessed 1-4 weeks after beginning their prescription of methadone, once they had reached a stable daily dose of this substance. It seems entirely possible that the groups’ performance may begin to improve with time, moving towards the level predicted by their premorbid estimates of intellectual functioning. There is some support in previous literature for this notion, provided by Gruber et al. (2006) who assessed heroin dependent individuals at the beginning of methadone maintenance and again after two months. This research showed that participants’ performance
improved significantly in the areas of verbal memory and learning, visuospatial memory and psychomotor speed. However, no improvements were observed in Gruber et al.’s (2006) study on several tests sensitive to executive functioning skills.

Given these results and the previous research in this area, a useful and interesting development to the present study would involve reassessing the group at regular intervals throughout their methadone maintenance program to test the hypothesis that improvement in neuropsychological functioning may take place. Ideally the group could be followed as far as complete withdrawal from methadone and assessed again once free from all opioids. The available evidence from previous research indicates that opioid free ex-heroin addicts perform at a level superior to methadone maintained ex heroin addicts, but below that of opioid naïve controls (Darke et al., 2002; Mintzer et al., 2005; Prosser et al., 2006; Verdejo et al., 2005). Although there are a number of issues in interpreting the results of these studies (as was discussed in chapter one), they suggest that long term opioid use may cause some level of permanent damage, but that at least some areas of neuropsychological impairment are subject to recovery with time following cessation of heroin use. It would therefore be reasonable to predict that the present groups’ neuropsychological functioning may improve with time and eventual complete opioid abstinence, but may not reach the level predicted by their premorbid estimate of intellectual functioning.

Summary of Hypotheses

The present study aimed to contribute further to the current knowledge base regarding the effects of opioids on neuropsychological functioning. The results of this study show significant decline in neuropsychological functioning in opioid dependent males while using heroin and once maintained on a daily methadone prescription. Specifically, participants were found to be impaired in the areas of Attention, Immediate Memory, Delayed Memory and Language, while using heroin with no impairment in Visuospatial/constructional skills. Once participants were maintained on a daily methadone dose, significant deficits remained in the areas of Attention, Immediate Memory and Language, with no significant impairments in the
areas of Delayed Memory or Visuospatial/constructional skills. There were no significant differences between participant’s performances while using heroin and once stabilised on methadone in any of the five domains of neuropsychological functioning assessed. However the significant impairment in Delayed Memory while participants were using heroin was no longer evident by the time they reached the methadone stage.

These results allow for the following tentative conclusions to be proposed, each of which may form the basis of future research in this area:

- Opioid use can result in impaired neuropsychological functioning in the areas of Attention, Immediate Memory, Delayed Memory and Language.
- Visuospatial/constructional skills are not affected by opioid use.
- There is no significant difference between the neuropsychological profile of opioid dependent individuals who are actively using heroin and that of the same individuals once stabilised on a daily dose of methadone.

However it is important to consider the following challenges to these conclusions:

- The neuropsychological impairment observed in opioid users may be a result of factors other than the direct effects of opioids. Although every effort was made to control for these factors, this was in practice a difficult task which will be discussed further in section 5.4.
- The small sample size included in the present study detracts from the strength of the results and there is a possibility that effects exist where none have been detected or alternatively, effects have been demonstrated erroneously, where none exist.
- Participants may have been tested too early in their methadone maintenance program for improvements in neuropsychological functioning to take place.

Clearly further research is necessary in these areas in order to more fully examine these issues. However the results of the present study are useful as they add support to the previous literature which reports neuropsychological impairment in opioid
users and pose some interesting questions for the future regarding the exact nature of the relationship between opioids and neuropsychology.

5.3 Clinical Implications
Regardless of the exact genesis of the problem, it is clear that opioid use is associated with neuropsychological impairment in a range of domains. These deficits may translate to real life problems with remembering appointment times or attending to or recalling important information such as the content of appointment with service providers. This, in turn, has important implications for clinical practice in terms of service provision for opioid addiction. All staff working with opioid users must receive training and information regarding the consequences of opioid dependence on neuropsychological functioning. Such professionals will range from GPs and nurses to probation officers, social workers and family support workers.

It is essential that every effort is made to support service users’ attention and memory by using reminders, encouraging use of aids such as diaries and notebooks, and ensuring that important information is written down. Appointments should be kept reasonably short and limited to a focus on one or two key issues. Service users’ comprehension and recall of these issues should be checked at the end of appointments and summaries provided.

An awareness of these impairments is also important with respect to longer term rehabilitation. For example these issues should be considered as part of programs aimed at assisting in return to work or college. Educating staff who are involved with such programs as well as potential employers or educational institutions about the impact of opioids on performance should allow for additional support to be provided where necessary.

5.4 Limitations of the Present Study
Zacny (1995) asserted that many studies of the effects of methadone in humans are compromised by a variety of methodological problems. These include the lack of appropriate controls, the inclusion of participants with polysubstance use, the
reliance on one or two arbitrarily selected neuropsychological tests (in particular the digit symbol substitution test) and the use of only small numbers of participants. The present study aimed to avoid some of these pitfalls in a number of ways. Firstly participants were screened for the presence of a number of factors associated with opioid dependence and those with a self-reported history of significant head injury or concurrent alcohol or substance misuse were excluded. In addition the group was restricted to males aged between 18 and 35 with objectively ascertained opiate dependency (as measured by the MINI). These inclusion and exclusion criteria were adopted in an attempt to obtain as homogenous a group as possible, in order to increase confidence in the notion that any observed effects could be attributed to the direct effects of opioid use on neuropsychological functioning. However there were a number of limitations of the present study’s design, some of which have been highlighted by Zacny (1995). Each of these will be discussed in this section.

There were several difficulties associated with using the type of screening and exclusion criteria included in the present study. These included the possibility that previous head injuries or previous and current substance and alcohol use were minimised or under-reported. Although every effort was made in designing this study to eliminate other factors known to be associated with neuropsychological deficits, it was ultimately not possible to obtain a completely ‘pure’ sample of opioid dependent participants without seriously compromising the study’s sample size. The present study was therefore limited in its capacity to make direct links between opioid use and neuropsychological deficits by the possible presence of numerous other factors associated with reduced functioning. It is however a reality that opioid use in the general population is comorbid with numerous other factors which are likely to contribute to reduced neuropsychological functioning. It is therefore extremely difficult to identify a sample of participants which will allow for the direct examination of the effects of opioids on the brain in the absence of any other confounding factors.

The present study did not include a control group of opioid naïve participants. The need for such a group is eliminated in part by the use of a premorbid estimate of
intellectual functioning. This allows for direct comparison of participants’ performance with their own premorbid level, rather than with the performance of a group of controls. However if a control group of demographically matched individuals had been included, and had obtained RBANS scores which were comparable to their premorbid estimate of intellectual functioning (NART score), this would serve to strengthen the assertion that the significant difference between the current opioid dependent group’s RBANS scores and premorbid scores reflect a genuine deficit which can be attributed to opioid use. Such a control group could be identified and assessed as a post hoc addition to the present study.

Zacny (1995) included the use of a limited number of arbitrarily selected tests amongst the weaknesses common to previous research. The present study aimed to strike a balance between using as comprehensive a battery as possible while minimising the demands on participant’s time. The RBANS was chosen as it contains a spectrum of short subtests of attention, memory, language, and visuospatial/constructional skills including tasks known to be sensitive to executive functioning, but can be completed in less than half an hour. It was also necessary to select a test with parallel forms which could be repeated within several weeks of initial administration. This requirement eliminated many of the assessment measures commonly employed in the field of neuropsychology which have only one form and generally should not be repeated until at least six months or a year after initial administration to control for practice effects. Ideally it would have been useful and informative to include a wider range of assessment measures which would provide a more detailed profile of neuropsychological functioning in this population. However it will be possible to augment the results of the present study in the future by examining the outcome of the study which was run concurrently to the present study with the same participants, using the CANTAB assessment.

A further shortcoming of previous research is small sample size, and unfortunately this was also a feature of the present study. A total of 14 participants was included in the present study, and were recruited over an 18 month period. This low sample size does not satisfy the recommended power for detecting statistical significance
recommended by Cohen (1992) and reduces the strength of the results of this study
and their ability to be generalised to the wider opioid using population. However a
number of challenges were associated with data collection and served to limit the
number of participants who took part. These are discussed in detail in section 5.5. It
is also worth noting that of the 19 published papers reviewed which found evidence
for a link between neuropsychological impairment and opioid use, more than half
(58%) included a sample size of 25 or less. This suggests that difficulties with
recruitment and retention may be a common feature in the field of opioid addiction
research.

5.5 Challenges Associated with the Present Study
There were a variety of challenges associated with each stage of the data collection
involved in this study. Some of these challenges were specific to the local context in
which the study took place, others were more general difficulties associated with
conducting a study in the field of opioid addiction.

The first challenge lay in identifying and recruiting individuals to the study.
Recruitment took place over a period of 18 months, and during this time the structure
of Fife NHS Addictions Service underwent significant redesign. At the beginning of
the study, individuals who wished to access the service attended a drop-in service
which was principally situated within an outpatient hospital ward and was open
during set hours, between Monday and Friday. This meant that any potential
participants for the study would pass through this clinic prior to beginning treatment
for opioid addiction. A link worker was identified who would take responsibility for
contacting the researchers if a suitable candidate attended the drop-in service. This
link worker was responsible for overseeing the reception area of this clinic and was
ideally placed to screen each new client for eligibility. This individual had copies of
information leaflets regarding the study which could be provided to potential
participants if they read the posters displayed in the waiting area regarding the study
and expressed an interest in taking part. Once identified by the link worker, potential
participants were contacted by telephone to arrange an initial appointment with one
of the researchers. However, several months after the study began, the drop in clinics
moved from the NHS Addictions Service clinic to a number of voluntary agencies across Fife. This meant that individuals wishing to access the NHS Addictions Service could attend any of a number of different clinics which were now staffed by workers from five different voluntary agencies. Once “triaged” at these drop in clinics, clients were assigned an NHS Addictions keyworker and offered follow up assessment and medical appointments before commencement on to prescribed methadone. This meant that a large number of voluntary and NHS staff were responsible for assisting in new clients’ assessments and progress towards methadone prescription, and there was no longer one key link worker who could be identified to screen all new clients. As a consequence the researchers had to dedicate time to approaching each of the voluntary agencies now involved as well as the NHS staff responsible for assessment to describe the study and request cooperation in identifying potential participants. This change in structure inevitably resulted in numerous suitable candidates passing through the service to the methadone prescription stage without being identified to the researchers. In addition there was a high cost in terms of research time required to make and maintain contact with the staff and organisations involved with triage and assessment.

A further issue associated with the new service structure was that often clients were not identified and the researchers contacted until there was little time remaining prior to the client commencing methadone maintenance therapy. Each potential participant was required to complete the questionnaire stage and assessment stage one while still using heroin. However, on occasion suitable clients were identified to the researchers with insufficient time remaining to complete these stages, and so it was not possible to include these individuals. In addition, if potential participants were identified too close to the planned date of their commencement on to prescribed methadone, it was no longer possible to offer the incentive of an earlier date for methadone commencement.

Other challenges involved in the completion of this study were more specific to the nature of the population being studied. Firstly, a number of individuals who were identified as suitable candidates were not willing to invest the time and effort
required to participate in the study. Unfortunately a record of how many participants were approached but who did not wish to take part was not kept. A second challenge lay in arranging geographically convenient locations for the researchers to meet with participants, as a number of them did not have their own car and could not afford to pay for public transport. Although it was possible to offer a financial incentive for taking part of £5 per appointment, this sum was only issued on completion of the study in order to improve participation rates. Therefore it was often necessary to arrange premises for appointments in hospitals or clinics which were local to the participant. However this was not always possible, resulting in increased non-attendance rates.

The exclusion criteria used by this study limited the number of potential participants available. Opioid dependency is frequently comorbid with other substance dependencies such as benzodiazepine dependence and with a history of head injury. By narrowing the pool of available participants to include only males aged 18-35 without concurrent substance or alcohol use or history of head injury, a number of heroin users seeking methadone treatment were excluded.

A further challenge concerned compliance with methadone maintenance therapy. Four of the fourteen participants included in this study failed to reach methadone stability and therefore were not able to complete stage two of assessment. This represents close to a 30 per cent rate of drop-out from the study. Of the four who failed to complete the study, one participant died (of suspected drug related causes) subsequent to methadone commencement but prior to methadone stability. One participant opted out of methadone commencement, expressing that he had decided that he did not feel that methadone maintenance was the right choice of treatment for him. The remaining two participants stopped taking methadone soon after commencement; one choosing to try ‘cold turkey’ and abstain from all opioids completely, the other returning to regular heroin use. Therefore each of these four participants was excluded from the study at different stages and for different reasons, providing just a snapshot of the barriers to successful progress from heroin use to methadone maintenance.
A final difficulty was associated with the logistics of maintaining contact with the participants included in the study. Contact was essential in order to arrange appointments and issue reminders regarding appointment times. However it was common for participants to have no mobile telephone or landline, offering instead the telephone number of a friend, partner or relative with whom messages could be left. This “go-between” person had to be relied upon to pass messages from researcher to participant and vice-versa. Participants who did have mobile telephones would frequently run out of calling credit and were therefore unable to listen to voicemail messages left for them by the researchers. Two participants were living in temporary homeless accommodation and a number of others had no fixed abode. This meant that participants’ addresses could change between appointments and appointment letters would never be received. The problem of maintaining contact was overcome in part by working closely with participants’ Addictions Service keyworkers to issue appointment reminders and making an effort to coordinate assessment appointments so that they took place prior or subsequent to the participant’s appointment with their keyworker. However this issue was costly in time for the researchers and resulted in a large number of failed appointments.

As a result of each of the challenges discussed, it was not possible to exceed a sample size of 14 participants in a period of 18 months. This small sample size reduces the power of and ability to generalise the results of this study, but reflects the problems associated with studying this population. Many of the previous studies in this area feature similarly small sample sizes, emphasising the challenges associated with recruiting/retaining participants in the context of opioid addiction.

5.6 Future Directions for Research
The results of the present study pose some interesting questions regarding the exact relationship between opioid use and neuropsychological functioning. Considerable progress could be made in this area by designing a longitudinal study of a large sample of opioid users as they progress from opioid dependency to complete abstinence. Such a study should aim to compare participants’ current functioning at
regular intervals with an estimate of their premorbid ability. A detailed record should also be kept of any other relevant factors such as a history of head injury or alcohol/substance dependence, comorbid substance and alcohol use, and comorbid psychiatric and psychological diagnoses. Objective measures of some of these factors such as urine analysis, CT brain scans, medical file reviews and validated questionnaire measures should be employed. Using this type of design, it could be possible to make links between any observed improvements or deterioration in neuropsychological functioning and significant events which co-occur with these changes. Such events might include withdrawal from opioids, withdrawal from other substances or alcohol or resolution of psychiatric/psychological difficulties. Any impairment which remains following prolonged abstinence from opioids (and alcohol/other substances) may be attributed to permanent damage to the brain caused by opioid abuse and/or other factors such as alcohol and substance abuse or previous head injury.

This type of design would also aim to include an accurate record of participants' duration of opioid use, level of use, and dose of methadone once they progress to methadone maintenance therapy. This information could be used to identify any associations between changes in these factors and concurrent changes in neuropsychological functioning.

5.7 Final Remarks

Having completed this study, it is useful to reflect upon the experience of conducting research in the field of opioid dependence and neuropsychological functioning. Each stage of this process has felt at times a confusing, frustrating and complex endeavour, from reviewing and interpreting the literature, much of which is conflicting or inconsistent, to recruiting participants in the context of a range of constraints and barriers, to interpreting the data in light of a variety of confounding factors and unexpected results.

In short, the opioid addict exists within a tangled web of inter-related factors commonly comorbid with substance misuse, each of which are known to impact on
physical, emotional, neuropsychological or social functioning. Any attempt to disentangle these factors from one another and examine the effects of each in isolation is ultimately futile, and it is an unfortunate reality that opioid use will continue to coexist with a range of adverse factors for as long as it remains an illicit substance of addiction. One clear message has emerged from the body of research which exists in this area however, which is that many opioid users will experience significant impairments in neuropsychological functioning. As opioid dependence continues to be rife on a global level it is crucial that more research is dedicated to understanding the nature and prognosis of this problem, in order that the most appropriate support and rehabilitation is made available for those who find themselves trapped in the grip of this addiction.
References


Appendices

Appendix 1: Ethical Permission Forms

Appendix 2: Participant Information Form

Appendix 3: Participant Consent Form

Appendix 4: Mini International Neuropsychiatric Interview
          – Screening Questionnaire

Appendix 5: National Adult Reading Test – Word List

Appendix 6: Graded Naming Test – Object List

Appendix 7: Repeatable Battery for the Assessment
          of Neuropsychological Status - Scoring Sheet
Appendix 1
Dear Dr Baldacchino

**Full title of study:** Neurotoxicity as a result of chronic exposure to methadone and other opiates: implications for the management of heroin misuse and chronic pain

**REC reference number:** 06/S1401/32

Thank you for your letter of 20 April 2006, responding to the Committee’s request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Administrator & Medical Advisor.

**Confirmation of ethical opinion**

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

**Ethical review of research sites**

The favourable opinion applies to the research sites listed on the attached form.

**Conditions of approval**

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

**Approved documents**

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

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**Research governance approval**

The study should not commence at any NHS Tayside site until the local Principal Investigator has obtained final research governance approval from NHS Tayside R&D Department.

**Statement of compliance**

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

**06/S1401/32 Please quote this number on all correspondence**

Yours sincerely

**Chair**

Enclosures: Standard approval conditions  
Site approval form

Copy to: NHS Fife, Cameron House  
NHS Tayside R & D Department
**Tayside Committee on Medical Research Ethics A**

**LIST OF SITES WITH A FAVOURABLE ETHICAL OPINION**

For all studies requiring site-specific assessment, this form is issued by the main REC to the Chief Investigator and sponsor with the favourable opinion letter and following subsequent notifications from site assessors. For issue 2 onwards, all sites with a favourable opinion are listed, adding the new sites approved.

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**Chief Investigator:** Dr Alexander Baldacchino

**Full title of study:** Neurotoxicity as a result of chronic exposure to methadone and other opioids: implications for the management of heroin misuse and chronic pain

This study was given a favourable ethical opinion by Tayside Committee on Medical Research Ethics A on 26 April 2006. The favourable opinion is extended to each of the sites listed below. The research may commence at each NHS site when management approval from the relevant NHS care organisation has been confirmed.

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<td>Clinical Senior Lecturer and Consultant Psychiatrist in Addictions</td>
<td>NHS Tayside</td>
<td>Tayside Committee on Medical Research Ethics A</td>
<td>03/05/2006</td>
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<td>Senior Lecturer (University of Dundee) and Consultant in Addiction Psychiatry (NHS Fife)</td>
<td>Pain Services, Queen Margaret Hospital, Dunfermline, Fife and Victoria Hospital, Kirkcaldy Fife</td>
<td>Fife Local Research Ethics Committee</td>
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<td>03/05/2006</td>
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</table>

Approved by the Chair on behalf of the REC:

(1) The notes column may be used by the main REC to record the early closure or withdrawal of a site (where notified by the Chief Investigator or sponsor), the suspension of termination of the favourable opinion for an individual site, or any other relevant development. The date should be recorded.
NOTICE OF SUBSTANTIAL AMENDMENT

For use in the case of all research other than clinical trials of investigational medicinal products (CTIMPs). For substantial amendments to CTIMPs, please use the EU-approved notice of amendment form (Annex 2 to ENTR/CT1) at http://eudraCT.emea.eu.int/document.html#guidance.

To be completed in typescript by the Chief Investigator in language comprehensible to a lay person and submitted to the Research Ethics Committee that gave a favourable opinion of the research ("the main REC"). In the case of multi-site studies, there is no need to send copies to other RECs unless specifically required by the main REC.


<table>
<thead>
<tr>
<th>Details of Chief Investigator:</th>
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<tbody>
<tr>
<td><strong>Name:</strong></td>
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<td><strong>Address:</strong></td>
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<tr>
<td><strong>Telephone:</strong></td>
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<td><strong>E-mail:</strong></td>
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<td><strong>Fax:</strong></td>
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</tbody>
</table>

<p>| Full title of study: | Neurotoxicity as a result of chronic exposure to methadone and other opiates: Implications for the management of heroin misuse and chronic pain |
| Name of main REC: | Tayside |
| <strong>REC reference number:</strong> | 06/S1401/32 |
| <strong>Date study commenced:</strong> | |
| <strong>Protocol reference (if applicable), current version and date:</strong> | |</p>
<table>
<thead>
<tr>
<th><strong>Amendment number and date:</strong></th>
<th>1 (07/12/06)</th>
</tr>
</thead>
</table>

**Type of amendment (indicate all that apply in bold)***

(a) Amendment to information previously given on the REC application form

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

If yes, please refer to relevant sections of the REC application in the "summary of changes" below.

(b) Amendment to the protocol

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

If yes, please submit either the revised protocol with a new version number and date, highlighting changes in bold, or a document listing the changes and giving both the previous and revised text.

(c) Amendment to the information sheet(s) and consent form(s) for participants, or to any other supporting documentation for the study

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

If yes, please submit all revised documents with new version numbers and dates, highlighting new text in bold.

---

**Is this a modified version of an amendment previously notified to the REC and given an unfavourable opinion?**

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
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</thead>
</table>

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**Summary of changes**

Briefly summarise the main changes proposed in this amendment using language comprehensible to a lay person. Explain the purpose of the changes and their significance for the study. In the case of a modified amendment, highlight the modifications that have been made.

If the amendment significantly alters the research design or methodology, or could otherwise affect the scientific value of the study, supporting scientific information should be given (or enclosed separately). Indicate whether or not additional scientific critique has been obtained.

Main Changes to initial application:

1. Replacement of the Composite International Diagnostic instrument Automated Version (CIDI-AUTO), with the Mini International Neuropsychiatric Interview (MINI).
2. The replacement of the The Composite International Diagnostic Interview Substance Abuse Module (CIDI-SAM) with the Maudsley Addiction Profile (MAP).

These replacements have been made as the MINI and the MAP are briefer and more user-friendly measures than the CIDI-AUTO and the CIDI-SAM but have comparable validity and reliability to the measures they replace. The information sheet provided to participants has been changed to include these replacements.

---

*Notice of amendment (non-CTIMP), version 3.1, November 2005*
Addition of one new assessment measure to the assessment battery. This is the Repeatable Battery for the Assessment of Neuropsychological Status. It is a brief, validated measure designed to measure any changes over time in a subject’s level of neuropsychological functioning, and so is highly appropriate for the purposes of this study. This test will be incorporated into the assessment of Cohort A.

The added value of this assessment is that it is repeatable, so will be free from learning effects. In addition, it is a paper and pen test, as opposed to the computerised format of the CANTAB. Therefore the results of this test may be more comparable to the results of previous studies in this area. This assessment examines areas of functioning which are comparable to those assessed by the CANTAB, so should provide results which will supplement and support those provided by the CANTAB. Finally, the RBANS is a relatively cheap and brief measure compared to the CANTAB, so may be a more accessible tool for future clinical use in this area.

Change to the originally proposed title: “Neurotoxicity as a result of chronic exposure to methadone and other opiates: Implications for the management of heroin misuse and chronic pain” to “Neuropsychological Function as a result of chronic exposure to methadone and other opiates (NEMO study)”. The new title is shorter and easier to understand.

Any other relevant information

Applicants may indicate any specific ethical issues relating to the amendment, on which the opinion of the REC is sought.

List of enclosed documents

<table>
<thead>
<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copy of the previous protocol</td>
<td>1</td>
<td>07/12/79</td>
</tr>
<tr>
<td>Revised copy of the previous protocol</td>
<td>1</td>
<td>07/12/79</td>
</tr>
</tbody>
</table>

Declaration

- I confirm that the information in this form is accurate to the best of my knowledge and I take full responsibility for it.
- I consider that it would be reasonable for the proposed amendment to be implemented.

Signature of Chief Investigator: ..........................................

Print name: .................................................................

Date of submission: ......................................................
Dear Dr Baldacchino

Study title: Neurotoxicity as a result of chronic exposure to methadone and other opiates: implications for the management of heroin misuse and chronic pain

REC reference: 06/S1401/32

Amendment number: 1
Amendment date: 12 December 2006

The above amendment was reviewed at the meeting of the Sub-Committee of the REC held on 21 December 2006.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation. I can also confirm that future correspondence will carry the revised title, ie, ‘Neuropsychological Function as a result of chronic exposure to methadone and other opiates (NEMO study)’. However, you must submit a copy of the revised Participant Information Sheet and the Consent Form with the relevant changes for our records. Please note that these should include a revised version number and new full date.

Approved documents

The documents reviewed and approved at the meeting were:

<table>
<thead>
<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Notice of Substantial Amendment (non-CTIMPs)</td>
<td>1</td>
<td>12 December 2006</td>
</tr>
</tbody>
</table>

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Research governance approval
All investigators and research collaborators in the NHS should notify the R&D Department for the relevant NHS care organisation of this amendment and check whether it affects research governance approval of the research.

Statement of compliance

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

Please quote this number on all correspondence

Yours sincerely

Miss Fiona Bain
Committee Co-ordinator

Copy to: NHS Fife, Cameron House
         NHS Tayside R&D Department

Enclosures List of names and professions of members who were present at the meeting
**Tayside Committee on Medical Research Ethics A**

**Attendance at Sub-Committee of the REC meeting on 21 December 2006**

<table>
<thead>
<tr>
<th>Name</th>
<th>Profession</th>
<th>Capacity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Fergus Daly</td>
<td>Statistician</td>
<td>Expert, Chair</td>
</tr>
<tr>
<td>Ms Anne Duthie</td>
<td>Project Manager LD Service Redesign</td>
<td>Expert</td>
</tr>
</tbody>
</table>

*Also in attendance:*

<table>
<thead>
<tr>
<th>Name</th>
<th>Position (or reason for attending)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miss Fiona Bain</td>
<td>LREC Administrator</td>
</tr>
<tr>
<td>Mr Angus MacConnachie</td>
<td>Medical/Scientific Advisor</td>
</tr>
</tbody>
</table>
Dear Alex

NEMO – Neurotoxicity as a result of chronic exposure to methadone and other opiates: implications for the management of heroin misuse and chronic pain

Thank you for submitting a copy of the amended protocol, study schedule and participant information sheet and Ethical approval letter notifying of an amendment to the above study. I can confirm that this amendment does not affect the Management Approval of the research which was previously issued.

Yours sincerely

DR STELLA CLARK
Medical Director, Primary Care
NHS Fife
Appendix 2
Participant information sheet (A): experimental group about to commence on a methadone treatment programme (Addiction Services in Fife and Dundee)

Centre Number: ___________________

Study Number: ___________________

Patient Identification Number for the study: ___________________

Study title: Neuropsychological function as a result of chronic exposure to methadone and other opiates (NEMO Study).

You have been invited to take part in this study as a client of the Addiction Services in either Dundee or Fife who is about to commence on a methadone treatment programme. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish.

- Part 1 tells you the purpose of this study and what will happen to you if you take part.
- Part 2 gives you more detailed information about the conduct of the study.
Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Part 1

Study title: Neuropsychological function as a result of chronic exposure to methadone and other opiates (NEMO study).

What is the purpose of the study?
The study will see whether a person’s mental well being is effected by taking regular opiates like methadone and heroin amongst others. No one really knows if taking opiates for a long time (more than 1 year) consistently does affect the way one interprets external events and also the way you react to such events. This study is part of a project that Dr Alexander Baldacchino is doing at Ninewells Hospital and Medical School, Dundee.

Why have I been chosen?
From the records and discussion with your key worker at the Addiction Services it shows that you have been using illicit opiates (usually heroin) for more than 1 year. There will be 28 other participants involved in this study who will be chosen for the same reason from services in Fife and Dundee.

Do I have to take part?
No. It is up to you to decide whether or not to take part. If you do, you will be given this information sheet to keep and be asked to sign a consent form. You are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?
If you agree to take part in the study you will be asked to attend for an assessment. You will be asked about your drug and alcohol use, medications, physical and mental health, your feelings and emotions. You will also be asked to complete a short test which estimates your expected level of intellectual functioning, or premorbid level of functioning. This assessment appointment will not take more than an hour. Then you will be invited back another time to have a computerised test that will show how you solve certain problems, how impulsive and the level and extent you take risks to hypothetical situations. This will again take another hour to complete. This computerised test will be repeated again during the process of tolerance testing and stabilisation on your methadone dose (total of 3 appointments in approximately a 1-2 month period). There will also be an opportunity to be tested with another neuropsychological test which will take about 30 minutes to complete. This is called the Repeatable Battery for the Assessment of
Neuropsychological Status and will be done before and after tolerance testing to methadone.

These meetings will be in addition to any treatment or help that you get from the service. They may even be after you have stopped using the same services. However we will arrange the extra meetings at a time that is convenient to you.

**What do I have to do?**
Once you have decided to participate in this study, the researcher will ask you the best time and date to meet in order to do the test in a quiet and comfortable environment. You are asked to be ready to be an active participant throughout the test procedure. The study will continue if you manage to successfully refrain from taking other drugs including alcohol when on methadone and/or other opiates as agreed in your treatment plan with the addiction/pain services. You will be asked to fill in questionnaires and use computerised test procedures that are simple to answer and operate. There will always be a researcher to help you throughout the study.

**What is the procedure that is being tested?**
The instruments that will be used in this study include the Mini International Neuropsychiatric Instrument (MINI) and the Maudsley Addiction Profile (MAP). These two instruments will ask about physical, mental health and dependence related problems. The National Adult Reading Test (NART) will assess your expected premorbid level of intellectual functioning. If you are unable to read an alternative test will be used in place of the NART. The Cambridge Neuropsychological Test Automated Battery (CANTAB) and Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) will measure memory, attention, planning and risk taking.

**What are the other possible disadvantages and risks of taking part?**
There are no physical risks involved in this study. However, you may find that talking about some of your feelings may make you feel uncomfortable, or bring back past memories. If this does happen you will be able to discuss this with the team member to see if further support is needed.

**What are the possible benefits of taking part?**
We cannot promise the study will help you but the information we get might help improve the treatment of people with chronic painful conditions and/or individuals with dependence related problems.

**What happens when the research study stops?**
At the end of the study a report will be written. However this report will not contain any names or individual details of the people that took part in the study.

**What if there is a problem?**
Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2.

In Fife:
Patient Liaison Office
Victoria Hospital
Hayfield Road
Kirkaldy
Fife KY 2 5AH
Telephone number: 01592 643355

In Tayside:
Patient Liaison Office
Level 7, Ninewells Hospital
Ninewells Avenue
Dundee DD2 1
Telephone number: 01382 660111

**Will my taking part in the study be kept confidential?**
Yes. All the information about your participation in this study will be kept confidential. The details are included in Part 2.

Your answers will normally only be seen by members of the research team. But if you tell us something that makes us believe that there is significant danger to either yourself, or other people, then we may have to pass the information to other agencies.

**Contact Details:**
If you have any questions about this study, either now or during the course of the study please contact me on

Dr Alexander Baldacchino
Centre for Addiction Research and Education Scotland (CARES)
Section of Psychiatry and Behavioural Sciences
Level 5, Ninewells Hospital and Medical School
Dundee DD1
Telephone number: 01382 623121/632414

And/or

Medical Offices
Stratheden Hospital
Cupar
Fife KY15 5RR
Telephone number: 01334 696366
This completes Part 1 of the Information Sheet. If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.

Part 2

Study title: Neuropsychological function as a result of chronic exposure to methadone and other opiates (NEMO study).

What will happen if I don't want to carry on with the study?
If you withdraw from the study, we will destroy all your identifiable samples, but we will need to use the data collected up to your withdrawal.

Again refusing to take part or withdraw from the study at any time will not affect any help or services that you will get.

What if there is a problem?
If you have concerns about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your questions. The person to contact is:

Dr Alexander Baldacchino  
Centre for Addiction Research and Education Scotland (CARES)  
Section of Psychiatry and Behavioural Sciences  
Level 5, Ninewells Hospital and Medical School  
Dundee DD1  
Telephone number: 01382 623121/632414

And/or

Medical Offices  
Stratheden Hospital  
Cupar  
Fife KY5 5RR  
Telephone number: 01334 696366

If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedures. Details can be obtained from:

In Fife:  
Patient Liaison Office  
Victoria Hospital  
Hayfield Road  
Kirkcaldy  
Fife KY2 5AH
In the event that something does go wrong and you are harmed during the research study there are no special compensation arrangements. If you are harmed and this is due to someone’s negligence then you may have grounds for a legal action for compensation against the University of Dundee and NHS Fife but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).

**Will my taking part in this study be kept confidential?**

All procedures for handling, processing, storage and destruction of their data are compliant with the Data Protection Act 1998.

Data will be collected through either a paper and/or computerised questionnaires. All information will be stored securely in a locked cabinet at the CARES office in Ninewells Hospital and Medical School, Dundee. The information is only identifiable through a coded process that only the Chief Investigator has access to the code hence ensuring anonymity. The information will then be converted into statistical variables and inputted on to a statistical computerised package (SPSS) again on computers at the CARES office and accessed only by the Chief Investigator. The results of the analysis of this data will then be used to help in the PhD thesis and future peer reviewed publications. This data will be retained for ten years at the CARES office and can only be used in other studies once further ethics approval is sought and obtained.

If you join the study, some parts of your medical records and the data collected for the study will be looked at by authorised persons such as representatives of regulatory authorities and by authorised people from the University of Dundee and NHS Fife to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and nothing that could reveal your identity will be disclosed outside the research site.

All information which is collected about you during the course of the research will be kept strictly confidential. Your answers will normally only be seen by members of the research team. But if you tell us something that makes us believe that there is significant danger to either yourself, or other people, then we may have to pass the information to other agencies.
**Involvement of the General Practitioner/ Specialist**

This study is not being conducted by your General Practitioner but your own GP may be notified of your participation in the research. This can only be done once you give us consent to inform your General Practitioner.

During the course of the study the Chief Investigator, Dr Alexander Baldacchino, might be asking your GP and/or Specialist at the Pain/Addiction Clinic for additional medical details or given feedback on study findings. This can only be done once you give us consent to inform your General Practitioner and/or Specialist.

**What will happen to the results of the research study?**

At the end of the study a report will be written. The results of the analysis of this data will then be used to help in a thesis and future peer reviewed publications.

You are able to get a feedback of the results of the questionnaire that you participated in after every study session. You can also ask the Chief Investigator for the results of your sessions at the end of the study.

You will not be identified in any report and/or publication unless you have consented to release such information.

**Who is organising and funding the research?**

This study has no external funding and all necessary expenses are paid by the Centre for Addiction Research and Education Scotland (CARES) endowment fund. We have recently applied for a research grant and as yet we have not received news if we were successful or not. The researchers conducting the study are not getting paid and your GP or other service providers have not been paid for asking you to take part in this study.

**Who has reviewed the study?**

This study was given a favourable ethical opinion for conduct in the NHS by the Tayside Research Ethics Committee.

Thank you for considering taking part or taking time to read this sheet.

Dr Alexander Baldacchino  
Clinical Senior Lecturer in Addictions and Consultant Psychiatrist in Addiction Psychiatry  
Chief Investigator to the research project number: 06/S1401/32
When completed give 1 to the patient/research participant and 1 for the researcher.

The patient/research participant will also be given a signed consent form together with a copy of this information sheet

July 2006
CONSENT FORM

Title of Project: Neuropsychological functioning as a result of chronic exposure to methadone and other opiates (NEMO study).

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the attached participant information sheet carefully. Talk to others about the study if you wish.

This form must be completed and signed by the research participant in the presence of someone with knowledge of the research designated by the Principal Investigator. This may be a doctor, nurse, clinical research assistant or other member of the research team who must countersign the form as witness to the participant’s signature.

Please tick (√) appropriate box

Have you read and understood the Participant Information Sheet? Yes □ No □

Have you been given an opportunity to ask questions and further discuss this study? Yes □ No □

Have you received satisfactory answers to all of your questions? Yes □ No □

Have you now received enough information about this study? Yes □ No □

Who have you spoken to? Dr/Mr/Mrs/Miss ............................................................

Do you understand that your participation is entirely voluntary? Yes □ No □

Do you understand that you are free to withdraw from this study:

• At any time? Yes □ No □

• Without having to give a reason for withdrawing? Yes □ No □

• Without this affecting your present or future medical care? Yes □ No □

Do you agree to any tissue (specify) used in this study being retained for use in future research? Yes □ No □ Not applicable □

Note that it is a statutory requirement that if you agree to take part in the study, your research records and, if necessary, your medical records are available for scrutiny by monitors of the sponsor organisation (which may be the NHS, University or a commercial organisation funding the study) and, in the case of clinical trials of medicines, the UK Regulatory Authorities.

Do you agree to take part in this study? Yes □ No □

Participant’s signature .................................................. Date ..............................

Participant’s name in block capital letters ....................................................................

Telephone contact (Participant) .................................. (Home) ..................(Work)

Signature witnessed by .............................................. Date ..............................

Witness name in block capital letters..............................................................................

THANK YOU for agreeing to take part in this research
Appendix 4
### MINI SCREEN

**Patient Name:**  
**Date of Birth:**

**Date of Interview:**  
*If YES, go to the corresponding M.I.N.I. module*

- Have you been **consistently** depressed or down, most of the day, nearly every day, for the past two weeks?  
  - NO YES → A

- In the past two weeks, have you been much less interested in most things or much less able to enjoy the things you used to enjoy **most of the time**?  
  - NO YES → A

- Have you felt sad, low or depressed **most of the time** for the last two years?  
  - NO YES → B

- In the past month did you think that you would be better off dead or wish you were dead?  
  - NO YES → C

- Have you **ever** had a period of time when you were feeling ‘up’ or ‘high’ or ‘hyper’ or so full of energy or full of yourself that you got into trouble, or that other people thought you were not your usual self? (Do not consider times when you were intoxicated on drugs or alcohol.)  
  - NO YES → D

- Have you **ever** been persistently irritable, for several days, so that you had arguments or verbal or physical fights, or shouted at people outside your family? Have you or others noticed that you have been more irritable or over reacted, compared to other people, even in situations that you felt were justified?  
  - NO YES → D

- Have you, on more than one occasion, had spells or attacks when you suddenly felt anxious, frightened, uncomfortable or uneasy, even in situations where most people would not feel that way? Did the spells surge to a peak, within 10 minutes of starting?  
  - NO YES → E
  
  **Code YES only if the spells peak within 10 minutes.**

- Do you feel anxious or uneasy in places or situations where you might have a panic attack or panic-like symptoms, or where help might not be available or escape might be difficult: like being in a crowd, standing in a line (queue), when you are away from home or alone at home, or when crossing a bridge, traveling in a bus, train or car?  
  - NO YES → F

- In the past **month** were you fearful or embarrassed being watched, being the focus of attention, or fearful of being humiliated? This includes things like speaking in public, eating in public or with others, writing while someone watches, or being in social situations.  
  - NO YES → G

- In the past **month** have you been bothered by recurrent thoughts, impulses, or images that were unwanted, distasteful, inappropriate, intrusive, or distressing? (e.g., the idea that you were dirty, contaminated or had germs, or fear of contaminating others, or fear of harming someone even though you didn’t want to, or fearing you would act on some impulse, or fear or superstitions that you would be responsible for things going wrong, or obsessions with sexual thoughts, images or impulses, or hoarding, collecting, or religious obsessions.)  
  - NO YES → H

Turn Page
If YES, go to the corresponding M.I.N.I. module

- In the past month, did you do something repeatedly without being able to resist doing it, like washing or cleaning excessively, counting or checking things over and over, or repeating, collecting, or arranging things, or other superstitious rituals?
  - NO
  - YES → H

- Have you ever experienced or witnessed or had to deal with an extremely traumatic event that included actual or threatened death or serious injury to you or someone else?
  - NO
  - YES → I

Examples of traumatic events include serious accidents, sexual or physical assault, a terrorist attack, being held hostage, kidnapping, fire, discovering a body, sudden death of someone close to you, war, or natural disaster.

- Did you respond to the trauma with intense fear, helplessness, or horror?
  - NO
  - YES → I

- During the past month, have you re-experienced the event in a distressing way (such as, dreams, intense recollections, flashbacks or physical reactions)?
  - NO
  - YES → J

- In the past 12 months, have you had 3 or more alcoholic drinks within a 3 hour period on 3 or more occasions?
  - NO
  - YES → K

- Now I am going to show you / READ THE LIST BELOW of street drugs or medicines. In the past 12 months, did you take any of these drugs more than once, to get high, to feel better, or to change your mood?

<table>
<thead>
<tr>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>amphetamines</td>
</tr>
<tr>
<td>cocaine</td>
</tr>
<tr>
<td>heroin</td>
</tr>
<tr>
<td>LSD</td>
</tr>
<tr>
<td>inhalants</td>
</tr>
<tr>
<td>THC, marijuana</td>
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<tr>
<td>speed</td>
</tr>
<tr>
<td>crystal meth</td>
</tr>
<tr>
<td>Dexedrine</td>
</tr>
<tr>
<td>Ritalin, diet pills, rush</td>
</tr>
<tr>
<td>crack</td>
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<tr>
<td>morphine, methadone</td>
</tr>
<tr>
<td>PCP, angel dust</td>
</tr>
<tr>
<td>MDA, MDMA</td>
</tr>
<tr>
<td>ecstasy, ketamine</td>
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<tr>
<td>glue</td>
</tr>
<tr>
<td>ether</td>
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<tr>
<td>GHB</td>
</tr>
<tr>
<td>steroids</td>
</tr>
<tr>
<td>cannabis, hashish</td>
</tr>
<tr>
<td>grass</td>
</tr>
<tr>
<td>weed, reefer, barbiturates, Valium, Xanax, Ativan</td>
</tr>
</tbody>
</table>

- How tall are you?
  - 4'9
  - 4'10
  - 4'11
  - 5'0
  - 5'1
  - 5'2
  - 5'3
  - 5'4
  - 5'5
  - 5'6
  - 5'7

- What was your lowest weight in the past 3 months?
  - ___________ lbs

Is patient's weight lower than the threshold corresponding to his/her height?

<table>
<thead>
<tr>
<th>Height (ft in)</th>
<th>4'9</th>
<th>4'10</th>
<th>4'11</th>
<th>5'0</th>
<th>5'1</th>
<th>5'2</th>
<th>5'3</th>
<th>5'4</th>
<th>5'5</th>
<th>5'6</th>
<th>5'7</th>
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<td>87</td>
<td>89</td>
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<td>108</td>
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<tr>
<td>Height (ft in)</td>
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<td>5'9</td>
<td>5'10</td>
<td>5'11</td>
<td>6'0</td>
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<td>6'2</td>
<td>6'3</td>
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<tr>
<td>Weight (lbs)</td>
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<td>118</td>
<td>122</td>
<td>125</td>
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<td>132</td>
<td>136</td>
<td>140</td>
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</table>

- In the past three months, did you have eating binges or times when you ate a very large amount of food within a 2-hour period?
  - NO
  - YES → N

- In the last 3 months, did you have eating binges as often as twice a week?
  - NO
  - YES → N

- Have you worried excessively or been anxious about several things over the past 6 months?
  - NO
  - YES → O
Appendix 5
### National Adult Reading Test (NART)
#### SECOND EDITION

**Word Card**

Hazel E. Nelson

<table>
<thead>
<tr>
<th>Left Column</th>
<th>Right Column</th>
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<tbody>
<tr>
<td>CHORD</td>
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<td>Puerperal</td>
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<tr>
<td>CATACOMB</td>
<td>AVER</td>
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<td>GAUCHE</td>
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<tr>
<td>THYME</td>
<td>TOPIARY</td>
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<td>HEIR</td>
<td>LEVIATHAN</td>
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<td>RADIX</td>
<td>BEATIFY</td>
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<td>PRELATE</td>
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<tr>
<td>GIST</td>
<td>LABILE</td>
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<tr>
<td>GOUGE</td>
<td>CAMPAHILE</td>
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Appendix 6
# Appendix 3

## Graded Naming Test items, ordered in difficulty

<table>
<thead>
<tr>
<th>Object name</th>
<th>Normal sample Percentage correct</th>
<th>Left hemisphere lesion group Percentage correct</th>
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<tbody>
<tr>
<td>1 Kangaroo</td>
<td>100 (100)</td>
<td>76.1</td>
</tr>
<tr>
<td>2 Scarecrow</td>
<td>98 (99)</td>
<td>80.4</td>
</tr>
<tr>
<td>3 Buoy</td>
<td>97 (93)</td>
<td>73.9</td>
</tr>
<tr>
<td>4 Thimble</td>
<td>96 (99)</td>
<td>71.7</td>
</tr>
<tr>
<td>5 Handcuffs</td>
<td>95 (96)</td>
<td>71.7</td>
</tr>
<tr>
<td>6 Tweezers</td>
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<td>69.6</td>
</tr>
<tr>
<td>7 Corkscrew</td>
<td>94 (95)</td>
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<td>8 Sporan</td>
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<tr>
<td>9 Tassel</td>
<td>92 (84)</td>
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<tr>
<td>10 Sundial</td>
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<td>11 Chopsticks</td>
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<td>60.9</td>
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<td>30 Retort</td>
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The figures in brackets are the percentage of correct responses of a second normal sample tested by Doreen Baxter at the Brook Hospital. The order of difficulty for the two normal samples and the difference in competence is likely to be due to an overall lower IQ in the latter population. (Baxter, in preparation.)
Appendix 7
<table>
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<th>Index Score</th>
<th>Immediate Memory</th>
<th>Visuospatial/Constructational</th>
<th>Language</th>
<th>Attention</th>
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Observations:

Confidence Interval %

Percentile

Index Score

Percentile Rank

Total Scale Index Score

<0.1 <0.1 <0.1

100 95 90

85 80 75

70 65 60

55 50 45

40 37 32

25 20 16

9 5 2

1 0.4 0.1

<0.1 <0.1 <0.1

99 99 99

155 150 145

140 135 130

125 120 115

110 105 100

95 90 85

80 75 70

65 60 55

50 45 40

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