The Imperial College Cambridge Manchester (ICCAM) platform study: An experimental medicine platform for evaluating new drugs for relapse prevention in addiction. Part A: Study description

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Abstract

Drug and alcohol dependence are global problems with substantial societal costs. There are few treatments for relapse prevention and therefore a pressing need for further study of brain mechanisms underpinning relapse circuitry. The Imperial College Cambridge Manchester (ICCAM) platform study is an experimental medicine approach to this problem: using functional magnetic resonance imaging (fMRI) techniques and selective pharmacological tools, it aims to explore the neuropharmacology of putative relapse pathways in cocaine, alcohol, opiate dependent, and healthy individuals to inform future drug development. Addiction studies typically involve small samples because of recruitment difficulties and attrition. We established the platform in three centres to assess the feasibility of a multisite approach to address these issues. Pharmacological modulation of reward, impulsivity and emotional reactivity were investigated in a monetary incentive delay task, an inhibitory control task, and an evocative images task, using selective antagonists for μ-opioid, dopamine D3 receptor (DRD3) and neurokinin 1 (NK1) receptors (naltrexone, GSK598809, vofopitant/aprepitant), in a placebo-controlled, randomised, crossover design. In two years, 609 scans were performed, with 155 individuals scanned at baseline. Attrition was low and the majority of individuals were sufficiently motivated to complete all five sessions (n=87). We describe herein the study design, main aims, recruitment numbers, sample characteristics, and explain the test hypotheses and anticipated study outputs.

Keywords

Addiction, functional magnetic resonance imaging, μ-opioid receptor, neurokinin 1 receptor, dopamine D3 receptor

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Introduction

Overall objective

The Imperial College Cambridge Manchester (ICCAM) cluster (http://www.iccam.org.uk) was formed as part of the Medical Research Council (MRC) addiction initiative. As part of this cluster, the ICCAM consortium was formed, initiating a clinical platform study (http://www.bbmh.manchester.ac.uk/ICCAM) which aimed to develop a brain imaging platform to assess candidate brain pathways underpinning addiction and relapse and potential new treatments for this disorder. In this first stage we assessed three pharmacological tools with high-likelihood, theoretically critical, and potentially treatment-targeting mechanisms of action. These drugs were assessed using cutting-edge psychological and functional magnetic resonance imaging (fMRI) paradigms addressing key relapse pathways in human alcohol, heroin and cocaine addiction. Together this research evaluated the delivery of a platform for the study of other candidate drugs for addiction.

In this platform study, the initial target mechanisms were selected based on evidence for a role in modulating processes involved in relapse and comprised: the dopamine D3 receptor (DRD3) targets the reward system; μ-opioid receptors, which mediate the reinforcing effects of opioids and alcohol, and are linked to impulsivity; and neurokinin 1 (NK1) receptors, implicated in emotional processing, stress and reward responses. They were also selected for their potential clinical efficacy given evidence strongly suggests that they are able modulate processes involved in relapse. In addition naltrexone was chosen since it has proven efficacy in relapse prevention for alcohol and opiate addiction and other neuroimaging studies have described its impact on similar tasks in addiction to which we could compare data from the ICCAM platform.

We show that it is possible to implement such a study across multiple neuroimaging sites, and that this 'proof-of-concept' approach can reduce recruitment burden, lead to high-throughput data collection and through the sharing of resources, can ultimately deliver an imaging platform which can be rolled out effectively to other sites for further testing of novel candidate drugs.

Background

The health, social and economic burden of substance abuse is well documented. Illicit drug and alcohol use disorders together contribute to about 20% of the burden of health from mental health disorders and notably the prevalence of alcohol, opioid and cocaine dependence increased between 1990–2010 (Whiteford et al., 2013). In the UK, about 6% of the population are alcohol dependent and 3% drug dependent (National Centre for Social Research and Department of Health Sciences, 2009). Together with alcohol abuse, the cost of alcohol dependence, to the National Health Service (NHS) is about £2.7 billion per year. Only a minority of alcohol dependent individuals are in treatment (~110,000) with about 40,000 leaving treatment abstinent (National Treatment Agency and Department of Health, 2013a).

There are about 300,000 heroin and/or crack users in the UK and although the majority (~200,000) are in contact with treatment services; of the ~60,000 that leave or who were not in treatment only about half were not using either heroin or cocaine (National Treatment Agency and Department of Health, 2013b). Due to the chronic relapsing nature of addiction, for those who do manage to achieve abstinence following treatment, the chances of subsequent relapse are high (Advisory Council on the Misuse of Drugs, 2013), with recovery outcomes estimated to be reliable only after five years of abstinence, after which only a minority will relapse (White, 2012).

Whilst psychological and pharmacological treatments for alcohol, opiate and stimulant dependence are available, there is a large treatment gap since many treated individuals do not achieve abstinence or reduce their alcohol/drug use to healthier levels (Lingford-Hughes et al., 2012).

For alcoholism, treatments such as disulfiram, acamprosate, naltrexone and nalmefene can improve drinking behaviour in a small proportion of individuals and there are as yet no clinically useful predictors of response. Aside from maintenance therapy, there is only one medication, naltrexone, licensed to support abstinence from opiate addiction, but it is taken only by a limited number of patients (Lingford-Hughes et al., 2012). There is no evidence of robust clinical effectiveness for any medication in the treatment of cocaine dependence.

There is therefore a pressing need to develop novel pharmacotherapies across the addictions. We suggest that such a development will arise from an approach derived from knowledge of brain mechanisms related to addiction and relapse. It is hoped that such an approach may also have value in predicting treatment response (Brewer et al., 2008; Moeller et al., 2010a, 2010b).

Neurobiological substrates of addiction and associated pharmacology

Our knowledge about the neurobiological correlates of alcohol and drug addiction has increased considerably over the last decade or so, but relatively little is known about the brain correlates of possible processes leading to relapse and even less about associated pharmacology. Clinically, addicts commonly cite 'craving' as a reason for relapse either to gain a reward or positive reinforcement or to overcome a stress or negative reinforcement (Le Moal, 2009; Piazza and Le Moal, 1998; Verheul et al., 1999), and there is some evidence to support this theory (Marhe et al., 2013; Preston et al., 2009). However studying craving and cue reactivity during an fMRI task in a robust reliable manner can be challenging since it can be harder to induce cue responses in alcoholism and possibly also in longer-term abstinent addicts (see Lingford-Hughes et al., 2006). The aim was also to explore processes which may relate to vulnerability in which inhibitory control, reward sensitivity and emotional processing may be important throughout the natural history of substance use disorder. Whilst craving and cue-response is extremely important in people with current symptoms or recent abstinence, the role of these processes in premorbid vulnerability and long term abstinence is less clear. In addition, cues would have to be substance specific, thus complicating the platform protocol.

A growing body of neurobiological evidence supports a role for impulsivity, deficits in inhibitory control and poor decision-making contributing to relapse (Loree et al., 2014; Noel et al., 2013), with stress being an important mediating factor (Koob and Kreek, 2007; Sinha, 2007). Dysregulation of the reward system,

deficits in executive function and/or sensitisation of brain stress and emotional circuitry are likely to contribute significantly to the establishment and perpetuation of addiction and relapse. The key structural elements governing these three neurobiological circuits include the basal ganglia, ventral prefrontal cortex (PFC) and extended amygdala respectively. Cognitive assays that efficiently exploit the functioning of these brain circuits may provide neurocognitive biomarkers of reward, inhibitory control and emotional processing that are deficient in addiction, and which may represent targets for future drug development against relapse.

Reward circuitry

Much evidence supports a role for the mesolimbic dopamine system in acute positive reinforcing (rewarding) effects of drugs in humans. The ventral striatum (VS) in the basal ganglia is a key part of this system, a region thought to be essential for dopamine-dependent reinforcement. Increased VS activity and increased dopamine levels have been observed to actual or expected drug reinforcement in addicted populations, and to monetary rewards in both addicted and non-addicted populations (Sescousse et al., 2013). During rewarding tasks that activate the ventral striatum, altered function is also seen in key lateral prefrontal cortical and orbitofrontal cortical (OFC) projection sites. These areas are involved in roles such as weighing up benefits versus costs, delay discounting and motivation for rewards (Elliott and Deakin, 2005), and the OFC has been identified as a critical neural substrate for craving in response to drug cues (Chase et al., 2011; Filbey et al., 2008). It has been proposed and increasingly recognised that the dorsal striatum assumes more of a role than the ventral striatum as drug use become habitual and compulsive, such as seen in addicts, (Everitt and Robbins, 2005) however as yet there are few validated fMRI paradigms to characterise such a role of the dorsal striatum (Sjoerds et al., 2013).

While the dopaminergic system is strongly implicated in stimulant and alcohol addiction (e.g. Ersche et al., 2010a; Leyton and Vezina, 2014), the prominence of its role in opioid addiction is less certain (e.g. Watson et al., 2013). Neither agonists nor antagonists of the dopaminergic system have proved clinically valuable to date, but none have specifically targeted the DRD3 which is thought to be the key subtype in alcohol, cocaine and opioid addiction (Heidbreder et al., 2005; Le Foll et al., 2005). For instance, preclinical studies suggest that DRD3 is critically involved in cocaine seeking and relapse of extinguished cocaine-seeking behaviour (Di Ciano et al., 2003; Pilla et al., 1999), and in ethanol preference and consumption after cue-induced reinstatement (Thanos et al., 2005). More recent human addiction studies support these findings. For example, positron emission tomography (PET) studies suggest DRD3 abnormalities in alcohol and cocaine dependence (Erritzoe et al., 2014; Payer et al., 2014), and post mortem studies in cocaine addiction indicate higher density of DRD3 in the ventral striatum (Segal et al., 1997; Staley and Mash, 1996). Furthermore, genetic studies demonstrate an association between DRD3 polymorphisms and opiate (Kuo et al., 2014) and alcohol dependence (Hack et al., 2011).

The role of opioid modulation of reward and the mesolimbic dopaminergic system is also well recognised, particularly for heroin and alcohol, although also for cocaine (Le Merrer et al., 2009). In abstinent alcohol, opioid and cocaine addicts, PET studies demonstrate increased μ-opioid receptor availability which is related to craving (Gorelick et al., 2005; Heinz et al., 2005; Williams et al., 2007, 2009). Naltrexone (opioid receptor antagonist) reduces relapse in alcoholic patients (Srisurapanont and Jarusuraisin, 2005) possibly by reducing alcohol-induced reward (Volpicelli et al., 1995) and it also reduces cue-induced activation of the ventral striatum (Myrick et al., 2008). The μ-opioid receptor polymorphism, A118G OPRM1, is linked to naltrexone efficacy (Anton et al., 2008) and modulating alcohol-induced dopamine levels (11C-raclopride PET) (Ramchandani et al., 2011).

There is growing preclinical evidence to support a key role of substance P (SP) and its NK1 target receptor in addiction (Commons, 2010). Its potential role was revealed by the finding that opioids were no longer rewarding in NK1-deficient mice (Murtra et al., 2000; Ripley et al., 2002) or in the presence of NK1 antagonists (Barbier et al., 2013; Jasmin et al., 2006). NK1 antagonism was also shown to mediate stress-induced reinstatement of alcohol and cocaine seeking (Schank et al., 2011, 2014). In addition, NK1-deficient mice consumed less alcohol (George et al., 2008) and did not show an escalation of alcohol intake after repeated cycles of deprivation or alcohol conditioned place preference (Heilig et al., 2010). Clinically, the NK1 antagonist aprepitant has been shown to reduce VS response in the monetary incentive delay (MID) task in healthy volunteers (Saji et al., 2013),

Together these data suggest that the D3, μ-opioid and NK1 receptors may represent targets for attenuation of reward, with potential for therapeutic utility in addiction and relapse prevention.

Inhibitory control circuitry

Impulsivity is a risk factor for the development of drug dependence. Individuals who engage in drug taking and who are most at risk of dependence typically display higher levels of trait impulsivity than controls (Ersche et al., 2010b, 2013; Verdejo-Garcia et al., 2008), and have deficits in self-control (Nigg et al., 2006). Impairments in inhibitory control, may have a profound impact on one's ability to restrain inappropriate behaviours (Lyvers, 2000), contributing to continued drug use and drug relapse. This may be due to a diminished capacity to recruit pre-frontal networks (George and Koob, 2010). The ventral prefrontal cortex in particular is important for inhibitory control. The lateral PFC, inferior frontal gyrus (IFG) and anterior cingulate cortex (ACC) have been implicated in response inhibition and self-monitoring (Aron et al., 2003, 2014; Carter et al., 1998; Garavan, 2002; Garavan et al., 1999; Hampshire et al., 2010; Watanabe et al., 2002), and are major neural substrates believed to underlie addiction (Goldstein and Volkow, 2002, 2011; Koob and Volkow, 2010; Peoples, 2002). There is evidence that these networks are impaired in addiction (especially to stimulants) and that they may be associated with abstinence and relapse. For example, right IFG abnormalities have been shown to be related to poor motor impulsivity in cocaine addicts and their siblings (Ersche et al., 2012), and the ACC has been found to be hypoactive in drug users during inhibitory control tasks (Forman et al., 2004; Hester and Garavan, 2004; Kaufman et al., 2003). The OFC has also been implicated in inhibitory control and addiction, since sub-regions are conceptualised to moderate impulsive choice,

particularly in the context of value-based decision-making (Haber and Knutson, 2010; Kringelbach and Rolls, 2004).

Inhibitory control networks are sensitive to manipulation by neurotransmitters such as dopamine and opioids. An association between dopamine and impulsivity is increasingly recognised. For instance, dopamine release after alcohol has been associated with impulsivity (Boileau et al., 2003), and blunted striatal dopamine release to amphetamine challenge was reported in subjects with high trait impulsivity, an effect that was modulated by stress (Oswald et al., 2007). Impulsivity has been shown to be related to the density of D3 receptors in the striatum both in animals (Dalley et al., 2007) and in humans (Boileau et al., 2013; Lee et al., 2009; Payer et al., 2014) suggesting that D3 receptors may represent a target for augmenting inhibitory control via their blockade to reduce impulsivity.

A role for the opioid system in impulsivity is also recognised. In mice, knocking out the μ receptor dramatically reduces impulsivity (Olmstead et al., 2009) and acute morphine increases impulsivity (Pattij et al., 2009). Abstinent alcohol, opioid and cocaine addicts have increased μ-opioid receptor availability which is related to craving (Gorelick et al., 2005; Heinz et al., 2005; Williams et al., 2007, 2009). Importantly, the increased availability of these μ-opioid receptors has been reported in regions that are critical for inhibitory control and error monitoring (e.g. ACC; frontal, middle and medial gyri). The μ-opioid receptor, in its dysregulated state in addiction, may therefore represent a neurochemical target for ameliorating cognitive control deficits that may be a core component of substance relapse.

Emotional processing circuitry

The amygdala mediates emotional responses to environmental stimuli. Its nuclei are essential in the acquisition, consolidation, and extinction of conditioned fear responses (LeDoux, 2000). Neuroimaging tasks that engage emotional processing networks demonstrate increased activation of the amygdala and regions of the frontal cortex in response to emotional stimuli. Emotional dysregulation is a key component of addiction (Aguilar de Arcos et al., 2005; Li and Sinha, 2008), and associated brain regions have been shown to be altered in alcohol, cocaine and heroin dependence (Aguilar de Arcos et al., 2008; Asensio et al., 2010; Gilman and Hommer, 2008), and to overlap with those networks activated during exposure to drug cues and distressing imagery, for example in amygdala, anterior cingulate cortex, medial PFC and dorsal striatum (Childress et al., 1999; Grant et al., 1996; Kilts et al., 2001). In cocaine addiction, increased activity in mPFC in response to stress imagery was associated with shorter time to relapse (Sinha and Li, 2007). In abstinent alcohol and cocaine addicts, distressing imagery increased craving and long-term anxiety and contributed to the risk of relapse (Fox et al., 2007; Sinha et al., 2009), possibly by affecting the same neurobehavioural control mechanisms implicated in impulsivity (Li and Sinha, 2008).

A role for SP is strongly implicated in emotional disorders, stress and addiction (Commons, 2010; Ebner et al., 2009). Emotional stressors have been shown to induce SP release in limbic structures such as amygdala and septum, and the magnitude of this effect depends on the severity of the stressor. NK1 receptors are highly expressed in these areas (Heilig et al., 2010), and stress-related behavioural responses are attenuated in NK1-deficient mice and inhibited by selective NK1 antagonists (Ebner et al., 2008; Holmes et al., 2003). Several NK1 antagonists are currently under clinical investigation for use in mood and stress-related disorders (Ebner et al., 2009). Pre-clinical evidence points to a potential role for NK1 antagonists in modulating animal models of addiction (Barbier et al., 2013; Jasmin et al., 2006; Schank et al., 2011). In humans, an NK1 antagonist was shown to suppress spontaneous alcohol cravings and attenuate concomitant cortisol responses to stress in anxious, recently detoxified alcoholics (George et al., 2008), suggesting potential for NK1 antagonists to attenuate stress-related components of addiction and relapse.

Choice of tasks and pharmacological manipulation

We chose to study the neurobiological correlates of reward, inhibitory control and emotional reactivity by using fMRI paradigms. We considered the following issues when selecting the tasks. Due to the nature of the platform we had to limit how many tasks were possible within a single scanning sessions and the total length of the scanning session. We chose tasks that have been previously well characterised in the literature, allowing us to define confidently regions of interest for imaging analysis. Given the complexity of the design, clear regions of interest (ROIs) based on substantial previous research was important. They were as follows:

1. The MID task is an event-related task which provides a measure of reward sensitivity and probe of ventral striatal function, and can distinguish between the appetitive (anticipatory) and consummatory (outcome or receipt) phases of reward processing (Knutson et al., 2001). VS activation during this task has been shown to be altered in alcohol dependence, related to impulsivity (Beck et al., 2009; Wrase et al., 2007), and in stimulant dependence (Bustamante et al., 2014; Jia et al., 2011; Schouw et al., 2013). Furthermore VS activation in response to this task is sensitive to pharmacological modulation by amphetamines (Knutson et al., 2004), olanzapine (Schlagenhauf et al., 2008) and catecholamine depletion (Hasler et al., 2009). Key contrast: win anticipation versus neutral anticipation.

2. The Go No-go (GNG) task provides a measure of inhibitory control, thought to be mediated by prefrontal-striatal circuitry (Morein-Zamir and Robbins, 2014). The event-related design assesses one's ability to suppress actions that are inappropriate (response inhibition), by contrasting infrequent inhibitory responses against an implicit go baseline (Garavan, 2002; Garavan et al., 2003). The rationale for choosing this task was that GNG is conceptually simple and does not place heavy demands on executive processes as many decision-making/gambling tasks do. In our protocol we wanted that all tasks could be the same and completed by any individual. The GNG task elicits widespread brain activation, including ventral PFC, ACC, pre-supplementary motor area (pre-SMA) and frontal regions such as the dorsolateral PFC and IFG, and various occipital and parietal regions (Criaud and Boulinguez, 2013; Simmonds et al., 2008). Response inhibition of this nature has been shown to be

altered in cocaine users (Connolly et al., 2012; Kaufman et al., 2003) and opiate addiction (Forman et al., 2004), and to be modulated by certain dopaminergic gene variants in heavy drinkers (Filbey et al., 2012). Key contrast: successful inhibitions versus implicit go baseline.

3. The Evocative Image Task (EIT) is an emotional processing task used to assess responses to aversive stimuli. The task was developed to probe stress-related emotional reactivity and evokes emotional distress by contrasting negative distressing (aversive) images with neutral images from the International Affective Picture System (IAPS) library. Photographs containing scenes of animate and inanimate objects or scenes were displayed in a block-design, with each block containing either neutral or aversive images of an injurious or threatening nature. In order that the task was not an index of cue reactivity, all images involving alcohol or drugs were not included in the task. The platform was unable to personalise the task; it was therefore comparable across the participants and could be different in all five sessions. The task was set up to serve as a stress-like experience and similar tasks have been shown to engage amygdala reactivity and have been employed to demonstrate altered emotional responses in alcohol, cocaine and heroin dependence (Aguilar de Arcos et al., 2008; Asensio et al., 2010; Gilman and Hommer, 2008) and modulation by NK1 antagonism (George et al., 2008; McCabe et al., 2009). Key contrast: aversive images versus neutral images.

The limited availability of medications for the treatment of addiction, and their lack of pharmacological diversity have made it difficult to investigate novel brain mechanisms that might prove useful for future treatments. We have summarised three pharmacological targets; D3 receptors, μ-opioid receptors and NK1 receptors that have good theoretical links to substance dependence, evidence of potential efficacy and key current or emerging roles in putative relapse processes. More importantly, examples of drugs exist for these targets which can be safely administered to humans. Naltrexone, the μ-opioid receptor antagonist, is a licensed medication for relapse prevention in abstinent opioid and alcohol-dependent patients and there is also evidence that it modulates processes of interest such as reward and impulsive choice (Mitchell et al., 2007; Myrick et al., 2008). It was therefore chosen as a reference medication for the study. The DRD3 antagonist GSK598809 was identified as a viable candidate to treat substance abuse and appetite control disorders (Dodds et al., 2012; Mogg et al., 2012; Mugnaini et al., 2013), and completed several Phase 1 clinical trials. Vofopitant (GR-205171), an example of a highly selective NK1 antagonist, was originally investigated as an alternative anti-emesis treatment (Diemunsch et al., 1999), then in psychiatric disorders such as anxiety, depression and post-traumatic stress disorder (PTSD) (e.g. Mathew et al., 2011), and NK1 antagonism is now a putative target for addiction therapeutics. GSK598809 and Vofopitant are investigational medicinal products that were under clinical investigation by GlaxoSmithKline Ltd (GSK) for their potential as medicinal drug candidates. Unfortunately in 2010 GSK decided to end neuroscience investment within certain fields, and work on GSK598809 and vofopitant was abandoned. The supply of GSK598809 was maintained for this study, however vofopitant expired on 31 July 2012 (approximately halfway through recruitment), the end-date

could not be extended and no new supply was available. Since this was a mechanistic study with considerable scientific rationale for the completion of the NK1 antagonist arm, the decision was taken to switch to aprepitant, an alternative NK1 antagonist and licensed medication, from 1 August 2012 onwards. This enabled completion of the study as originally planned.

Aims

To address the treatment gap in clinical addiction by increasing our knowledge of brain mechanisms of relapse, we established ICCAM, a collaboration between Imperial College London, and the Universities of Cambridge and Manchester to explore and characterise the neural mechanisms of, and treatments for, addiction in cocaine, alcohol, and opiate dependence. The platform aimed to understand more about candidate brain pathways underpinning addiction and potential future relapse and their modulation following a single dose of pharmacological probe and is not a clinical trial. Our platform approach can provide evidence to support further studies of the clinical efficacy, including randomised controlled trials, of medication targeting a particular neurobiology and/or neuropharmacology. Concerning characterising relapse, data from this platform can be linked with substance related outcomes to assess the predictive value of task performance and neural activations during task performance under placebo condition and modulation of the pharmacological challenges. This collaboration was also key to optimise use of existing imaging infrastructure and addiction treatment services to be able to conduct this study in a timely manner that would be required to deliver new treatments.

The primary aims of the ICCAM platform study were to investigate:

1. The effects of alcohol, opioid and cocaine dependence on brain function and structure in comparison with matched healthy controls.
2. The effects of μ-opioid (naltrexone), DRD3 (GSK598809) and NK1 (vofopitant/aprepitant) receptor antagonism on identified brain networks associated with reward sensitivity, inhibitory control and emotional responses.
3. The relationship between clinical, behavioural, genetic and neurocognitive measures and key brain imaging markers of relapse vulnerability identified in dependent individuals.
4. The relationship between secondary measures (e.g. mood, stress, length of dependence, see Table 1) and brain activation in response to medication.
5. The contribution to task response made by each neurotransmitter system and identification of putative adaptation in substance dependence.
6. Whether identified markers of alcohol, cocaine or opiate dependence or relapse vulnerability predict subsequent relapse.

Main hypotheses of platform study

DRD3 receptor antagonism will modulate activity in reward and inhibitory control circuitry, and thus might be useful for preventing relapse, particularly in alcohol and cocaine addicts.
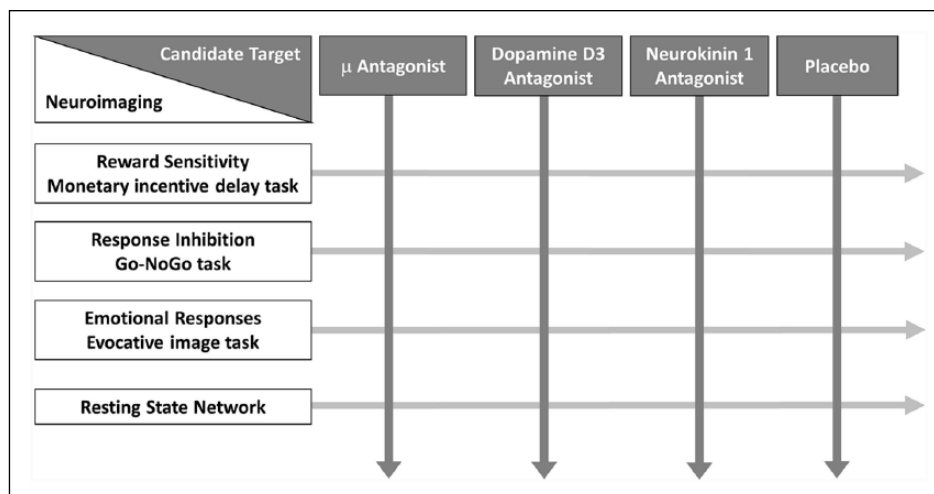
Figure 1. Experimental design; four-way crossover investigating effects of μ-opioid, dopamine D3 receptor and neurokinin 1 antagonism on addiction and relapse pathways in functional magnetic resonance imaging paradigms assessing reward, inhibitory and emotional responses.
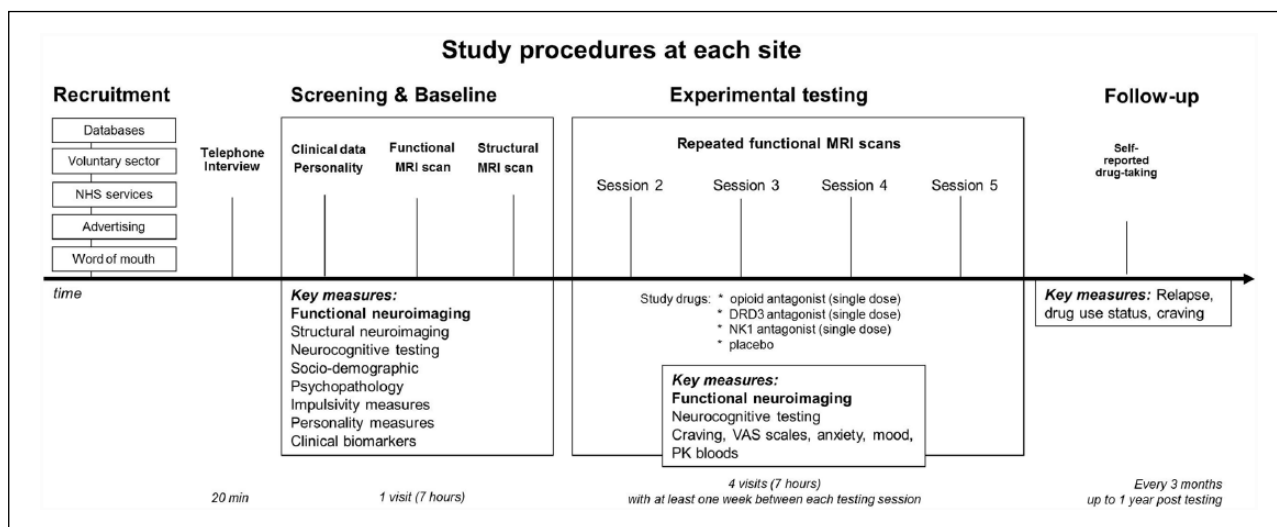

Figure 2. Study procedures carried out at Imperial College, Cambridge University and Manchester University clinical research centres. MRI: magnetic resonance imaging; NHS: National Health Service; VAS: Visual Analogue Scale; PK: pharmacokinetic.

Antagonism of μ-opioid receptors will modulate activation of key regions associated with inhibitory control and reward sensitivity, and thus might be useful for reducing relapse mediated by these mechanisms in alcohol, heroin and cocaine addicts.

NK1 antagonism will attenuate limbic responses to distressing aversive images across addictions, therefore reducing stress-related impulsivity and hence relapse in alcohol, heroin and cocaine addicts.

Study design

In order to test these hypotheses, ICCAM employed a multi-centre, double-blind, placebo-controlled, pseudo-randomised, four-way crossover, follow-up design (Figures 1 and 2).

Since the novelty of the design precluded formal power calculations, we targeted recruitment of *n*=20 per group based on

previous data. Acute pharmacological challenge in fMRI studies with patient groups and healthy volunteers have been shown to require approximately 20 subjects per group using both task-related and resting-state designs, demonstrating significant drug effects as well as significant group-by-drug interactions (Dodds et al., 2012; Ersche et al., 2010a, 2011a; Nielsen et al., 2012).

Participants attended up to five identical functional brain imaging sessions in either London, Cambridge or Manchester. At session one, participants were screened and invited to attend a baseline scan and provide other baseline measures. Eligible participants were invited to attend four further experimental sessions (sessions two to five) at which an identical functional imaging platform was performed, two hours after the acute oral administration of placebo (vitamin C), naltrexone (50 mg), GSK598809 (60 mg), or one of the NK1 receptor antagonists (vofopitant 10 mg or aprepitant 80 mg) in a double-blind, pseudo-randomised

cross-over design. Each session was separated by at least five days. Due to anticipated high attrition rates in the experimental arm, pseudo-randomisation was adopted whereby placebo and naltrexone were always administered in the first two experimental sessions, and GSK598809 and vofopitant/aprepitant in the last two sessions. This was to ensure that data were collected for at least the placebo arm, and therefore mitigate the potential loss of entire data sets for comparison if attrition rates were high. After study completion, participants were followed-up for one year via semi-structured telephone interview every three months, to obtain self-reported measures of relapse and any ongoing drug use.

Study participants

Participants were recruited from local drug and alcohol services within the National Health Service (NHS) and third (voluntary) sector, from healthy volunteer databases, via multimedia advertising including fliers, posters, social media, local newspapers, websites, homepage (http://www.bbmh.manchester.ac.uk/ICCAM/) and via word of mouth. Recruitment was facilitated by the local Mental Health Research Networks (http://www.crn.nihr.ac.uk/mentalhealth) through partnering with NHS and third sector organisations (for full list see acknowledgements). In setting-up and establishing the ICCAM platform we included those addicts who had achieved a stable period in their abstinence to assess whether completing the baseline and four experimental sessions was feasible. Whilst the risk of relapse does decreases with time, it does persist and so does have relevance to those addicts with shorter periods of abstinence.

The clinical test centres were the National Institute for Health Research (NIHR)/Wellcome Trust Imperial Clinical Research Facility, the NIHR/Wellcome Trust Cambridge Clinical Research Facility and the Clinical Trials Unit at Salford Royal NHS Foundation Trust. Magnetic resonance imaging (MRI) scans were performed in the adjoining centres at Imanova Limited (formerly the GSK Clinical Imaging Centre), Manchester Translational Imaging Unit (3T MRI Facility) and Wolfson Brain Imaging Centre respectively.

The study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from West London and Gene Therapy Advisory Committee National Research Ethics Service committee (11/H0707/9) and relevant research governance and Participant Identification Centre (PIC) approvals obtained.

Inclusion criteria

Inclusion criteria were individuals who met *Diagnostic and statistical manual of mental disorders. 4th edition* (DSM-IV) criteria (American Psychiatric Association, 2000) for alcohol, cocaine or opiate dependence and who would be abstinent for at least four weeks prior to the experimental sessions (sessions two to five). There was no upper limit for abstinence length. Healthy controls were recruited who had never met these criteria and where possible, were matched for gender, age and smoking status. All participants were aged 20–64 years, and able to read, comprehend and record information in English.

Exclusion criteria for participation in any session included current use of regular prescription or non-prescription medication that could not be paused for the study duration, or would interfere with study integrity or subject safety (including but not

limited to antipsychotics, anticonvulsants, antidepressants, disulfiram, acamprosate, naltrexone, varenicline), current primary axis I diagnosis, past history of psychosis (unless drug-induced and brief), past history of enduring severe mental illness (e.g. schizophrenia, bipolar affective disorder), other current or past psychiatric history that, in the opinion of the investigator, contraindicated participation. Secondary or lifetime history of depression or anxiety was permitted since this is a very common comorbidity. Other exclusions included a history or presence of a significant neurological diagnosis that may have influenced the outcome or analysis of scan results (including but not limited to stroke, epilepsy, space occupying lesions, multiple sclerosis, Parkinson's disease, vascular dementia, transient ischemic attack, clinically significant head injury), claustrophobia or inability to lie still in the MRI scanner for up to 90 min, presence of a cardiac pacemaker, other electronic device or other MRI contraindication, including pregnancy, as assessed by a standard pre-MRI questionnaire. The healthy control group were free of any Axis I DSM-IV psychiatric diagnoses, other than lifetime history of major depressive disorder or any anxiety disorders and had no history of drug or alcohol dependence (except nicotine).

Additional exclusions for participating in experimental sessions included current or past respiratory, gastrointestinal, hepatic or renal disease or other condition known to interfere with drug absorption, distribution, metabolism or excretion, diabetes, diagnosis of any endocrine disorder including hyperthyroidism and Cushing's syndrome, a screening electrocardiogram (ECG) with a QTcB or QTcF>450 ms or another clinically significant ECG abnormality, any of the following liver function tests abnormalities at screening: alkaline phosphatase>upper limit of normal (ULN), AST, ALT>2×ULN or gamma-glutamyl transferase (GGT)>4×ULN, exposure to an investigational product within 90 days, five half-lives or twice the duration of the biological effect prior to the first experimental session (whichever is longer), exposure to more than three new investigational medicinal products within 12 months prior to the scan, history of sensitivity to any of the study medications, or components thereof, or a history of drug or other allergy that contraindicated participation.

Additional exclusion criteria for participating in any individual session included positive breath alcohol, positive urine drug test (including amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) unless as a result of permitted prescription medication or known interactions and participants were neither in acute withdrawal nor intoxicated. Participants were requested to refrain from cannabis use for at least seven days prior to each session but positive results for cannabinoids were permitted given the long half-life of cannabinoid metabolites.

Screening and baseline session

An initial telephone interview was conducted to identify participants who met basic recruitment criteria. Eligible participants were invited to attend a screening and baseline assessment (session one). At this visit, written informed consent and demographic information were obtained and study eligibility was assessed by way of interview, routine blood samples for clinical chemistry and haematology, breath alcohol, urinary drug screen, pregnancy test, ECG and pre-MRI questionnaire. Participants were interviewed by a psychiatrist in order to assess whether they met DSM-IV criteria for dependence and were currently abstinent. Current dependence

diagnoses were assigned and other lifetime dependence disorders were coded. The Alcohol Use Disorders Identification Test (AUDIT) questionnaire was administered to all participants excluding current alcohol dependent individuals to highlight potentially harmful alcohol use which was further probed by clinical interview. The presence of Axis I psychiatric diagnoses were screened using a summarised version of the Structured Clinical Interview for DSM-IV (MINI, (Sheehan et al., 1998), and a study physician undertook a further psychiatric history, including family history, and performed a medical and physical examination. Current suicidality was assessed using the Columbia Suicide Severity Rating Scale (C-SSRS). Structural brain scan abnormalities were assessed by a neuroradiologist (AW). All psychiatric and substance dependence histories were subsequently reviewed by two psychiatrists (RF, FP) to ensure uniformity of diagnostic thresholds across sites, and any discrepancies arbitrated by a third psychiatrist (AL-H). Eligibility queries were raised at weekly teleconferences with clinical or research representatives from all three sites so that consensus could be reached.

A detailed account of lifetime drug and alcohol use was obtained, using a combination of clinical interview, the The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) scale and drug timeline follow-back, in which measures of drugs ever used, age of first use, age of regular use, days since last use (months abstinent), years of use, frequency and amount of use were recorded for each substance. A comprehensive battery of measures was collected to provide cognitive, behavioural, psychological, and genetic characterisation of each subject (Table 1). Blood samples were obtained for DNA, RNA and protein extraction, to be used for genetic analysis. Neurocognitive tasks that had been validated in addiction populations (Ersche et al., 2006, 2011b; Lawrence et al., 2009; Rogers et al., 1999) were taken from the CANTAB neuropsychological test battery (www.camcog.com, Stop Signal Task, Intra-Extra Dimensional Set Shift, Spatial Working Memory, Rapid Visual Information Processing, Cambridge Gambling Task), with an additional Reinforced Go-Nogo task (Crockett et al., 2009), all administered through the CANTAB suite.

Experimental sessions

At experimental visits (sessions two to five), an eligibility check was performed. Participants' intervening drug use and concomitant medication were checked and participants completed an alcohol breath test, pregnancy test and urine drugs of abuse screen. Participants were then dosed two hours prior to each 60-minute experimental scan session. Bond and Lader visual analogue scale (VAS) rating scales were obtained at six time points throughout the testing day to determine drug effects. The following safety measures were obtained throughout each testing day at several time points relative to dosing: ECG (–20 min, +40 min, +5 h 30 min), blood pressure, oxygen saturation and heart rate (–20 min, +40 min, +4 h, and +5 h 30 min). A blood sample was obtained at approximately three hours post-dose to obtain drug levels. The neurocognitive tasks (see Table 1) were performed at approximately four hours post dose.

Smokers were given the opportunity to smoke as desired up to one hour before the scanning and thus were not in acute nicotine withdrawal. Caffeine intake was permitted in the morning in habitual caffeine users to avoid withdrawal, but restricted thereafter. Participants were provided with a small snack on arrival, prior to drug administration, but food intake after drug administration was restricted until after the scan to ensure that drug absorption was not unduly affected.

Imaging tasks and acquisition

At each of the five visits, participants underwent a 60-minute brain MRI imaging session comprising four functional paradigms in the following order; resting state scan, MID task, GNG task, Evocative Image Task; this order was not varied between visits. Participants familiarised themselves with these tasks outside the scanner first in order to minimize learning effects. Each task was based on previous literature, but adapted such that all functional tasks fitted into a one-hour time slot such that each task could be run twice. Blood-oxygen level dependent (BOLD) fMRI was performed using 3T scanners at each site. At the baseline visit, a high resolution structural scan and a diffusion tensor imaging sequence using 64 directions were additionally acquired for comparison between groups. For the high-resolution structural images, sequences developed specifically for multicentre/cross-manufacturer studies were used. Acquisition parameters and stimulus presentation packages were harmonised to reduce between-site variability. The full details of task descriptions and acquisition parameters are detailed elsewhere (McGonigle et al., in preparation).

The MID task from Knutson et al. (2001) was adapted to fit in the scanning session alongside the other components and was essentially the same in each session (the order of win, loss and neutral varied between sessions). Participants could win or lose money depending upon how quickly they reacted to a target stimulus. The task contained win, loss and neutral trials. For the win trials, participants could win £0.50 if they responded quickly enough, and for the loss trials, participants lost £0.50 if they did not respond quickly enough. For the neutral trials participants neither won nor lost money but they were still required to respond as quickly as possible. The task on-screen presentation comprised a cue indicating trial type, a jittered anticipation period, a target stimulus to which participants had to respond as quickly as possible, then a feedback display indicating win, loss or no gain. The duration of the target stimulus (starting duration 280 ms for win and 240 ms for loss trials) differed depending upon the accuracy of participants: successful responses resulted in a reduction in target stimulus duration of 10 ms, and missed responses resulted in an increase of 10 ms, until the floor and ceiling durations of 150 and 300 ms respectively were reached. The task was designed to give an approximate winnings total of £10.

The GNG task from Garavan et al. (2002) was adapted to fit in the scanning session alongside the other components and essentially was the same in each session (the timing of presentation of 'stop' and 'go' varied between sessions). Participants were presented with a series of letter Xs and letter Ys in alternating pattern, and were asked to respond with a button press as fast as possible to each letter presented (go trials), except when the letter was the same as the previous letter, where the participant had to withhold a response (no-go trials). Each letter was presented on screen for 900 ms, followed by an inter-stimulus interval of 100 ms consisting of a blank screen. No-go trials were presented at unpredictable intervals throughout the task in pseudo-random fashion. Each run contained 250 trials of which 220 were go and 30 were no-go trials.

The Evocative Image Task employed images presented in a block-design paradigm with negative distressing (aversive) and neutral images from the IAPS library (http://csea.phhp.ufl.edu/

Table 1. All secondary measures captured at each centre at baseline, during experimental (drug) sessions, and at follow-up.

Baseline assessment	Rating scale or measure
Drug and alcohol use	
Vulnerability and neurodevelopmental risk markers	Drugs ever used, age first used, age of regular use, category of drug use
Quantity and severity of use	Exposure, number of medically-assisted alcohol detoxifications
Abstinence	Months abstinent
Rating scales	
Emotional states	Beck Depression Inventory (BDI-II), Spielberger Trait Anxiety Index (STAI-T)
Personality traits	Barratt Impulsiveness Scale (BIS-11), (negative) Urgency, (lack of) Perseverance, (lack of) Premeditation, Sensation Seeking, and Positive Urgency (UPPS-P) impulsive behaviour scale, Behavioural Inhibition and Activation Scale (BISBAS), Kirby Delay-discounting questionnaire, Obsessive-Compulsive Inventory (OCI-R), Drug Related Locus of Control (DR-LOC)
Stress-sensitivity	Childhood Trauma Questionnaire (CTQ), Perceived Stress Scale (PSS-14)
Acute craving	Obsessive Compulsive Drug Use Scales (OCDUS) for cocaine, heroin and alcohol, Craving 10 cm Visual Analogue Scale (VAS)
Risk of relapse	Time to Relapse Questionnaire (TRQ)
Drug use	Fagerström test for nicotine dependence, Alcohol Use Disorders Identification Test (AUDIT), ASSIST questionnaire v3.0
Neurocognitive tests	
Response inhibition	Stop Signal Task (CANTAB)
Executive function	Intra-Extra Dimensional Set Shift task (CANTAB)
Working memory	Digit span
Premorbid IQ	Wechsler Test of Adult Reading (WTAR)
Genetic testing	
Genotyping and gene expression	Plasma, buffycoat, whole blood (RNA PAXgene)
Experimental sessions	
Assessment tools	
Emotional states	Beck Depression Inventory (BDI-II), Spielberger State Anxiety Index (STAI-S)
Acute craving	10 cm Visual Analogue Scale (VAS)
Withdrawal	Cocaine Selective Severity Assessment (CSSA), Clinical Institute Withdrawal Assessment for Alcohol (CIWA), Clinical Opiate Withdrawal Scale (COWS)
Subjective drug effects	VAS Bond and Lader scales
Neurocognitive tests	
Frontal lobe and executive dysfunction	Spatial Working Memory (CANTAB)
Sustained attention/vigilance	Rapid Visual Information Processing (CANTAB)
Decision making, risk-taking behaviour	Cambridge Gamble Task (CANTAB)
Motor response inhibition, reward/punishment sensitivity	Reinforced Go-Nogo task
Safety measures	Oxygen saturation, ECG, blood pressure, heart rate, pharmacokinetic blood sample
Follow up telephone interview	
Ongoing drug and alcohol use, outcome profile	Incidence of relapse within 12 months following study completion. Internally developed instrument containing questions relating to relapse circumstances, drug use details, quality of life, social support, occupation

media/iapsmessage.html). The task contained 240 non-drug or alcohol related images consisting of 120 neutral and 120 aversive images such that 48 unique pictures could be presented at each of the five sessions with no images appearing twice. Eight blocks of six images were presented for 5 s each, with each neutral block followed by an aversive one. Between sessions, and between blocks, images were counterbalanced equally for valence and arousal scores, and the order of stimulus type presentation was identical between sessions (injury, threat, human, inanimate).

During the resting state scan, participants were scanned lying quietly at rest for 6 min, eyes closed and were asked to let their mind wander but not to fall asleep.

Drug preparation and pharmacy

GSK supplied the GSK598809 (60 mg) and vofopitant (10 mg) medication. Naltrexone (50 mg) and aprepitant (80 mg) were available through British National Formulary. Drug doses were based on therapeutic dosage (naltrexone 50 mg, aprepitant 80 mg) and doses shown to exhibit >80% occupancy as determined by PET (Bergstrom et al., 2004; Searle et al., 2010). A dose of 80 mg aprepitant was also chosen because it represented an equivalent brain occupancy level to that achieved by vofopitant (10 mg) at the time of scanning. The Tmax for all compounds after oral administration is 1.5–4 h (Majumdar et al., 2006; Te Beek et al.,

2012), therefore participants were dosed two hours prior to each experimental scan session to ensure high plasma concentrations for the duration of the scan and beyond to when the neuropsychological test battery was performed.

Drug preparation, labelling and packaging was performed by UCLH Pharmacy Manufacturing Unit. The placebo was vitamin C (100 mg, supplier: Sigma, manufacturer: Norbrook). Naltrexone (50 mg Nalorex, manufacturer: Bristol-Myers Squibb), GSK598809 (60 mg, supplied by GSK, containing 60 mg of GSK598809B free base as the L-tartrate sesquihydrate salt GSK598809D), vofopitant (GR205171, 10 mg containing GR205171X as the dihydrochloride salt, GR205171A, supplied by GSK) and aprepitant (80 mg Emend, supplier MSD) were prepared and packaged according to Investigational Medicinal Product guidelines. Each medication was supplied in identical white opaque bottles and administered by independent nursing staff, such that both researcher and participant remained blinded.

Data management, storage and analysis

Full details of fMRI data capture, management, analysis and storage will appear elsewhere (McGonigle et al., in preparation). The CANTAB tasks and the majority of baseline questionnaires were captured and stored electronically. All hand-written data collected within case report forms (CRFs) were subsequently managed using REDCap (Research Electronic Data Capture) tools hosted at the University of Cambridge (Harris et al., 2009). REDCap is a secure, web-based application designed to support data capture for research studies, providing: (a) an intuitive interface for validated data entry; (b) audit trails for tracking data manipulation and export procedures; (c) automated export procedures for seamless data downloads to common statistical packages; and (d) procedures for importing data from external sources. It also provides fully-transparent data entry logging and methods for data cleaning and quality control to be implemented.

Statistical methods employed herein were the one-way analysis of variance (ANOVA) with Bonferroni post-hoc test for continuous variables and chi squared test for categorical variables, available in IBM SPSS Statistics version 21.

Results

Here, we present the outcome of the recruitment strategy and summary characteristics of the recruited sample. Data analysis will be presented elsewhere.

Recruitment numbers

A total of 190 people consented to take part in the study across all three sites between October 2011–September 2013 (Figure 3). Of these, 176 underwent the 90-minute baseline scan session, and 155 (82%) were eligible for inclusion in baseline analyses. Eligible participants (*n*=136) were further invited to complete the experimental sessions (Figure 4). Altogether 104 participants were randomised and 87 participants completed the whole study design (baseline scan plus placebo, naltrexone, GSK598809 and vofopitant/aprepitant scans). Of the non-completers (*n*=17), six participants completed at least three sessions (*n*=5 completed a placebo and a naltrexone scan and *n*=1 completed a placebo,
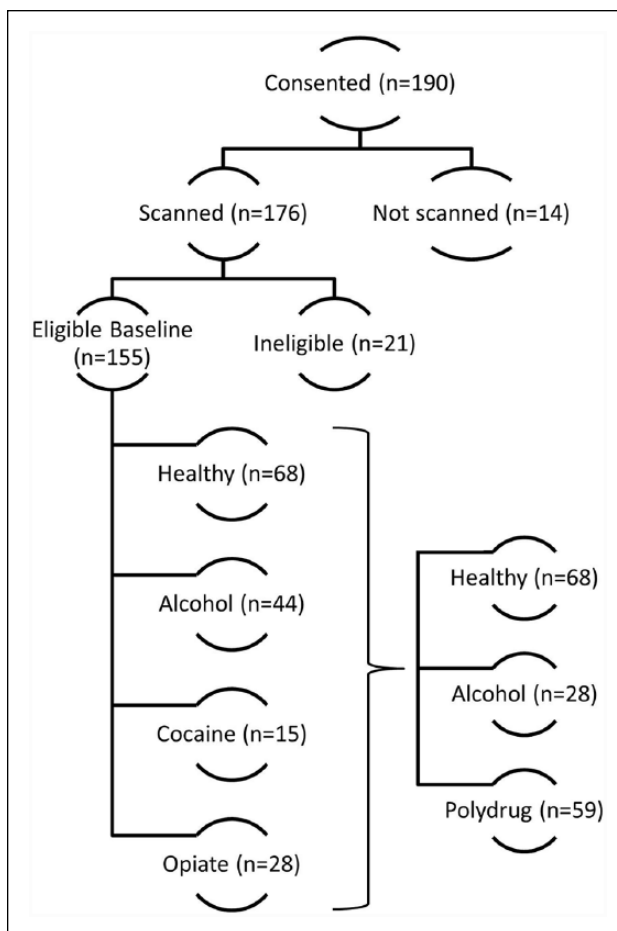

Figure 3. Recruitment tree diagram for baseline analysis. Drug groups are shown according to 'primary' dependence diagnosis (left panel) and overall dependence diagnoses, excluding nicotine (right panel). There were 12 participants included in the polydrug group who were only dependent on cocaine or opiates but were included due to sub-threshold dependence (harmful or heavy use) to at least one other substance.

naltrexone and GSK598809 scan) and these participants can also be included in analyses for those particular drug comparisons. For the NK1 antagonist arm, 26 participants received vofopitant, and 58 received aprepitant.

Of the 155 people eligible for inclusion in baseline analyses, 68 were healthy controls, and 87 had a diagnosis of alcohol, cocaine and/or opiate dependence. Of the 87 completers, 35 were healthy controls, and 52 had a diagnosis of alcohol, cocaine and/or opiate dependence.

Drug dependence groups

Determining the groups and their alcohol/drug use was a critical foundation for the ICCAM platform. The original aim was to recruit three distinct groups of addicts: alcohol, opiate and cocaine-dependent. The outcome of this grouping, according to a participant's 'primary' drug of dependence, is shown in Figures 3 and 4 (left hand panel). Of those eligible who completed the baseline session (*n*=87), 44 had alcohol, 15 had cocaine and 28 had opiate dependence as their primary dependence (Figure 3).
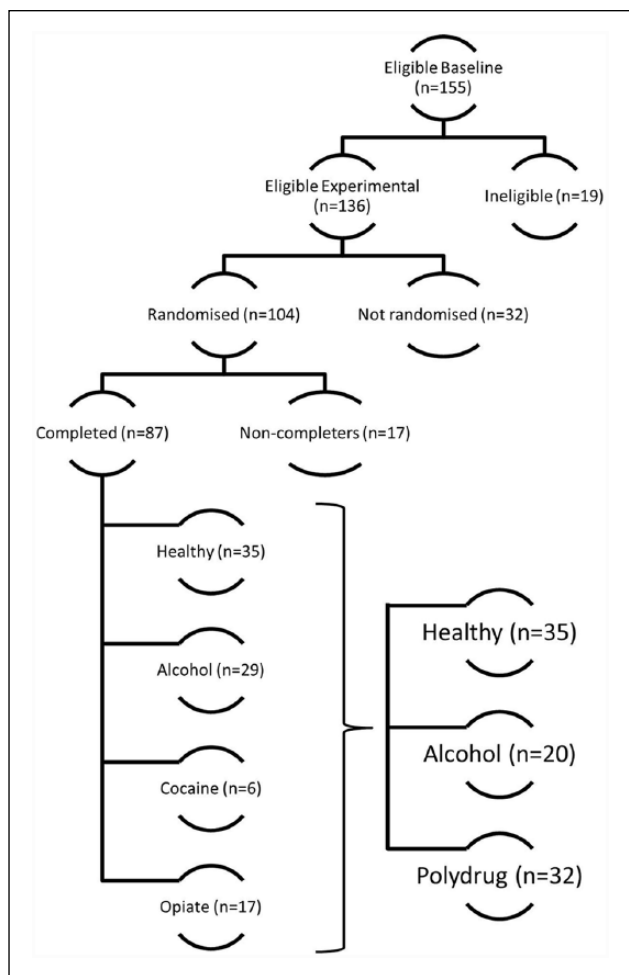
Figure 4. Recruitment tree diagram for experimental sessions. Drug groups are shown according to 'primary' dependence diagnosis (left panel) and overall dependence diagnoses, excluding nicotine (right panel). There were six participants included in the polydrug group that completed the study who were only dependent on cocaine or opiates but were included in this group due to sub-threshold dependence (harmful or heavy use) to at least one other substance.

Of those who completed all five sessions, (*n*=52), 29 had alcohol, 17 had opiate and only six had cocaine as their primary dependence (Figure 4). However, classification of drug dependence according to primary dependence *only* was not sufficient to adequately define the sample for several important reasons. Dependency on one drug was not representative of our highly co-dependent sample, particularly in opiate and cocaine dependent subjects (Table 2, Figure 5). In line with what is observed in clinical practice, a large proportion of the sample consisted of addicts with a history of multiple substance abuse, many of which reached dependence thresholds at one time or another. In addition, the method for determining what might constitute a 'primary' dependence appeared to differ across sites, and was not always straightforward, for example where two drugs were always used together (e.g. crack cocaine and heroin, alcohol and cocaine). Table 2 shows the frequencies for lifetime diagnosis of drug and alcohol addiction in our sample. Only substances meeting criteria for dependence are shown. The overlap of alcohol,

Table 2. Summary of lifetime drug and alcohol dependence frequencies for all those with drug and/or alcohol dependence (*n*=87).

Lifetime diagnosis of dependence	Baseline (*n*=87) (%)	Completers (*n*=52) (%)
Alcohol	64 (74%)	41 (79%)
Cocaine	45 (52%)	25 (48%)
Opiate	39 (45%)	21 (40%)
Other dependence	21 (24%)[a]	11 (21%)[b]
Overall dependence groups for analyses		
Alcohol *only*	28 (32%)	20 (38%)
Polydrug	59 (68%)	32 (62%)

Completers attended all five sessions. Data exclude nicotine dependence. The alcohol *only* group only had alcohol dependence. The polydrug group had two or more dependencies but also included those participants who had only one dependence on either cocaine or opiates but who had additional heavy or harmful use of at least one other substance, so were clinically more like polydrug users.
[a]Amphetamine (9), benzodiazepine (11), ketamine (1), gamma hydroxybutyric acid (GHB) (1), inhalants (1).
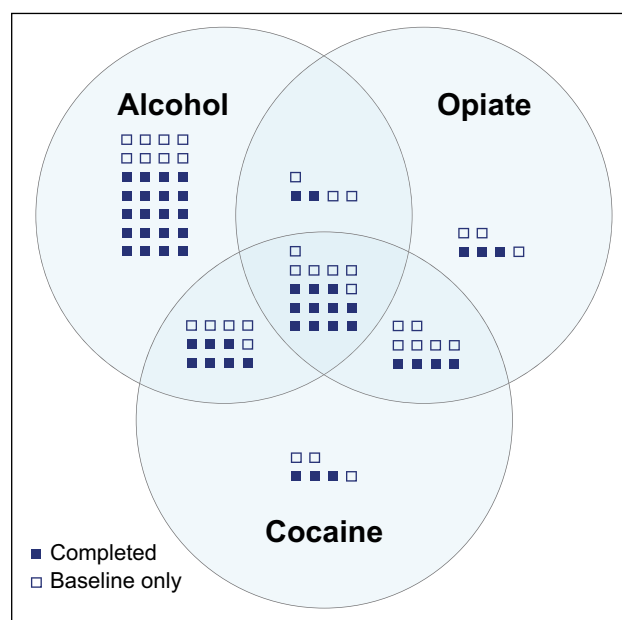[b]Amphetamine (5), benzodiazepine (5), GHB (1), inhalants (1).

Figure 5. Venn diagram shows incidence of lifetime dependence between alcohol, cocaine and opiates in our sample. Open squares represent participants who completed a baseline scan, and closed squares represent participants who completed all five sessions, including baseline. Data exclude nicotine dependence.
NB only co-dependencies between alcohol, cocaine and opiates are shown (*n*=84). Other drug co-dependencies are not (*n*=3); one participant with alcohol and amphetamine dependence, one with opiate and benzodiazepine dependence, and one with alcohol, amphetamine and benzodiazepine dependence. See Table 2 for incidence of lifetime co-dependence with other drugs.

cocaine and opiate dependency across the sample is depicted in Figure 5. It can be seen that of the total sample of drug and alcohol addicts (*n*=87), 74% had a lifetime history of alcohol addiction, 52% of cocaine addiction, and 45% of opiate addiction. 24% had a lifetime history of an addiction to additional substances such as amphetamines and benzodiazepines such that overall, 55% had a history of stimulant dependence. A further

Table 3. Imperial College Cambridge Manchester (ICCAM) demographic variables – all completers (*n*=87).

	Healthy control group (H), *n*=35	Alcohol group (A), *n*=20	Polydrug group (P), *n*=32	Group comparisons
Age (years)	41.2±9.1	45.4±9.0	38.5±8.0	F=3.92, df 2,84, p=0.024, P<A
Age range (years)	21–64	30–60	25–58	
Gender ratio M:F	27:8 (77%:23%)	16:4 (80%:20%)	25:7 (78%:22%)	ns
Years of education	13.5±2.7	12.5±2.9	11.0±2.1	F=8.02, df 2,84, p=0.001, H>P
Current smokers, *n* (%)	20 (57.1)	14 (70)	26 (81.3)	ns
Verbal intelligence WTAR IQ adjusted score	105.9±10.1	104.9±8.4	98.5±11.6	F=4.73, df 2,84, p=0.011, H>P
Body mass index (BMI)	26.5±3.7	25.6±4.5	25.5±3.8	ns
Current psychiatric diagnosis, *n* (%)	0	3 (15)	1 (3.1)	–
Past psychiatric diagnosis, *n* (%)	8 (22.9)	10 (50)	13 (40.6)	ns
Family history of dependence, *n* (%)	3 (8.6)	7 (35)	16 (50)	X^2=14.017, p=0.001
Family history of psychiatric disorder, *n* (%)	8 (22.9)	7 (35)	9 (28.1)	ns
AUDIT (total score)	4.9±3.1	–	6.7±3.3 (*n*=12)	ns

Data are mean ± standard deviation unless otherwise stated. AUDIT: Alcohol Use Disorders Identification Test; ns: not significant; SD: standard deviation; WTAR: Wechsler Test of Adult Reading.

proportion of the sample had a lifetime history of abusing additional substances at levels that met criteria for harmful or heavy use (data not shown). For some substances of abuse, such as benzodiazepines and, particularly, cannabis, it was often difficult to determine dependence due to patterns of co-existing use, prescription use and an absence of obvious harm from *specific* use of these substances. In these instances, such use was included in the heavy/harmful category, and not coded as dependence.

When lifetime dependence was taken into account, two distinct groups emerged (Table 2 and Figures 3 and 4); alcohol addicts (*n*=28) meeting criteria for lifetime diagnosis for alcohol dependence *only* (excluding nicotine), and poly-drug addicts (*n*=47), defined as having had a lifetime diagnosis of dependence to two or more substances (excluding nicotine). A further 12 participants were included in the polydrug group for the purposes of demographics and further analysis. These participants had only used one substance to levels meeting dependence criteria, either cocaine or opiate dependence (*n*=6 cocaine, *n*=6 opiate, excluding nicotine). However, their overall drug use profile was clinically much more like that of the polydrug group because each one also reported heavy or harmful use of at least one other substance of abuse. Given that the majority of addicts smoke tobacco, rather than include nicotine as another drug, participants were matched with controls for smoking status in the experimental arm of the study (Table 3). Its impact will be explored elsewhere in the platform.

Attrition

Attrition rates were lower than anticipated. We had predicted that the drop-out rate during the experimental sessions would be high, primarily due to lapses and/or relapse or an inability to complete five sessions, hence the reason for implementing the pseudo-randomisation. However individuals in our sample, in particular the drug and alcohol dependent individuals, were generally motivated and reliable, and the majority remained abstinent for the duration of the study. Of those who consented,

82% (155/190) completed the baseline session and were eligible for inclusion in the analysis, and 84% (87/104) of those who were randomised completed the remaining four sessions (Figures 3 and 4). The majority of attrition occurred between the baseline visit and randomisation, due to ineligibility (*n*=19) or loss of interest (mainly healthy volunteers, *n*=16). The key to the low attrition may therefore have been the structured and detailed telephone screening carried out by competent researchers with a good knowledge of addiction. In addition, extended abstinence lengths may have been a factor in determining low attrition rates. Addiction studies in abstinent users typically recruit participants who have shorter duration of abstinence than that found in our sample: in those completers with alcohol dependence *only*, average abstinence length from alcohol (mean±standard deviation (SD)) at the baseline session was 13.9±19.0 months. In the polydrug group completers, those with primarily alcohol, cocaine and opiate dependence were abstinent for 12.3±11.8, 10.7±9.20 and 31.4±45.5 months from alcohol, cocaine and opiates respectively. The longer abstinence from opiates may reflect participants' need for longer recovery periods before considering taking part in research, or them having shifted to other drugs; many in this group have shorter abstinences from dependent use of other drugs.

Failures to scan and exclusions from the baseline analyses were due to positive drug urine screens at baseline (*n*=5), excessive drug or alcohol use (in healthy controls, *n*=13), failure to maintain abstinence (*n*=2), claustrophobia (*n*=2), psychiatric comorbidity (*n*=4), body mass index (BMI)>35 (*n*=2), neurological abnormality (*n*=1), other (*n*=6). Exclusions from experimental sessions were due to abnormal ECGs (*n*=8), deranged blood results or failure to provide blood samples (*n*=7), positive drug screens (*n*=2), other medical exclusions (*n*=2). Reasons for non-randomisation were lost interest (*n*=19), lost contact (*n*=3), too busy (*n*=3), other (*n*=7). Reasons for non-completion were relapse or positive drug screen (*n*=4), too busy (*n*=3), lost interest (*n*=2), moved away (*n*=2), lost contact (*n*=1), other (*n*=5).

Table 4. Imperial College Cambridge Manchester (ICCAM) demographic variables – all baseline (*n*=155).

	Healthy control group (H), *n*=68	Alcohol group (A), *n*=28	Polydrug group (P), *n*=59	Group comparisons
Age (years)	39.8±10.1	46.3±8.7	39.1±8.6	F=6.34, df 2,152, p=0.002, H<A, P<A
Age range (years)	21–64	30–60	25–64	
Gender ratio M:F	50:18 (74%:26%)	22:6 (79%:21%)	49:10 (83%:17%)	ns
Years of education (mean, SD)	14.2±2.7	12.4±2.8	11.4±2.2	F=19.0, df 2,152, p=0.000, H>A, H>P
Current smokers, *n* (%)	32 (47.1)	20 (71.4)	45 (76.3)	X^2=12.655, p=0.002
Verbal intelligence WTAR IQ adjusted score	109.0±8.6	105.2±7.7	99.3±10.9	F=16.8, df 2,152, p=0.00, H>P, A>P
Body mass index (BMI)	25.4±3.9	25.8±4.6	25.7±4.2	ns
Current psychiatric diagnosis, *n* (%)	0 (0)	3 (10.7)	1 (1.7)	–
Past psychiatric diagnosis, *n* (%)	15 (22.1)	15 (53.6)	26 (44.1)	X^2=11.137, p=0.004
Family history of dependence, *n* (%)	5 (7.3)	9 (32.1)	28 (47.5)	X^2=25.259, p=0.000
Family history of psychiatric disorder (*n*)	14 (20.6)	7 (25.0)	19 (32.2)	–
AUDIT (total score)	4.8±2.9	–	6.0±3.7 (*n*=23)	ns

AUDIT: Alcohol Use Disorders Identification Test; ns: not significant; SD: standard deviation; WTAR: Wechsler Test of Adult Reading.

Demographics

For the completers of all experimental sessions (*n*=87), groups were well matched within and between sites for age, gender and smoking status (Table 3), which will enable comparisons of controls versus alcohol and controls versus polydrug groups to be made without further controlling for these variables. Due to the polydrug group being significantly younger than the alcohol group, three-way comparisons may be more problematic. For baseline analyses (*n*=155), groups were less well matched overall with significant effects of age (alcoholics were significantly older than control and polydrug groups) and smoking, (Table 4). Careful matching of groups could be conducted in further analyses, and consideration given to these variables in data interpretation. In other measures, years of education and premorbid IQ (Wechsler Test of Adult Reading (WTAR) IQ adjusted score) were significantly lower in the polydrug group compared with controls in both the baseline and completer group comparisons, and were lower in alcoholics in the baseline group comparison. This is not unexpected as these factors are predictors of addiction, and are commonly found in addiction disorders.

Benefits and challenges of ICCAM platform design

The platform is designed to allow the rapid testing of multiple compounds on several tasks of relevance to relapse, in addiction populations. Imaging at multiple centres in parallel accelerates the rate at which a study of this size may be completed, while also increasing the potential recruitment pool. Over the two years of recruitment and data collection, 609 imaging sessions were completed across the three centres giving a rate of over one scan per weekday.

The obvious advantages of multisite studies were realised through the sharing of expertise, infrastructure and capacity, making use of the best clinical research facilities, MRI scanners and combining three groups with experience of recruiting addiction populations across a diverse geographical area. These centres contain large comprehensive addiction services with research-facilitative clinicians who are experienced in supporting research studies. A dedicated team of researchers is pre-requisite in making a platform study work. Despite ethical approval given for all the sites, the subsequent local Research & Development (R&D) approval and governance processes differed in the three sites resulting in further challenges in standardising procedures and delays. Overcoming such issues will need consideration and addressing as platform studies have recently been recommended as an efficient strategy to evaluate multiple treatments (Berry et al., 2015). Widening the recruitment area should reduce the likelihood of recruitment bias towards particular types or severity of addictions, with the hope that results are more likely to reflect the whole treatment population. Local mental health research networks were also utilised through the NIHR adoption scheme (http://www.crn.nihr.ac.uk/), which provided Clinical Studies Officers to facilitate face to face recruitment on-site.

However, challenges in recruitment were encountered despite sharing resources. Addiction services in the UK are undergoing huge changes, with many inpatient services becoming increasingly community-based. NHS services are increasingly shared with the third sector with multiple reconfigurations and retendering processes underway. The burden caused by the tendering process adds uncertainty for service providers, diverts resources and reduces the drive to participate in research. Identifying referral sources for potential recruits was therefore challenging, and required good links to addiction services to be maintained and developed. Knowledge of service providers, service users and user champions was essential to get the study adopted by these organisations to allow recruiters to make appropriate contacts. Although NHS services are well placed to support research participation through various schemes, third sector organisations are less so. This may be an increasing problem across mental health services in the UK as contracts are awarded to external providers. Once the study commenced, it was found that face-to-face introductions to the project at user group meetings, and word of mouth were the most successful recruitment methods for addicts. Recruitment of controls was also problematic due to the time commitment required for five

whole-day sessions, and the need for smokers. A multi-faceted approach however proved adequate for recruitment. Overall recruitment goals were therefore met, but the emphasis on drug of dependence shifted due to co-dependence and multiple lifetime dependencies, and this should be further considered in future studies especially if interest is in one drug of dependence only.

The low attrition rates are encouraging, since the anticipated drop-out rate led to the early decision to bias the randomisation such that placebo and naltrexone were always included within the first two experimental sessions. This ensured that at least one entire dataset with a placebo comparator was achieved with the platform. In the event, attrition after commencing the experimental arm was relatively low and thus future studies could move to a fully balanced, four-way crossover design with some confidence that the vast majority of participants would complete the study.

Conclusions and projected outcomes

The ICCAM platform is a new experimental medicine approach. The aim was to develop a platform using known agents with good theoretical links to addiction and some indication of efficacy, using tasks that tap into pathways implicated in reward processing, response inhibition and exposure to aversive images, then expand this out to include novel compounds, with the idea that the relationships between drug actions on the three tasks will enable predictions of outcomes in clinical trials. Forthcoming results will be published detailing the findings with the drugs studied to demonstrate the utility of the platform approach for assessing the effects of existing compounds on our candidate mechanisms. We selected addicts who had achieved some stability in their abstinence and without current clinically significant comorbidities to enable us to establish the platform since if they were not able to complete all or part of the protocol, it was highly unlikely that those less stable or compliant would be able to do so. Other publications will describe use of this platform platform in addicts with shorter duration of abstinence. We will utilise this platform to characterise comorbidities such as alcohol and depression and their relative contribution to any apparent dysregulation.

In practical terms the ICCAM platform study has been a success; we have successfully set up a platform from which we can investigate these brain mechanisms and their pharmacological modulation. Added value has already come from the use of the platform in other areas of addiction including gambling and nicotine addiction where studies are ongoing within the consortium and associated addiction cluster. As such, the platform can now be used for future studies, both within academia and industry. The tasks and other aspects of the platform are available for other researchers to use and those wishing to do so should apply to the corresponding author, David Nutt for details. Added value may also come from the subsequent evaluation of parallel animal studies that have been conducted, with a view to using preclinical models to map human relapse pathways and utilise forward and back translation to enable more confident exploitation of current preclinical models, and inform future research areas for human drug development (e.g. Dalley et al., 2007).

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