

# **Neurocognitive Function in Substance Dependence**

A thesis submitted to the University of Manchester for the degree of  
Doctor of Philosophy in the Faculty of Medical and Human Sciences

2015

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## List of Abbreviations

<b>AbD</b>	abstinent substance dependent
<b>ACC</b>	anterior cingulate cortex
<b>ACPC</b>	anterior commissure - posterior commissure
<b>ADHD</b>	Attention Deficit/Hyperactivity Disorder
<b>AIC</b>	Akaike information criterion
<b>ANOVA</b>	analysis of variance
<b>APA</b>	Active-Passive Avoidance Task
<b>ASRC</b>	Alcohol Stimulus-Response Compatibility Task
<b>BART</b>	Balloon Analogue Risk-Taking task
<b>BAS</b>	Behaviour Activation System
<b>BDI-II</b>	Beck Depression Inventory II
<b>BFI</b>	Big Five Inventory
<b>BIC</b>	Bayesian information criterion
<b>BIS</b>	Behaviour Inhibition System
<b>BIS/BAS</b>	Behaviour Inhibition/Activation System
<b>BIS-11</b>	Barratt Impulsiveness Scale 11
<b>BOLD</b>	blood oxygen level dependent
<b>CNS</b>	central nervous system
<b>CRF</b>	corticotropin-releasing factor
<b>CTQ</b>	Childhood Trauma Questionnaire
<b>dIPFC</b>	dorsolateral prefrontal cortex
<b>dmPFC</b>	dorsal medial prefrontal cortex
<b>DSM-IV</b>	Diagnostic and Statistical Manual for Mental Disorders
<b>EIT</b>	Evocative Images Task
<b>EPI</b>	Echo-planar imaging
<b>fMRI</b>	functional magnetic resonance imaging
<b>FWE</b>	family wise error
<b>GABA</b>	gamma-aminobutyric acid
<b>GNG</b>	Go/No-Go
<b>IAPS</b>	International Affective Picture System
<b>ICCAM</b>	Imperial College, Cambridge and Manchester
<b>IED</b>	Intra-Extra Dimensional Set Shift
<b>IFG</b>	inferior frontal gyrus
<b>IGT</b>	Iowa Gambling Task
<b>IRISA</b>	impaired Response Inhibition and Saliency Attribution
<b>IST</b>	Information Sampling Task
<b>LCCA</b>	Latent Class Cluster Analysis
<b>MANOVA</b>	multivariate analysis of variance
<b>MFF</b>	Matching Familiar Figures task
<b>MIST</b>	Montreal Imaging Stress Task
<b>mPFC</b>	medial prefrontal cortex
<b>MPH</b>	methylphenidate
<b>MR</b>	magnetic resonance

<b>MRI</b>	magnetic resonance imaging
<b>NAcc</b>	nucleus accumbens
<b>NIHR</b>	National Institute for Health Research
<b>OCD</b>	Obsessive Compulsive Disorder
<b>OCDUS</b>	Obsessive-Compulsive Drug Use Scale
<b>OCI-R</b>	Obsessive-Compulsive Inventory
<b>OFC</b>	orbitofrontal cortex
<b>PFC</b>	prefrontal cortex
<b>preSMA</b>	pre-supplementary motor area
<b>PSS-14</b>	Perceived Stress Scale
<b>PTSD</b>	Post-Traumatic Stress Disorder
<b>REC</b>	Research Ethics Committee
<b>ROI</b>	region of interest
<b>RT</b>	reaction time
<b>SCID</b>	Structured Clinical Interview for DSM-IV
<b>SD</b>	standard deviation
<b>SIT</b>	Stress Induction Task
<b>SPM</b>	Statistical Parametric Mapping
<b>SPSS</b>	Statistical Package for Social Sciences
<b>ssABIC</b>	sample-size-adjusted Bayesian information criterion
<b>SSRT</b>	Stop-Signal Reaction Time
<b>SSS</b>	Sensation Seeking Scale
<b>SST</b>	Stop Signal Task
<b>STAI</b>	Spielberger State/Trait Anxiety Index
<b>SVC</b>	small volume correction
<b>TE</b>	echo time
<b>TR</b>	repetition time
<b>TSST</b>	Trier Social Stress Test
<b>UPPS-P</b>	UPPS Impulsive Behaviour Scale
<b>US</b>	unconditioned stimulus
<b>VAS</b>	Visual Analogue Scale
<b>vmPFC</b>	ventromedial prefrontal cortex
<b>WCST</b>	Wisconsin Card Sorting Task
<b>WS</b>	warning stimuli
<b>3T</b>	3 tesla
<b>5CSRTT</b>	Five Choice Serial Reaction Time Task

## Abstract

The University of Manchester, Eleanor Taylor, Doctor of Philosophy (PhD)  
Thesis Title: Neurocognitive Function in Substance Dependence, September 2015

**Background:** Changes in neuropsychological and emotional systems are associated with substance dependence and reduce the chance of successfully maintaining abstinence after treatment. Impulsivity is strongly associated with substance dependence and is a risk factor for development, a consequence of excessive use and a marker for poor treatment outcomes. The focus of this thesis is impulsivity, as well as emotional and motivational factors, in the context of harmful substance use and dependence. The thesis is formed of two parts; the first (Studies 1 and 2) focusses on the multi-faceted role of impulsivity in substance dependence. The second part (Studies 3 and 4) investigates negative reinforcement and automatic approach and avoidance behaviour in heavy alcohol use.

**Study 1:** A multi-dimensional investigation of impulsivity in abstinent substance dependent individuals using three complementary techniques: self-report, behavioural and neural measures. Results suggest that self-report measures of impulsivity are more sensitive in abstinent individuals than behavioural or fMRI measures.

**Study 2:** An alternative approach to the classification of substance dependent individuals; using Latent Profile Analysis, abstinent substance dependent participants from Study 1 were regrouped based on personality risk factors rather than primary dependence. Important differences were detected within a previously undifferentiated group of abstinent substance dependent individuals; notably the greater incidence of childhood adversity and stimulant dependence history in one group, while the other did not differ from controls.

**Study 3:** A behavioural investigation of the effect of stress induction on automatic approach and avoidance in heavy drinking individuals compared to light drinkers. Results indicated no differential effect of stress. These findings may suggest that the behaviour of older, more established heavy drinkers is comparable to that of alcohol dependent participants and reflects an advanced stage along the spectrum of alcohol use and dependence.

**Study 4:** An fMRI investigation conducted on a subset of participants from Study 3 using neuroimaging paradigms to assess automatic approach and avoidance behaviour in heavy drinking individuals compared to light drinkers. Results can be interpreted to suggest that heavy drinkers approach alcohol in a less controlled manner than light drinkers, and that trait anxiety may be involved in the extent of avoidance behaviour.

**Conclusions:** Although there are more questions raised by this research than are answered, some general conclusions can be drawn. Specifically, impulsivity measures need to be made more appropriate to all stages of substance use and dependence. Furthermore I propose a longitudinal theory of substance use and dependence with different neurocognitive profiles at each stage, as well as individual differences throughout the trajectory. This has implications for future addiction research that should enable better understanding for the benefit of clinical practice and treatment of substance related disorders.



## **Declaration**

No portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.



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## Acknowledgements

The most important people to thank are my supervisors, Rebecca Elliott and Bill Deakin. I am still surprised I managed to convince them to take me on as a PhD student and I am very aware of how fortunate I have been to work with two incredible people, whose good company far exceeds their daunting brilliance and expertise. Rebecca in particular has been the most excellent mentor and role model, providing support in all manner of ways that range from academic advice to consolatory Eccles cakes. I owe her more than she knows.

I would also like to thank all those involved in the ICCAM Platform Study. Although far from an easy ride, it has been an invaluable experience that, should I have my time over, I would definitely choose again. Thank you especially to Anna Murphy who showed me the ropes and has been a great support since, not to mention a good friend.

My gratitude also goes to the wonderful radiographers as well as all the staff at the Clinical Research Facilities at the Central Manchester and Salford Royal Hospitals, without whom this research could not have been completed. Also, thank you to Shane McKie for his patient SPM tutorship and everyone else in the magnificent Neuroscience & Psychiatry Unit. In particular, I would like to thank Martyn Mcfarquhar; a genius and generally wonderful person. Perhaps I achieved larger word counts on days without his good company, but I hate to think where I would have been without his statistical expertise.

But then I have particular gratitude to a few really special people. The first are Mum and Dad, for supporting me all these years, for inspiring me to make the most of my stubborn genes, and for their unquestioning (if biased) faith in my ability to do so.

Secondly, are Rachel and Kate who deserve special praise for their unwavering friendship, especially when listening to the trials and tribulations of a doctoral student.

Then there is Tom who deserves a fairly substantial proportion of this PhD, and probably also a medal for hard service. While he had no idea what he was letting himself in for, I am so pleased he carried on; putting up with the emotional rollercoaster and the hours of commuting. All other research pales into insignificance without him as “Lead Pilot”.

And finally, I must thank all the volunteers who took part in this research. Besides not being able to do it without their participation, they are why I enjoyed the last four years so much. These interesting characters fuelled my inquisitive nature and made me want to ask the questions that not only fill this thesis, but also encourage me to pursue them further.



## **Format**

This thesis is in alternative format to facilitate the author's career by producing the research in the form of papers for publication in peer-reviewed journals. This format has been approved by the Faculty of Medical and Human Sciences. Chapter 1 is a general introduction of the literature and methodology relevant to this research. Chapter 2 contains four separate studies that have been prepared for submission to suitable peer-reviews journals. Chapter 3 is a general discussion of the four studies in Chapter 2.



# **Chapter 1: General Introduction**

## **1.1. The Problem of Addiction**

Substance dependence is a persistent disorder that is characterised by compulsive seeking and taking of drugs, loss of control over intake, and negative emotional states during withdrawal (Koob 2008). It is a multifactorial condition involving social, environmental, cognitive and neurobiological factors that is defined as the “shift from controlled drug use to compulsive drug use with loss of control over intake despite adverse consequences” (Volkow et al. 2011, p. 15037). Substance addiction is a significant health and social concern, which costs UK tax payers £15 billion a year, and alcohol-related harm alone is estimated at £21 billion a year (CSJ 2013). To date we are still far from successful treatment with relapse rates remaining at 65-75% (Sinha 2011) and individuals frequently returning to treatment in repetitive cycles of detox and relapse (Neto et al. 2007).

Attention will be concentrated on the substances of cocaine, opioids and especially alcohol. Indeed, alcohol, heroin and crack cocaine can be considered the most harmful substances based on multi-criteria decision analysis using 16 harm criteria encompassing physical, social and psychological harms to the individual and to others (Nutt et al. 2010). There will also be a focus on alcohol use, which is the most harmful substance according to this analysis and, when excessive, is thought to be prodromal for alcohol dependence (Kranzler et al. 1990; Dawson & Aecher 1993). Heavy alcohol use accounts for 5.1% of the global burden of disease and injury, particularly in the UK in which 11.1 % suffer from alcohol use disorders (WHO 2014).

There are a number of ways to view addiction in order to understand it. For example, we can look at the pharmacological changes that occur during drug use and how dependent individuals differ from those who can use drugs without problem. We can also study the epidemiology of the disorder to gain an overall picture of its patterns, causes and effects, while animal models and genetic investigations are also useful. This thesis, however, will focus on the neurocognition that is involved in the vulnerability, maintenance and relapse of addiction, incorporating the behavioural and neural aspects. Neurocognition includes memory, attention, problem solving, language, visuospatial processing, and emotion, all of which can be measured by the study of behaviour and its neural correlates.

## **1.2. Neurocognitive Approaches**

Changes in structural, functional and emotional systems are all associated with substance dependence (Asensio et al. 2010), and may reduce the chance of successful maintenance of abstinence. Some of these differences in structure, neuropsychology and emotion are seen prior to the development of dependence and are associated with increased vulnerability for developing the disorder, while others are a result of continued drug exposure. It is important to understand the mechanisms that are involved at all stages to help prevent development of dependence, reduce maintenance of use and lower the risk of relapse following treatment.

In a review of the literature, Volkow and colleagues (2010) propose a number of neurocognitive dysfunctions present in substance dependence that reflect three specific challenges: an under-sensitive reward circuit; an over-sensitive memory circuit for conditioned drug-related expectations (e.g. to drugs, cues and stress); and a weakened inhibitory control circuit. Repeated drug exposure disrupts these specific circuits, resulting in deficits in learning (conditioning, memory and habituation), executive function (inhibitory control, delayed gratification and decision-making), cognitive awareness (interoception), and emotion (mood and stress reactivity; Volkow et al., 2010); resulting in an imbalance between overactive motivational systems and underactive regulation systems (Wiers et al. 2007; Bechara 2005; Volkow et al. 2004). Drug-reward is a key concept in substance use as it plays a large part in the continuation of drug use that can lead to the development of dependence. It is associated with neurochemical changes in the brain, particularly within the mesolimbic dopaminergic system, but also involves glutamate, GABA, corticotropin-releasing factor (CRF) and the endogenous opioid system (Volkow et al. 2011). While reward and memory circuits are important in addiction, the main focus of this thesis will be on the weakened inhibitory circuit, but with some attention given to the motivational influences on impulsive behaviour, particularly negative reinforcement through negative affective states of stress. This investigation of neurocognitive function in substance dependence, therefore, will focus on impulsivity and how the role of stress influences individual differences through negative reinforcement.

## **1.3. Impulsivity and Addiction**

There has been much investigation into the role of impulsivity in addiction; it is a known risk factor for development of dependence (Perry & Carroll 2008; Verdejo-García et al.

2008; Ersche et al. 2010; Hogarth 2011), a consequence of excessive drug use (Dallery & Locey 2005; Winstanley 2007) and a marker for poor treatment outcomes (Moeller et al. 2001; Patkar et al. 2004). Impulsivity is action without forethought, involving premature responding, poor response inhibition and low tolerance for delay (Evenden 1999). Impulsivity involves the choice of immediate drug-related rewards over future negative consequences, such as family, social, legal or psychiatric problems (Bechara et al., 2001), as well as the ability to inhibit the prepotent response to use when surrounded by drug-related cues (Volkow et al. 2011).

### *Types of Impulsivity*

Impulsivity is a multifaceted construct (Evenden 1999) that can be explained in many ways. Dalley, Everitt and Robbins (2011) separate out five types of impulsivity: reflection impulsivity, impulsive action, action cancellation, impulsive choice, and risky decision making. Sensation seeking is also considered part of impulsivity. Referring to action motivated by the drive for the most rewarding outcome or “sensation” of the behaviour (Dawe & Loxton 2004; Zuckerman 1994), it is associated with greater sensitivity to the reinforcing effects of drug use (Kelly et al. 2006; Stoops et al. 2007). High sensation seeking is reported in alcohol dependence (Noël et al. 2011), alcohol use disorders in young adults (Shin et al. 2012; Gillespie et al. 2012), is related to the frequency and quantity of alcohol and poly-substance use in young adults (Chakroun et al. 2004; Woicik et al. 2009), and is predictive of the development of alcohol dependence (Cloninger et al. 1988). Sensation seeking is also frequently linked with cocaine dependence (Patkar et al. 2004; Ersche et al. 2010; Mahoney et al. 2015), as well as poorer treatment outcomes in cocaine dependent individuals (Patkar et al. 2004). However, the link with opioid dependence is less clear as some studies report higher sensation seeking (Le Bon et al. 2004; Lemenager et al. 2011), while others do not (Nielsen et al. 2012).

There are numerous, specific methods for measuring impulsivity, but these are often found not to correlate with each other. This is perhaps a result of its multidimensional nature, with different types of impulsivity being controlled by distinct mechanisms. Some argue that impulsivity is an “umbrella” construct covering a number of unrelated concepts (Enticott et al. 2006; Dick et al. 2010). This suggestion is supported by a study using principle component analysis on a number of measures of impulsivity that found no correlation between impulsive action, impulsive choice and self-reported impulsivity (Broos

et al. 2012). However, by using a varied range of measures, we might be able to piece together the complicated role that each of these different aspects play in substance use and dependence.

### *The Impulsivity-Compulsivity Spectrum*

The construct of compulsivity and the shift of behaviour from impulsivity to compulsivity in the development of addiction must also be considered. Everitt and colleagues (2005; 2008) state that substance dependence constitutes this shift to compulsive drug use and results in automatic, habitual and continuous drug use, without consideration of the behavioural outcome. High levels of impulsivity are associated with compulsive drug seeking and taking behaviour (Verdejo-García et al. 2008; Dalley et al. 2011; Potenza & Taylor 2009). For example, high-impulsive rats fail to reduce cocaine self-administration following punishment by electric shock (Belin et al. 2008; Economidou et al. 2009), and rats that show more persistence in the face of negative outcomes are more likely to develop compulsive drug use (Belin et al. 2008). Similarly, impulsive choice predicted perseveration of nicotine self-administration in rats (Diergaarde et al. 2008). Impulsivity is also related to compulsivity measures in non-drug situations such as perseveration during reversal learning (Dalley et al. 2011). Similar motivational and decisional circuits mediate the different behaviour of impulsive and compulsive drug use, including the limbic cortical structures and their “top-down” control by cortical regions, particularly the prefrontal cortex (PFC; Dalley et al., 2011).

### *Neural Substrates of Impulsivity*

Investigation of the neural substrates of impulsivity provides further evidence for the complex, multifaceted nature of impulsivity (Dalley et al. 2011). Impulsivity in substance dependence is seen in the dysfunctional top-down control of subcortical structures, such as the nucleus accumbens (NAcc) within the ventral striatum, by the frontal brain regions of the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC) and PFC (Volkow et al. 2011; Hester & Garavan 2004; Garavan et al. 2008; Kaufman et al. 2003). The top-down influences on the NAcc include the hippocampus and PFC (Goto & Grace 2008), as well as connections via the motor cortex for response inhibition (Narayanan & Laubach 2006). Reduced activation of these frontal regions is strongly associated with decreased inhibitory control and is reflected in the shift to compulsive drug use (Dalley et al. 2011). For example, disinhibition has been related to the lateral PFC of non-human primates (Iversen & Mishkin



1970) as well as the OFC of rodents (Belin et al. 2008). Reduced activation of the ventromedial (vm)PFC is associated with impulsive choice, as seen in alcohol and cocaine dependence (for a review see Potenza & Taylor 2009), and the inability to withhold premature responses seen in the reinstatement of drug seeking behaviour may be due to a deficient top-down PFC system that fails to regulate striatum-influenced behaviour (Dalley et al. 2011).

Top-down control by frontal regions is required to regulate the motivational drive of subcortical structures, such as the ventral striatum, that does not evaluate the consequences of the action being initiated. The ventral striatum is particularly related to drug reward as it is a focal point of the mesolimbic dopaminergic system (Koob 2000; Nestler 2005; Koob et al. 1998), which plays an influential role in substance dependence as all drugs of abuse increase brain dopamine levels (Volkow, Wang, Fowler, Tomasi, & Telang, 2011). Within the ventral striatum the NAcc is implicated in premature responding (an indication of impulsivity) in the rodent Five Choice Serial Reaction Time Task (5CSRTT) in relation to drug use (Basar et al. 2010; Dalley et al. 2011). Dopamine increase in this region by d-amphetamine administration exacerbates premature responding, while dopamine blockade and depletion are seen to reduce this effect (Cole & Robbins 1989; Pattij et al. 2007), indicating that greater levels of dopamine in the ventral striatum increase impulsive behaviour.

Dopamine's association with impulsivity also likely links repeated drug use with the development into compulsive drug use. Reductions in dopamine as a consequence of sustained drug use are associated with metabolic changes in the frontal cortex (Volkow et al. 2011) that disrupt inhibitory control (Volkow & Fowler, 2000; Volkow et al., 1993), with the result that drug users are less able to constrain the bottom-up motivation to seek out and use drugs. For example, evidence of this is seen in rodent studies where correlations were found between impulsivity and low dopamine receptor availability (Dalley et al. 2007), between impulsivity and drug self-administration (Belin et al. 2008), as well as between reduced dopamine receptor availability and cocaine self-administration in rodents (Everitt et al. 2008) as well as in non-human primates (Nader et al. 2006). Additionally, lesions to the infra-limbic PFC induce premature responding in the 5CSRTT (Chudasama et al. 2003). The relationship between impulsivity and dopamine is also reported in humans, as reduced dopamine receptor availability is associated with cocaine use (Volkow et al.

2010), as well as with the subjective liking of methylphenidate (MPH; Volkow et al., 1999). Methamphetamine users with high Barratt Impulsiveness Scale (BIS-11) scores show reduced striatal dopamine receptor binding compared to controls (Lee et al. 2009), and even abstinent individuals have marked reductions in dopamine receptor availability (Volkow et al. 2010). This evidence implicates the role of the dopaminergic system in impulsivity, as the greater levels of dopamine there are in subcortical regions, the less top-down systems are able to control them.

Inhibitory control in healthy human participants is associated with activation in the inferior frontal gyrus (IFG), ACC and dorsolateral (dl)PFC as well as the inferior and superior parietal cortices. Reduced activations in these regions are often reported in substance dependent individuals compared to controls, and is assumed to reflect inhibitory control deficits (for a review, see Luijten et al. 2014). Findings from functional magnetic resonance imaging (fMRI) studies have identified a “stop circuit” that is implemented during response inhibition (Dalley et al. 2011), including the right IFG, ACC, the pre-supplementary and motor cortex, basal ganglia and a “hyperdirect” cortical projection to the sub-thalamic nucleus (Aron, Behrens, Smith, Frank, & Poldrack, 2007). The left frontal cortex is also implicated, although some activations may be the result of attention rather than inhibition (for a review, see Dalley et al. 2011). However, fMRI studies of inhibitory control in substance dependence are relatively limited with very few investigations of alcohol or opioid dependence. Support for these neural correlates of impulsivity in rodents and non-human primates are generally in concordance with human studies, although rodent findings are limited in how they translate to human cortical links because rats do not have the same extensive cortical structure as humans.

### *Models of Impulsivity and Addiction*

There are many possible explanations for the role of impulsivity in addiction. One is that the neurotoxic effects caused by repeated drug use damage the top-down control of the PFC (Everitt & Robbins 2005). The shift from drug use to dependence is reflected in a reduction of top-down control by the OFC and vmPFC to compulsive striatal control (Everitt & Robbins 2005). Decision-making choices of dependent individuals also reflect this shift in that they prefer smaller immediate rewards compared to controls (Dalley et al. 2011). Individuals with higher scores on the Obsessive-Compulsive Drug Use Scale (OCDUS) had the most reduced OFC volumes (Ersche et al. 2011), suggesting that they are unable to

withhold drug-related behaviour when presented with drug-related cues (Volkow & Fowler, 2000). Similar volume reductions are also found in alcohol, heroin and cocaine dependent individuals (Goldstein & Volkow, 2002).

Substance use may also expose pre-existing deficits that are exacerbated by repeated drug exposure and result in insufficiently monitored processes that reduce inhibitory control and increase incentive-driven behaviour (Goldstein & Volkow, 2002). The evidence of the effect of drugs on impulsivity is mixed, however, as some studies report increased impulsivity with excessive drug use (Perry & Carroll 2008), while stimulants reduce impulsive choice (Garavan et al. 2008) and alcohol increases impulsive responding in cocaine users (de Wit 2009). This leads to the suggestion that drug use may be a form of self-medication to compensate for pre-existing deficits, producing a homeostatic rebalancing effect that has initial reinforcing value (Dalley et al. 2007). For example, impulsivity is reduced following amphetamine consumption, and is effective in reducing impulsivity in Attention Deficit/Hyperactivity Disorder (ADHD; Aron, Dowson, et al. 2003). In addition, high-impulsive rats with lower dopamine receptor availability self-administered more cocaine than low-impulsive rats (Nader et al. 2006). Once drug use reaches bingeing or habitual levels, the medicating benefits are outweighed by the neurotoxic effects of repeated drug exposure. However, the restoration of inhibitory control is mainly limited to stimulant drugs as other substances, particularly opioids, do not have the same effect on the mesolimbic dopamine system (Daglish et al. 2008).

### *Impulsivity as a Vulnerability Marker for Addiction*

Impulsivity can also be considered as an intermediate phenotype, or “endophenotype” (Gottesman & Gould 2003), for substance dependence (Potenza & Taylor 2009; Ersche et al. 2010). For example, high-impulsive rats show steeper discounting for food pellets, consume more alcohol than low-impulsive rats (Poulos et al. 1995), and self-administer more cocaine (Perry & Carroll 2008). Human studies have also identified impulsivity prior to dependence (Nigg et al. 2006), as well as in groups with high risk for addiction, such as ADHD, children of dependent individuals (Verdejo-García et al. 2008), as well as siblings of stimulant dependent individuals (Ersche et al. 2010). Similarly, there is evidence of a genetic influence in the extent to which individuals discount larger delayed rewards for smaller immediate ones (Anokhin et al. 2014). It is possible that a faulty PFC occurs first, providing an addiction vulnerability, and subsequent drug exposure causes striatal damage.

Evidence from family studies shows that normal PFC function in individuals with family history of alcohol dependence have the potential for “protection” from addiction (Volkow et al., 2006). This is potentially due to higher dopamine receptor levels maintaining normal functioning of the PFC and helping to control impulsive actions that might otherwise lead them to addiction.

### *Impulsivity and Addiction: Summary and Implications*

As discussed in this section, impulsivity is apparent both before and after drug exposure, is mediated by complex neuronal mechanisms, and contributes differently in each individual (Dalley et al. 2011) to the vulnerability, maintenance and relapse of substance dependence. Neural substrates of impulsivity focus on the frontal cortical regions, particularly the IFG, dlPFC and ACC, which provide top-down control over the subcortical regions of the ventral striatum and NAcc. Dysfunctional frontal regions result in less control over subcortical regions, producing more impulsive behaviour.

Models of impulsivity in addiction include the idea that the damage caused by repeated drug use creates impulsive behaviours or exposes pre-existing deficits. Other possible explanations include the idea of unconscious self-medication and homeostatic rebalance, or that high impulsivity is causal in the development of compulsive drug use and dependence, and that pre-existing impulsivity is exacerbated by repeated drug exposure, leading to addiction in particularly vulnerable individuals. While there is limited evidence to indicate the extent to which each of these models is reflective of substance dependence, this thesis will argue that they all play a role, but to different extents in each individual. This will be discussed further in section 1.5. Individual Differences.

## **1.4. Avoidance and Negative Reinforcement: The Role of Stress in Addiction**

The process of behavioural reinforcement is also important to consider when investigating substance dependence. Reinforcement acts to drive behaviour, by strengthening its association with either the presentation of a rewarding outcome (positive) or the removal of a punishing event (negative). The process of positive reinforcement allows the strengthening of an action to enable the individual to gain maximum utility from a rewarding outcome. Conversely, when faced with an unpleasant event, negative reinforcement acts to strengthen behaviours that allow the individual to avoid unpleasant

outcomes. With repeated drug exposure, there is a shift from the initial positive reinforcement of drug use (e.g. the high), to the negative reinforcement gained from avoiding withdrawal (Koob, 2008). Repeated drug use creates withdrawal, which then sets up a negative reinforcement situation where individuals are motivated to continue use in order to avoid the negative anhedonia and dysphoria of withdrawal (Koob, Stinus, Le Moal, & Bloom, 1989). This in turn exacerbates the withdrawal symptoms and initiates a cycle of dysregulation that gradually worsens as reward from neurotransmitters are reduced in an “opponent process” (Koob & Le Moal 2008) while more anti-reward mechanisms are recruited and anti-stress mechanisms become less efficient.

The importance of negative reinforcement in substance dependence leads us to the important role played by stress. Known to be influential in the development and maintenance of dependence as well as the risk for later relapse following detoxification, stress is implicated in dependence on opioids (Fatseas et al. 2011) alcohol (Sinha et al. 2009) and cocaine (Karlsgodt et al. 2003). Stress can be defined in two ways: as a response to demands on the body indexed by physiological changes; or as arousal of emotion and activation systems (Koob, 2008). Drug use itself can be seen as a stressor: either as the immediate physiological effects of ingesting a psychoactive substance; or as the emotional and motivational changes that result from repeated drug use. Both these primary and secondary drug effects are important in addiction as they serve to maintain drug using behaviour through the negative reinforcement produced by the avoidance of these aversive states. These will be discussed further in the sections that follow.

### *Physiological Changes: Primary Drug Effects*

Drug-induced stress can be seen as a purely physiological entity, in which the body responds to the ingestion of drugs as stressors to the body. Stress-systems are then recruited in an attempt to restore the homeostatic balance of the body. The brain is particularly affected with the use of psychoactive substances and thus, recruits brain-stress systems that contribute to the negative emotional state of withdrawal resulting from repeated drug use that prevents homeostatic balance being achieved (Koob, 2008) and further disrupts homeostatic mechanisms of emotions.

Known as allostasis, the “residual deviation from normal brain reward threshold regulation” (Koob, 2008; pp. 28) involves a chronically elevated reward set point (fuelled by

numerous neurobiological changes) and a combination of a decrease in function of reward circuits, loss of executive control and facilitation of stimulus-response associations. The dysregulation of emotional states is caused by interactions between CRF and noradrenaline in the brainstem and basal forebrain, between orexin and CRF in the hypothalamus and basal forebrain, as well as between CRF and vasopressin and orexin (Koob, 2008). With repeated drug use the brain attempts to re-stabilise the molecular, cellular and neurocircuitry changes, which in turn, disrupts emotional regulation. In addition, brain stress-systems are recruited while brain anti-stress-systems are compromised, preventing sufficient management of stress. For example, alcohol dependent individuals who continue to drink to relieve stress aggravate the situation as the persistent alcohol consumption only leads to physical and psychological problems (Wand 2008). Environmental stressors exacerbate the situation, as seen in rodent models where foot-shock stress induction reinstates heroin and cocaine relapse (Shaham et al. 2000), while CRF antagonists reduce the rate of this reinstatement (for a review, see De Vries & Shippenberg, 2002). These stressors leave a residual neural trace that allows for rapid “re-addiction”, even after prolonged abstinence (Koob, 2008).

### *Emotional Changes: Secondary Drug Effects*

Stress also plays a role in substance dependence through the dysregulation of emotional processing. Poor emotional regulation is reported in substance dependence (Aguilar de Arcos et al. 2005; Li & Sinha 2008), particularly in alcohol (Gilman & Hommer 2008), cocaine (Asensio et al. 2010) and heroin dependence (Aguilar de Arcos et al. 2008). For example, cocaine and opioid dependent individuals are less aroused by erotic stimuli than controls, but show more arousal for unpleasant stimuli (Aguilar de Arcos et al., 2008; 2005). Chronic opioid users are more sensitive to acute punishment (Ersche et al. 2005) as well as pain (Pud et al. 2006), and this is reflected in neuroendocrine and cardiovascular alterations seen in abstinent heroin dependent individuals (Gerra et al. 2003), suggesting that there is a heightened sensitivity to negative stimuli, which is related to the dysfunction of hedonic experience.

Stress reactivity is regulated by the central nervous system (CNS) through limbic and prefrontal regions that include the amygdala, hippocampus, ACC, medial (m)PFC, and dorsal striatum (Herman et al. 2005). Together these mediate emotional responses to environmental stimuli. Asensio and colleagues (2010) identified an emotional network that

includes the amygdala, mPFC, OFC and occipito-temporal areas. In line with previous research (e.g. Wang et al., 2010), Asensio et al. propose that hypoactivation of this network indicates deficiencies in reward evaluation, motivational and saliency attribution for pleasant stimuli, and control of emotional cognitive processing, with the suggestion that substance dependent individuals are less able to experience pleasure from natural reinforcers. Activation in these regions is also seen when viewing drug-related cues and aversive stimuli that induce craving in cocaine dependent individuals (Grant et al. 1996; Childress et al. 1999; Kilts et al. 2001). In addition, cocaine dependent individuals show reduced response to stress in para-limbic regions including the ACC and hippocampus compared to controls, indicating poorer regulation of stress reactivity, with those who relapsed sooner showing greater mPFC activity in response to stressful imagery (Sinha & Li 2007). Similarly, greater relapse risk was associated with alcohol and cocaine dependent individuals who reported higher levels of craving and anxiety (Sinha et al. 2009; Fox et al. 2007).

The amygdala is particularly implicated in responses to emotional stimuli as it is involved in preparing the body for response (LeDoux 2009). The amygdala responds to both pleasant and unpleasant images (Asensio et al. 2010), evaluates emotional salience of stimuli (Liberzon et al. 2003), and has connections with the PFC (Amaral & Price 1984; Price 2003) that mediate automatic responses to emotional stimuli (Williams et al. 2001). The amygdala's connection with other limbic and prefrontal regions is functionally altered during and after stress induction (Hermans et al. 2011; Vaisvaser et al. 2013; Veer et al. 2011) so that amygdala-hippocampal functional connectivity is enhanced immediately following stress induction (Vaisvaser et al. 2013).

Additionally, hypoactivation of the dorsal and ventral striatum, thalamus, parietal cortex and dorsal medial (dm)PFC have been observed in cocaine users compared to controls when viewing pleasant images (Asensio et al. 2010). The decrease in striatal response during natural rewards in cocaine users corresponds with the reduced dopamine receptors that are seen in drug dependent individuals (Volkow et al., 2007) and also accounts for their reported lower enjoyment of natural rewards (Meseguer et al. 2007). Goldstein and Volkow (2002) propose that the reduction of dopamine receptors in drug users results in impaired Response Inhibition and Saliency Attribution (iRISA), suggesting that extended drug use increases saliency for drug-related cues while reducing sensitivity for non-drug-

related cues and the inhibitory control over disadvantageous behaviours. In support of this account, low dopamine receptors in cocaine dependent individuals are associated with lower ACC activation in response to emotionally-salient tasks (Volkow et al., 1993). Similarly, cocaine dependent individuals show less activation change in response to monetary value conditions, related to poor self-control, lower dopamine receptor availability and more potent craving (Goldstein et al., 2007; Goldstein et al., 2009). This altered salience attribution produces a less invigorating daily life, which leads to vulnerable individuals searching for alternative methods of arousal, such as continued drug use.

### *Environmental Stress*

External stressors also create a number of problems in cognitive processing. For example, poor performance on decision making tasks was seen in individuals with high trait anxiety (Miu et al. 2008), negative affect (Suhr & Tsanadis 2007), sensation seeking (Suhr & Tsanadis 2007; van Honk et al. 2002) and stress sensitivity (van den Bos et al. 2009). This influence of stress on decision making is also reported in substance dependence; abstinent opioid dependent individuals showed poorer decision making ability following stress created by the Trier Social Stress Test (TSST; Zhang et al. 2011), and following drug cue exposure (Wang et al., 2012). Iowa Gambling Task (IGT) decision making performance was also negatively correlated with trait and state anxiety in abstinent opioid dependent individuals (Lemenager et al. 2011).

### *Stress, Negative Reinforcement and Avoidance Behaviour*

Stress is especially apparent in the development and maintenance of addiction (Li & Sinha 2008), and this is particularly evident in avoidance behaviour. By avoiding aversive stimuli that induce negative affective states an individual is providing themselves with a form of negative reinforcement (Koob, 2009). It can be argued that substance dependence involves both pathological approach and avoidance behaviour: approach in the compulsive motivation to pursue the hedonic incentive of the drug high, mediated by positive reinforcement; and avoidance in the prevention of unpleasant events, such as withdrawal, mediated by negative reinforcement. In addition, drug users are unable to control and inhibit such behaviour because the negative consequences of drug taking reduce their inhibitory control. The decision to approach or avoid stimuli involves executive functioning and decision making capacities that are dependent on the context and other associated information, such as valence, salience, probability, and timing.



As drug use continues and becomes chronic, the body down-regulates the pleasurable feelings, so that both current and detoxified users experience reduced positive reinforcement for drug taking (Volkow et al. 2010). Responses to natural rewards, such as food and sex, are also reduced, resulting in a compulsive “vicious circle” (Comings & Blum 2000), in which the motivation to seek drugs is yet further increased (Volkow et al. 2010). In addition, there is a shift from positive reinforcement driving drug taking behaviour to that of negative reinforcement of avoiding symptoms of withdrawal (Koob 2008). Again, this initiates a destructive cycle that is increasingly susceptible to added stressors and is fundamental in the development and maintenance of drug addiction. For example, abstinent alcohol dependent individuals report higher ratings of negative mood and display greater attentional bias for negative emotional words than controls (Duka et al. 2002), while increased brain responses to negative affective stimuli are also seen in alcohol dependent individuals in comparison to reduced or no responses to positive affective stimuli (Gilman & Hommer 2008). Critically, the dysfunctional avoidance behaviour seen in substance dependence may also be related to external stressors, or to individual differences in levels of pre-existing negative affective states.

### *Saliency Attribution and Attentional Bias*

As a result of the hedonic reward induced by substance use, these substances and their related cues take on a motivational salience or a “wanting” of the substance (Robinson & Berridge 1993; 2003; 2008). Through their association with reward cues, previously neutral stimuli acquire incentive salience (via Pavlovian mechanisms), producing craving created by release of dopamine. For example, greater dorsal striatal dopamine levels that correlated with reports of craving were seen in cocaine dependent individuals while watching cocaine-related videos compared to neutral videos (Volkow et al., 2006), while individuals with the greatest severity of dependence showed the greatest dopamine response to cocaine cues (Volkow et al., 2010). In addition, preclinical studies find that rats begin to pair neutral stimuli with the reinforcement of receiving the drug and then begin to reinstate drug self-administration in response to this conditioned neutral stimulus, rather than the drug itself (Phillips et al. 2003).

Incentive salience creates an attentional bias for the substance so that an individual’s attention is “grabbed” by these substance-related cues, as seen in a wealth of studies on

attentional bias in alcohol use (for a review, see Field & Cox, 2008). As a consequence of attentional bias for substance-related cues, automatic approach behaviour towards these cues is also reported in heavy compared to low drinkers (Field et al. 2008; Field et al. 2011), as well as for nicotine (Mogg et al. 2005) and cannabis (Cousijn et al. 2012). Consistent approach of drug-cues results in repeated exposure to these substances and their related cues, which exacerbates the attentional bias and strengthens the cycle further (Robinson & Berridge, 2008; Wiers et al., 2007). These enhanced neural and psychological responses to drug cues are influential in the transition from controlled drug use to addiction, maintenance of dependence and triggering relapse (Everitt et al. 2001), even following lengthy abstinence.

Stress and the induction of negative affective states are seen to increase attentional bias to substance-related cues, such that it increases the risk of developing dependence. For example, increases in attentional bias following induction of stress or negative affective states are reported in heavy drinkers compared to controls (Field and Powell 2007; Grant, Stewart, and Birch 2007), those who self-report coping drinking motives (Birch et al., 2004; Field & Quigley, 2009), and those who self-report escape drinking motives (Forestell et al. 2012). In addition, induction of negative mood states increases reports of alcohol craving (Cooney et al. 1997; Willner et al. 1998), and higher heart rate reactivity to stress-primed alcohol-cues in alcohol dependent individuals that predicted relapse at six month follow up (Garland et al. 2012). Such evidence may suggest that stress influences drug use via these incentive salience processes.

### *Vulnerability and Motives for Substance Use*

Stress is also a risk factor for the development of dependence and, particularly during childhood, contributes to individual vulnerability to the disorder (Andersen & Teicher 2009; Dube et al. 2003). Many drugs of abuse have anxiolytic and anti-depressant properties (George et al. 2008; Lejuez et al. 2006) that provide users with a form of self-medication to relieve or avoid negative affective states, such as depression and anxiety (Koob & Le Moal 2008; Becker et al. 2012). For example, high self-reported anxiety is associated with opioid use as well as problem drinking in young adults and adolescents (Woicik et al. 2009), while hopelessness and sedative drug use are associated with quantity of use in adolescents and young adults. On the other hand, positive emotionality appears to protect against substance dependence (Volkow et al. 2011).

Stress is involved with the motives for initiating substance use, particularly within alcohol use, where coping, enhancement, conformity and social motives for alcohol consumption are reported (Cooper 1994). Related to these are the valence (positive vs. negative) and source (internal vs. external) of these motives (Goldstein & Flett 2009; Cox & Klinger 1988). Individuals with internal motivations for drinking alcohol had higher levels of alcohol consumption than those with non-internal motivations (Cooper 1994), in line with previous literature that suggests internally-motivated drinking is more likely to become problematic (Kushner et al. 2001; Rutledge & Sher 2001). Individuals with coping motives to drink had higher negative affect and lower positive affect than those with enhancement motives and those without internal drinking motivations (Kuntsche et al. 2008), while 31% of variance in drinking consequences can be explained by these motives. Although the evidence for the role that each of these motives play is mixed (for a review, see Kuntsche et al. 2008), it is clear however, that coping motives are a driving factor for alcohol use in adolescents and young adults (Kuntsche et al. 2005; 2006). These motives, especially when exacerbated by physiological, emotional or external stressors, may lead to later problematic use and potential dependence.

### *Neural Substrates of Avoidance and Negative Reinforcement*

There is substantial evidence for the role of stress in addiction. It can be seen in the physiological consequences of substance use, the disruption of emotional processing, as well as a driver for initiating and maintaining substance use through avoidance of pre-existing negative affective states. By avoiding negative affective states through drug use, the individual provides themselves with negative reinforcement and the behaviour is thus strengthened. If avoidance behaviour continues it strengthens further and can become problematic, such that it may be a route into the development of dependence.

The NAcc has been identified for its role in active avoidance of aversive stimuli (Ammassari-Teule et al. 2000; Hoebel et al. 2007; Levita et al. 2002; Schwienbacher et al. 2004). Processing both rewarding and aversive stimuli (Becerra et al. 2001; Jensen et al. 2003; Levita et al. 2009; Reynolds & Berridge 2001), the NAcc has a bivalent function and is suggested to be a site for transferring motivational and emotional signals from the PFC, amygdala and hippocampus to produce appropriate adaptive behavioural responses (Levita et al., 2009). It is innervated by regions such as the amygdala, OFC, insula, cingulate cortex, midline- and intra-laminar thalamic nuclei (Breiter et al., 1996; Levita et al., 2009), and is

involved in gating and modulating goal-directed behaviour in order to detect both aversive and rewarding stimuli in the environment (Cardinal et al. 2002) and prepare a motor action response.

Levita and colleagues (2012) found left NAcc activation during active avoidance of aversive visual stimuli and right NAcc deactivation during passive avoidance, reflecting an instrumental attempt to escape the negative stimuli as well as neuronal inhibition to withhold an action that would result in presentation of the aversive stimuli respectively. Levita and colleagues suggest that the NAcc is part of an approach-avoidance behaviour network that modulates “instrumental action to optimise reward gain and avoid risk” (pp. 197; Levita et al., 2012). In addition, higher anxiety levels were associated with greater left NAcc activation during active avoidance and greater right NAcc deactivation during passive avoidance (Levita et al., 2012), in line with the suggestion that anxiety sensitivity reflects a behavioural inhibition system (Gray 1990) that is activated by aversive, novel and innate fear stimuli (Barrós-Loscertales et al. 2006). Inputs from anxiety structures, such as the amygdala, control how information is gated in the NAcc to influence motivation appropriate to the situation at hand (Nestler & Carlezon 2006). As we can see, the mechanisms involved in motivation are also linked with anxiety and stress-reactivity. Further investigation of these in relation to substance-related cues and behaviour are important for our understanding of the development and maintenance of substance dependence, as well as increasing the risk of relapse.

### *Stress and Impulsivity in Addiction*

Sinha's (2008) stress-vulnerability theory suggests that stress exacerbates individual differences, such as the increased impulsivity rates seen in substance dependent individuals. With regards to alcohol use, both impulsivity and stress are associated with increased alcohol consumption (Simons et al. 2004; Sinha 2008; Lejuez et al. 2010), plus self-reported impulsivity is seen to mediate the effect of stress on alcohol use behaviour (Fox et al. 2010; Hamilton et al. 2013). This relates to “affective impulsivity”, and refers to the ability to control behaviour in the face of extreme positive or negative affect (Whiteside & Lynam 2001).

In particular, Negative Urgency from the UPPS Impulsive Behaviour Scale (Whiteside & Lynam 2001; 2003) refers to behavioural regulation in the context of negative emotional

states. With emphasis on negative reinforcement, it has been related to coping motives in problematic drinking university students (Adams et al. 2012), distinguishes cocaine dependent individuals from controls (Torres et al. 2013), and predicts severity of dependence-related problems (Verdejo-García et al. 2007). Additionally, substance dependent individuals with higher negative urgency scores are more likely to use drugs to remove negative emotional states (Whiteside & Lynam, 2001), while high- and low-impulsive methamphetamine users were distinguished by their depression scores (Semple et al. 2005). This fits with the allostasis idea of addiction (Koob & Le Moal, 2001) and, thus, is possible that emotional lability as well as impulsivity increases chance of substance dependence.

Stress can also reduce individual control over other cognitive processes, making it harder to remain abstinent. The experience of stress reduces the amount of resources that can be assigned to behavioural control, such as to prefrontal regions involved in the control of affective states (Phillips et al. 2003a) and craving (Brody et al. 2007; Kober et al. 2010). Consequently, craving becomes harder to regulate (Amat et al. 2005; Phillips et al. 2003b; Robbins 2005), making individuals more susceptible to relapse (Weiss 2005). For example, psychological stress increased craving in cocaine dependent individuals (Sinha et al. 1999; 2000), while poor decision making performance following drug-cue exposure was also associated with increased craving (Wang et al., 2012).

Stress can also influence saliency value, increasing its potency and further decreasing prefrontal control (Volkow et al., 2010). For example, stress induction using both TSST and cortisol administration were seen to enhance free-recall of drug-related but not neutral words in abstinent heroin dependent individuals (Zhao et al. 2010). These effects of stress on memory were then blocked by administration of  $\beta$ -adrenoceptor antagonist propranolol, indicating a return to normal functioning with the removal of stress. This poor emotional control may compel affected individuals to seek alternative ways to manage their emotions, such as with continued drug use. There is also evidence that personality (especially associated with mood regulation) is linked with substance use, in particular that poor mood regulators resort to alcohol as a means of emotional control (for a review, see Kuntsche et al. 2006). Personality characteristics often associated with drinking motives are sensation seeking (Comeau et al. 2001; Cooper et al. 1995; Read et al. 2003), neuroticism

(Stewart & Devine 2000; Stewart et al. 2001), anxiety sensitivity (Kushner et al. 2001; Novak et al. 2003), and negative affect (Carpenter & Hasin 1999; Pardini et al. 2004).

### *Summary of the Role of Stress in Substance Dependence*

Stress plays a number of roles in addiction and is influential at all three levels of vulnerability, maintenance and relapse. The initial positive reinforcement of the drug-induced high motivates continuation of drug use, which then shifts to negative reinforcement to avoid withdrawal. During this shift, the body attempts to rebalance the homeostasis that is disturbed by drug “demands”, gradually recruiting brain stress systems at the cost of brain anti-stress systems. This results in a negative cycle that is increasingly susceptible to additional stressors and is fundamental to the development and maintenance of drug addiction, while increasing the potential for later relapse. Additional processes of emotion are also disrupted in addiction, reducing arousal for positive stimuli, while increasing arousal for negative stimuli. This is a result of a number of changes that affect saliency attribution as well as memory and learning processes, which can be explained by the down-regulated dopamine release that accompanies repeated drug exposure. These changes result in a cycle of negative reinforcement that begins to replace the positive reinforcement of initial drug use. Finally, stress reactivity has also been identified as a vulnerability factor for the development of dependence, as many substances provide relief from pre-existing negative affective states (Koob, 2004). These negative affective states may be present prior to initial drug use, but also can be a result of the inevitable risks of the lifestyle that accompanies substance dependence. As a result, these roles of stress act as negative reinforcement that strengthens drug using behaviour.

## **1.5. Individual Differences**

So far this chapter has discussed the differences that separate substance dependent individuals from healthy controls. While this is fundamental to the understanding of substance dependence, we also need to consider the range of individual differences within the substance dependent population. For example, Bechara et al (2002) identified two subgroups of substance dependent individuals one who showed no difference in IGT decision making performance, but another who did.

One particular difference focusses on the roles of the dopaminergic and opioid systems, both of which depend on the integrity of the NAcc (De Vries & Shippenberg 2002). Opioids

induce neuronal inhibition in the NAcc and ventral pallidum via GABA input; in the PFC, amygdala, and medial dorsal thalamus via glutamate input; and in the pedunculo pontine tegmental nucleus via acetylcholine input (De Vries & Shippenberg 2002). This cortical-pallidal-striatal circuit is dense in opioid receptors (Mansour et al. 1995) and is thought to mediate goal-directed behaviour (Mogenson et al. 1980) as well as psychostimulant reward (De Vries & Shippenberg 2002; Koob et al. 1998; Pierce & Kalivas 1997). Nevertheless, while dopamine is responsible for learning associations and producing the motivation involved in drug reinforcement, opioids mediate the reinforcing hedonic pleasure of drug use (Le Merrer et al. 2009).

As a result of these differences between opioid and dopamine reward, it has been argued that opioid dependence may be behaviourally and neurobiologically distinct from stimulant dependence (Badiani et al. 2011). The link with impulsivity in opioid dependence is less clear than with other substances, particularly stimulant dependence for which impulsivity is a well-established risk factor (for a review, see Dalley et al., 2011). Although increased impulsivity is reported in opioid dependent individuals (Kirby, Petry, & Bickel, 1999), even when separated from their cocaine dependence (Nielsen et al. 2012), other studies report that individuals dependent on cocaine are more impulsive than those dependent on heroin (Bornovalova et al. 2005; Vassileva et al. 2014). Similarly, levels of impulsivity in rats predicted escalation of cocaine self-administration (Dalley et al. 2007), but not of heroin self-administration (McNamara et al. 2010), while elevated impulsivity seen in opioid dependent individuals is thought to be a result of drug exposure rather than a pre-existing risk factor (Harty et al. 2011; Schippers et al. 2012). Differences in impulsivity in stimulant compared to opioid dependence leads us to the idea that certain personality traits are associated with dependence to specific drug groups. For example, anxiety sensitivity and hopelessness are more linked to anxiolytic and opioid dependence, sensation seeking with risk for alcohol dependence, and impulsivity with risk for cocaine dependence (Conrod et al. 2000).

However, other studies do not support this view (Chakroun et al. 2004; Gillespie et al. 2012). In particular Shaffer and colleagues (2004) proposed the existence of an “addiction syndrome” in which an individual becomes dependent on a particular substance (or behaviour, such as gambling) as a result of other external influences. These might include the experience of early life stressors, personality types and predisposing genetics, or the

availability of certain substances. In line with this, Swendsen and Le Moal (2011) suggest that levels of vulnerability to addiction fall into three factor categories: sociodemographic; psychiatric and psychological; biological and genetic. In reality, these levels overlap enormously and, most likely, are not completely separable. Swendsen and Le Moal also found that the most commonly cited explanations for psychiatric and substance dependence co-morbidity were causal models, where an initial disorder that increases the risk (directly or indirectly) for substance dependence and leads to self-medication, or shared etiological models where a separate factor increases risk of both conditions. They conclude that the outcome of dependence is largely arbitrary; rather that these other factors should be addressed during treatment.

To add to this idea of individual differences within substance dependence, Becker and colleagues (2012) propose the existence of two routes into dependence: a sensation seeking type that is driven by positive reinforcement; and a self-medicating type that is driven by negative reinforcement. The authors highlight these two routes to account for sex differences in addiction vulnerability, supported by evidence that males are more likely to engage in risky behaviours including drug use and sensation seeking, while females are more likely to self-medicate to reduce negative emotional states. In line with this 30-40% of problem drug using individuals have had at least one mood or anxiety disorder in their lifetime (Conway et al. 2006; Back et al. 2011; Wilcox & Yates 1993). Furthermore, a study that used real-time electronic diaries to track drug use, mood and craving found individuals more often reported good moods prior to cocaine use, and negative feelings prior to heroin craving (Epstein et al. 2009).

In line with the extensive literature on individual differences within healthy populations, it is intuitively appealing that substance dependent populations will also have such variations. Becker et al.'s model suggests how these variations relate to impulsivity and stress-reactivity, which are the focus of this thesis, although there is less emphasis placed on the sex differences or whether the profiles relate to specific substance preferences. Thus, the concern is that individual differences may be more important than the substances used by dependent individuals in understanding the mechanisms that are fundamental to their dependence.



## 1.6. Methodological Issues

As with any area of research, there are a number of methodological issues that arise. Within the study of addiction these issues particularly relate to sample selection and the levels of measurement used. While there are no rules on how to deal with such problems, there are some important factors that should be considered, which are discussed below.

### *Sample Selection*

A contentious issue within addiction research is that of sample selection. As there are many substances on which individuals can become dependent, we have to first choose the specific substance on which to focus. While some theorise that addiction is a generalised disorder and the substance of addiction is determined by the drug availability surrounding the individual at the time (Shaffer et al. 2004), others argue that there are fundamental differences between drug users of different substances. For example opioid dependent individuals are suggested to be fundamentally different from those dependent on stimulants (Baldacchino et al. 2015) and show behaviourally distinct patterns (Badiani et al. 2011; Vassileva et al. 2014), such as the higher levels of risk taking seen in cocaine dependent compared to heroin dependent individuals (Bornovalova et al. 2005).

There is also the issue of poly-substance dependence. Few individuals limit their use to one substance, with the result that it is almost impossible to disentangle the specific effects of each. Some investigations attempt to sidestep this issue by recruiting polydrug dependent individuals and comparing groups with and without the substance in question. However, this is far from a perfect solution as there are often additive effects, such as with the combined use of alcohol and cocaine that produces the metabolite cocaethylene, which is more detrimental to cognition than either alcohol or cocaine when used independently (Andrews 1997; Carroll et al. 1993; Jatlow et al. 1996). As yet, there is limited investigation into this question of poly-substance dependence. For example, a review of studies of inhibitory control within addiction by Smith et al. (2014) noted how little consistency there was in describing the different combinations and amounts of substances used by the “same” groups of substance dependent individuals.

Another concern within sample selection of substance dependent populations is the prevalence of co-morbidity with other mental health disorders (Conway et al. 2006; Swendsen & Le Moal 2011). For example, 30-40% of individuals with substance use

problems have had at least one mood or anxiety disorder as well (Conway et al. 2006; Back et al. 2011; Wilcox & Yates 1993). Even with past mental health issues, this causes a problem for determining whether the constructs we are measuring are solely related to dependence. One way to address this is to recruit suitably matched control participants with similar mental health histories. It is also important to match controls for other demographic variables in order to ensure that any group differences found are not due to differences in variables such as age, IQ and education. This can sometime be difficult to achieve, for example the nature of addiction often results in early school leaving either as a result of the drug use itself or due to other factors that contribute to dependence vulnerability, including childhood adversity and parental substance dependence (Dube et al. 2003; Sorocco et al. 2015). However, it is impossible to recruit perfectly matched controls (see Schulte et al. 2014), and the inclusion of differences such as IQ cannot be removed completely by their entry as covariates in the analysis (Meehl, 1970), meaning that these differences need to be taken into account when drawing conclusions from findings.

### *Smoking*

We should also take into consideration the influence of smoking, as this is commonly seen in combination with heavy substance use and dependence. There are complex effects of chronic and acute nicotine in humans (Nees 2015), which we need to take into account when studying the effects of other substances. For example, smoking and nicotine administration upregulate nicotinic acetylcholine receptors (Jasinska et al. 2014), which like other drugs, stimulate dopamine release in the ventral striatum (see De Biasi & Dani 2011 for a review) and produce reinforcing effects that contribute to the development of dependence (for a review, see Rose 2006). Therefore, if control participants who smoke are recruited, technically they are not without dependence, although many studies consider them to be so. However, due to the prevalence of smoking in the general population as well as the cognitive impact of smoking, the best option is usually to match control participants for smoking status.

The evidence for the influence of nicotine on cognition is complex. Nicotine is seen to enhance cognition, particularly attention and memory (for a review, see Heishman et al. 2010), but chronic smoking is associated with cognitive deficits in middle age (Kalmijn 2002; Richards et al. 2003). Nevertheless, nicotine's modulation of a number of different brain

networks and transmitter systems generally enhances executive functioning (for a review, see Jasinska et al. 2014), particularly through its influence of dopaminergic pathways. With reference to impulsivity, smokers show greater discounting of monetary rewards than non-smokers (e.g. Mitchell 1999; Sweitzer et al. 2008). Similarly, rats show dose dependent increases in temporal discounting of rewards with acute nicotine administration and long-lasting impulsivity in chronic nicotine administration (Dallery & Locey 2005). Structural changes as a result of smoking are also noted, for example MR volumetric investigations report reductions in prefrontal, anterior cingulate, parietal and temporal cortices, as well as the cerebellum (Brody et al. 2004; Gallinat et al. 2006).

### *Levels of Measurement*

A second methodological issue relates to any aspect of neurocognition, in that there are three different levels of measurement that can be used: self-report, behavioural and neural. This issue is especially pertinent in the study of impulsivity in addiction, as a result of the multifaceted nature of impulsivity.

Firstly, self-report measures can be divided into cognitive impulsivity and emotional impulsivity (Fernández-Serrano et al. 2012). Cognitive impulsivity, such as reflection and attentional impulsivity are assessed by the Barratt Impulsiveness Scale (BIS; Patton, Stanford, & Barratt, 1995), and higher scores compared to controls are seen in heroin (Nielsen et al. 2012), alcohol (Evren et al. 2012; Papachristou et al. 2013; von Diemen et al. 2008) and cocaine dependence (Meunier et al. 2012; Ersche et al. 2010). Emotional impulsivity, such as Positive and Negative Urgency are assessed by the UPPS Impulsive Behaviour Scale (UPPS; Whiteside & Lynam 2001; 2003) and can be seen in the influence of positive and negative reinforcement on inhibitory control (Woicik et al. 2009), both of which are influential in poly-substance users. Such measures, particularly the UPPS, are useful because they assess the emotional aspects of impulsivity that are missed in many behavioural impulsivity measures, thus making them more ecologically valid. However, limitations of this self-report approach are just that; they are reliant on individual report, which is susceptible to bias, as well as on honesty and individual insight (Verdejo-García et al. 2008).

Secondly, cognitive behavioural measures are objective methods that are not susceptible to individual bias, variability in honesty or personal insight (Bari & Robbins 2013). These are

also more specific to the different aspects of impulsivity (see section 1.2 on types of impulsivity). Commonly used in the study of substance use and dependence are the Go/No-Go (GNG) and the Stop Signal (SST) tasks, which measure motor inhibitory control. The GNG is a measure of impulsive action, measuring the ability to inhibit a response before it is initiated, while the SST is a measure of action cancellation, assessing inhibition of a response after it is initiated (Dalley et al. 2011). Examples of other specific tasks include the Information Sampling Task (IST) and the Matching Familiar Figures (MFF) tasks that measure reflection impulsivity, the Balloon Analogue Risk-Taking (BART) task that measures risky decision making, and the Iowa Gambling Task (IGT) and delay discounting tasks (such as the Kirby; Kirby & Maraković, 1996) that measure impulsive choice. The Kirby finds that substance dependent individuals forfeit long-term gain (e.g. good health) for short-term immediate reward (Kirby et al. 1999; Perry & Carroll 2008; Verdejo-García et al. 2008; Potenza & Taylor 2009; Bechara et al. 2001).

Additional cognitive control is also measured using the colour-word Stroop task, which measures cognitive control when naming incongruent colour words or naming the colour of emotion- or substance-related words. While the latter is usually used as a measure of attentional bias, both involve inhibitory control to withhold the incorrect response (the word) in favour of the correct response (naming the colour). The Intra-Extra Dimensional Set Shift (IED) task measures cognitive flexibility; the ability to adapt to changing environments by inhibiting the prepotent response to persevere with established behavioural patterns. Derived from the Wisconsin Card Sorting Task (WCST), the IED is a test of rule acquisition and reversal, featuring visual discrimination, attentional set formation maintenance, shifting and flexibility of attention; assessing fronto-striatal brain regions that are linked with impulsivity (Volkow et al., 2011). Inhibitory control is required at each rule change to withhold the behaviour required for the previous rule, as measured by the number of errors made at each stage. Evidence of impaired cognitive flexibility is reported in heroin and amphetamine abusing individuals (Ornstein et al. 2000), as well as in alcohol dependence, which is also associated with lower grey matter densities in frontal brain regions (Trick et al. 2014). These impairments and structural differences were linearly associated with the number of detoxifications participants had experienced, implicating either the process of detoxification as causal, or that those with more impairment were at greater risk of relapse.

Inevitably, there are also some limitations of cognitive behavioural tasks, most notably that they only measure one aspect of cognition at a time, similar to one item on self-report measures. This means that they may be more useful in a battery of impulsivity tasks to produce multi-task behavioural indices (Sharma et al. 2014) rather than when used independently. In addition, these tasks only assess the current situation and they are thought to be more sensitive to state impulsivity (Stevens et al. 2015; Cyders & Coskunpinar 2012; Sharma et al. 2014), which means they are more susceptible to transitory emotional or environmental influences. There is also the question of ecological validity: how well is impulsive behaviour operationalised by the withholding of button-press response at the sound of a beep? While some cognitive tasks are arguably more realistic than others, for example delay discounting measures, these are more inclined to reliance on individual insight and bias as with self-report measures. In this instance, self-report measures are better able to reflect long-term stable traits that involve emotionally-relevant aspects more akin to every-day impulsive behaviours that can lead to the individual to problematic situations.

Thirdly, neuroimaging measures are based on many of the cognitive tasks mentioned above. While neural measures have the same limitations as behavioural tasks, they have the added advantage of measuring brain function alongside behavioural performance. Within the study of impulsivity, the SST and GNG are used widely (for a meta-analysis, see Smith et al. 2014) and are associated with the top-down control of subcortical structures, such as the ventral striatum, by the frontal cortical regions of the OFC, ACC, dlPFC and IFG, (Garavan et al. 2006; Simmonds et al. 2008; Chambers et al. 2009); reduced activation in these frontal regions is strongly associated with decreased inhibitory control in substance dependence (Kaufman et al. 2003; Hester & Garavan 2004; Morein-Zamir et al. 2013). In addition, neural measures can often highlight functional differences between substance dependent individuals and controls that are not apparent in their behavioural performance alone, such as reported in inhibitory control in cannabis dependent individuals (Tapert et al. 2007). This has provided an indication of the neural mechanisms behind poor impulse control, in order to understand it better and perhaps ask more pertinent questions.

None of these measures are perfect alone; each has its own advantages and disadvantages, which can be balanced out when all levels of measurement are used in combination. However, the multitudes of different ways of measuring the same construct mean that it is

hard to generalise across them (for a review, see Sharma et al. 2014). For example, versions of the SST with a lower percentage (25%) of stops correlate better than those with a higher percentage (40-50%) of stops (for a review, see Lansbergen et al. 2007). In general, self-report and cognitive measures of impulsivity are poorly correlated (Reynolds et al. 2006; Broos et al. 2012; Sharma et al. 2014) and some even question whether they should all be termed measures of impulsivity but be divided into separate constructs (Sharma et al. 2014). This is likely due to the multifaceted nature of impulsivity and the specificity of the cognitive behavioural measures that conceptualise distinct attributes in different ways. For example, self-reported BIS-11 impulsivity did not explain behavioural response inhibition (using the SST), but the subdomain of Urgency from the UPPS did explain this (Wilbertz et al. 2014).

Although all these measures are assumed to evaluate the trait construct of impulsivity, behavioural measures are generally thought to measure a transitory state, while trait impulsivity is typically measured using self-report measures (Stevens et al. 2015). Nevertheless, these different aspects of impulsivity share an “overall recruitment of inhibitory volitional control” (pp. 682; Dalley et al 2011) that is required at different stages during the response process. It is likely that the different measures are particular to the different response stages of choice, preparation and initiation. However, using all three levels of measurement (self-report, behavioural and neural) provide us with a general picture from which we can focus down into the specific cognitive and neuroimaging tasks.

### *Other Methodological Considerations*

Once we have considered the levels of measurement, we also need to consider the relevance of “hot” versus “cold” cognition. Hot cognition implies that there is motivated reasoning and an individual’s emotion influences the behaviours that we measure with cognitive tasks. This is important in the study of addiction, especially with regards to relapse in abstinent substance dependent individuals who may behave differently than current users, but report that factors such as stress increase craving and thus increase the risk of relapse (Fox et al. 2007; Sinha & Li 2007). The majority of tasks used for measuring impulsivity in addiction (as mentioned above) are based on cold cognition, such as the GNG, whereas tasks such as delay discounting have an emotionally salient outcome. By investigating how emotional states influence cognitive mechanisms, we can begin to understand how individual differences in stress response impact on the vulnerability to and

maintenance of substance dependence. It may be this difference in managing stress that separates an individual prone to development of dependence from one who is not.

We can adapt original tasks to be more emotion-relevant by the addition of drug cue-specific elements, which inform about behaviour in relation to the substance of dependence. For example, when alcohol-specific images are used for go-trials in the SST, alcohol dependent participants show a marked increase in impulsive responding (Zack et al. 2011). Relevant feature stimulus response compatibility tasks have also been used in alcohol dependence and heavy drinking, finding that performance is related to drinking behaviour (Field et al., 2011; Kersbergen, Woud, & Field, 2015) and can be a significant predictor of hazardous drinking (Kersbergen et al. 2015). Similar versions of these tasks have also been used to retrain alcohol dependent individuals to improve treatment outcomes (Eberl et al., 2012; Wiers, Eberl, Rinck, Becker, & Lindenmeyer, 2011). Cue-specific studies also provide information on the effect of impulsivity on drug-related behaviours. For example, impulsivity predicts hazardous drinking and alcohol approach tendencies (Christiansen et al. 2012), and inhibition training reduced alcohol intake (Houben et al. 2012). As a result, addiction research should incorporate more substance-related elements into the neurocognitive assessment of impulsivity in substance dependence.

Finally, we also need to keep in mind that all these neurocognitive measurements are conducted against a background of poor cognition in substance dependent individuals. Years of neurocognitive research have identified a number of generalised cognitive impairments that are associated with substance dependence. For example, poor episodic memory, executive functioning, decision making and emotional processing are all related to chronic substance use, while alcohol and stimulant use are linked more specifically with deficits in impulsive action and cognitive flexibility (for a review, see Fernández-Serrano et al. 2011). Even after sustained abstinence, there appears to be limited evidence of recovery (Schulte et al. 2014).

There is also substantial evidence for brain damage as a result of alcohol use, particularly larger ventricles as well as reduced frontal lobe and hippocampal volumes (Delamonte 1988; Wobrock et al. 2009; Demirakca et al. 2011; Bühler & Mann 2011). The extent of grey matter reduction is thought to be a result of alcohol withdrawal as it is associated with the number of detoxifications (Obernier et al. 2002; Trick et al. 2014) and in turn is associated

with poorer cognitive performance (Duka et al. 2002; Loeber et al.; Cardenas et al. 2011), specifically executive tasks (e.g. Jang et al. 2007; Chanraud et al. 2007; Fein et al. 2009) and notably in inhibitory control (Trick et al. 2014). Although not as visibly obvious as alcohol brain damage, chronic use of cocaine is also associated with reduction in cerebellar grey matter volume (Sim et al. 2007), as well as volume reductions in the striatum (Barrós-Loscertales et al. 2011) and OFC (Ersche et al. 2011), as well as vascular damage (Madoz-Gúrpide et al. 2009). Similarly, although there is comparatively less evidence, there are also reports of grey matter reductions as a result of prolonged opioid use in the PFC, ACC and temporal cortex (Yuan et al. 2009). Thus, we must bear this evidence in mind when conducting functional investigations of substance dependence in order to control for these structural differences.

## **1.7. Summary**

This chapter has highlighted the need for further investigation into substance dependence, which causes serious medical, social and economic problems worldwide. It described some of the harms to drug users that include alterations to neuropsychological, structural and functional systems, which have the potential to affect their vulnerability for dependence development, maintenance of drug use, and increase relapse risk following detoxification. This chapter has then highlighted two important neurocognitive aspects of substance dependence, the role of impulsivity and the role of stress through negative reinforcement, as well as discussed some of the key methodological considerations.

The first main section of this chapter discussed the multifaceted construct of impulsivity and the many routes by which it may be associated with substance dependence. The literature suggests that impulsivity is exacerbated by substance exposure, but it is also a pre-existing trait that increases vulnerability for addiction. Neural substrates of impulsivity particularly focus on the top-down control of subcortical structures by frontal regions, which is compromised during the shift to compulsive drug use.

The second section considered the role of stress in the development, maintenance and relapse of substance dependence through the process of negative reinforcement. Physiological effects of drug use result in physiological stress changes seen in the body's attempts to rebalance the homeostasis that drug use disturbs, which progressively worsens and has secondary effects seen in emotional changes that influence saliency attribution,



memory and learning processing, so that arousal for positive stimuli is reduced, while it is increased for negative stimuli. Both these roles are significant in the development and maintenance of drug addiction, as well as increasing the potential for relapse. Stress also plays a significant role in vulnerability for the development of substance dependence. Neural substrates of stress and emotional responses particularly involve the amygdala as well as the NAcc in avoidance behaviour.

The third section of this chapter discussed the importance of individual differences within the substance dependent population; something that is largely overlooked in addiction research. Drawing on the discussions of impulsivity and then stress in addiction, this third section considers how these two important aspects may be related to the various individual profiles within substance dependence that may reflect very different underlying causes for drug use.

The final section discussed a number of methodological issues within addiction research. This covered the decisions required for suitable sample selection, the appropriate use of different levels of measurement within neurocognitive research, and the importance of incorporating emotion and cue-specific aspects into these measurements as well as taking into account the background of cognitive impairment as a result of substance use.

These discussions highlight a number of areas that need to be considered in addiction research, and are investigated in the four separate studies that are presented in Chapter 2. The first is that the vast majority of impulsivity research is conducted using one or two measures and only in one substance using population at a time, with little reflection on polydrug dependence. **Study 1** addresses this by investigating a number of different measures of impulsivity, using three levels of measurement in a large varied sample of substance dependent individuals, including those with polydrug dependence. Another issue raised in this introductory chapter is the importance of individual differences and the different profiles of substance dependence. This is addressed by **Study 2**, which attempts to use a data-driven approach to classify substance dependent individuals on their personality risk factors based on impulsivity and affective measures, rather than the substances used.

This chapter also discussed the role that emotion plays in the development of substance dependence, particularly in relation to stress. Because there are arguments that stress is highly involved in the early stages of substance dependence development through the process of negative reinforcement, **Study 3** investigates the effect of stress on early heavy alcohol use and the automatic behaviour related to attentional bias and cue-approach. Finally, **Study 4** investigates the neural correlates of this alcohol-approach behaviour, incorporating another level of measurement in addition to **Study 3** with the use of functional imaging.

Thus, the following four hypotheses are investigated:

1. Not all the current methods for measuring impulsivity in substance dependent individuals are appropriate at every stage of dependence or for each participant group.
2. The current classifications of dependent individuals based on primary substance do not best reflect the different profiles within addiction.
3. Stress is influential in the progression of heavy drinking to alcohol dependence through the process of negative reinforcement.
4. Differential neural processing of automatic approach and avoidance behaviour is involved in the early stages of substance dependence.

Through these investigations this thesis will attempt to bring together the role of impulsivity and emotion in substance dependence while considering the different levels of measurement and individual differences of substance dependent individuals, as well as exploring the role that stress plays in influencing substance-related behaviours.

## Chapter 2: Papers

### 2.1 Study 1: Impulsivity in alcohol and poly-drug dependence: a multi-dimensional approach

#### *Submission*

This paper has been prepared for submission, has been reviewed and is due to be re-submitted within the next month to *Psychopharmacology* (<http://www.springer.com/biomed/neuroscience/journal/213>).

#### *Individual contribution*

The data in this paper were collected as part of the ICCAM Platform Study, a multi-centre collaborative project shared between Imperial College, the University of Cambridge and the University of Manchester. I was one of two researchers who collected data at Manchester. I also conducted all the analyses presented in this paper, and prepared the manuscript.

\*A full list of ICCAM Platform collaborators can be found in the Appendix.

## Impulsivity in alcohol and poly-drug dependence: a multi-dimensional approach

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**Rationale:** Dependence on drugs and alcohol is frequently associated with impaired impulse control, but deficits are rarely compared across individuals dependent on different substances using several measures within a single study. **Objectives:** We investigated impulsivity in abstinent substance dependent individuals (AbD) using three complementary techniques: self-report, neuropsychological and neuroimaging. We hypothesised that AbDs would show increased impulsivity across all modalities, and that this might vary with the substances involved. **Methods:** Data were collected from the ICCAM study: 46 control and 68 AbDs (excluding nicotine), comprising a group dependent on alcohol (n=26) and a group dependent on multiple substances including alcohol, opioids or stimulants (“polydrug” dependent, n=42). All participants completed a series of self-report measures of impulsivity: Barratt Impulsiveness Scale, UPPS Impulsive Behaviour Scale, Behaviour Inhibition/Activation System and Obsessive-Compulsive Inventory. They also performed three behavioural tasks: Stop Signal, Intra-Extra Dimensional Set Shift and Kirby Delay Discounting; and completed a Go/NoGo task during fMRI. **Results:** AbDs scored significantly higher than controls on self-report measures, but alcohol and polydrug dependent groups did not differ significantly from each other. During fMRI polydrug participants showed hyperactivation in left inferior frontal gyrus compared with controls during successful inhibitions. There were no group differences on neuropsychological measures.

**Conclusions:** The results suggest that the current set of self-report measures of impulsivity are more sensitive to impulsivity in abstinent individuals than the behavioural or fMRI measures of neuronal activity. This highlights the importance of developing behavioural measures to assess different aspects of impulsivity rather than simple motor inhibition, alongside corresponding cognitive challenges for fMRI.

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## Introduction

Impulsivity is action without forethought, involves premature responding, poor response inhibition and low tolerance for delay (Evenden 1999). It is frequently associated with substance dependence (Dalley et al. 2011; de Wit, 2009; Perry & Carroll, 2008; Verdejo-García et al. 2008) and the extent of impulsivity is related to the severity of substance use and dependence (Verdejo-García et al. 2008; Belin et al. 2008). Although humans use many different substances legally and illegally, heroin, cocaine and alcohol are rated as the most harmful in the UK (Nutt et al. 2010); these were the focus of the present study.

When investigating the link with substance dependence, impulsivity has been measured in many ways, using either self-report questionnaires or behavioural measures (Verdejo-García et al. 2008). However, self-report and behavioural measures are rarely correlated (Bari & Robbins 2013; Broos et al. 2012) as each measure looks at distinct attributes, often conceptualised in very different ways. Self-report measures, such as the widely-used Barratt Impulsiveness Scale (BIS-11; Patton et al. 1995), are assumed to be relatively stable trait constructs, while behavioural measures are dependent on specific strategies that may differ between individuals and testing sessions (Bari & Robbins 2013). While self-report measures may be more ecologically valid, they are reliant on individual insight and are susceptible to bias (Verdejo-García et al. 2008).

Two commonly used cognitive paradigms are the Go/NoGo Task (GNG), which measures the ability to inhibit a response before it is initiated, and the Stop Signal Task (SST), which measures inhibition of a response after it is initiated. Both tasks have revealed decreased inhibitory control in cocaine dependence (Ersche et al., 2011; Fernández-Serrano et al. 2012; Kaufman et al. 2003) and alcohol dependence (Sjoerds et al. 2014). A recent meta-analysis of these tasks (Smith et al. 2014) found decreased inhibitory control in alcohol and cocaine dependence, but not in opioid dependence. However, there were very few studies using the GNG task in opioid users and none using the SST. One study since has used the SST in opioid dependence, finding increased impulsivity (Liao et al. 2014).

Studies of the neural substrates of impulsivity emphasise the importance of top-down control of subcortical structures, such as the nucleus accumbens (ventral striatum) by frontal brain regions particularly the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (dlPFC; Aron et al. 2003; Hester & Garavan, 2004;

Kaufman et al., 2003). The inferior frontal gyrus (IFG), especially right sided, ACC and dlPFC are frequently implicated in SST and GNG tasks (Chambers et al. 2009; Garavan et al. 2006; Simmonds et al. 2008). Reduced activations associated with poorer inhibitory control in stimulant users have been observed in the ACC and pre-supplementary motor area (preSMA; Kaufman et al. 2003; Hester & Garavan 2004; Li et al. 2008), as well as the right superior frontal gyrus (Hester & Garavan 2004) and right insula (Kaufman et al. 2003). Reduced prefrontal activation associated with decreased inhibitory control has also been observed in alcohol dependent individuals (Li et al. 2009), while neuroimaging studies comparing opioid dependent individuals to controls have found performance impairments accompanied by reduced prefrontal, insula and limbic system responses (Forman et al. 2004; Fu et al. 2008).

Recent investigations of impulsivity pay particular attention to the multifaceted nature of the construct and suggest that different forms of impulsivity are influential at different stages of dependence. For example, impulsive choice (measured using delay discounting and Iowa Gambling Task measures) predicts relapse, while impulsive action (measured using SST) does not differentiate abstinent and relapsed participants (Stevens et al. 2015). High impulsive choice is associated with continued drug use and poor maintenance of abstinence (Passeti et al. 2008; MacKillop & Kahler 2009; Washio et al. 2011; Stevens et al. 2013; Stevens et al. 2014), while impulsive action is thought to be related to initial sensitivity (Diergaarde et al. 2008; Broos et al. 2012). Stevens et al. (2015) also suggest that behavioural measures are more useful than trait measures for detecting relapse risk, and imply that the different types of measures may be more useful at the different stages of addiction.

In addition, there is evidence for recovery of executive functioning during abstinence (Schulte et al., 2014; Stavro et al. 2013; Sullivan et al. 2000), which means we need to consider individual length of abstinence. There is also evidence of normalisation of behavioural inhibitory control (Hopwood et al. 2011; Morie et al. 2014; Bell et al. 2014), although other studies have reported that behavioural impulsivity is still elevated in abstinent alcohol dependent participants with mean length of abstinence of six months (Naim-Feil et al. 2014). However, length of abstinence may be more critical in terms of recovery past 12 months as 65-75% of substance dependent individuals (AbD) relapse within 12 months of treatment discharge (Sinha 2011). Because poor treatment retention

and early relapse are associated with higher impulsivity in dependence (Moeller et al. 2001; Patkar et al. 2004; Evren et al. 2012), it may be that more impulsive individuals who can maintain abstinence to six months but no further, are different in terms of their impulsivity to those who achieve 12 months or longer abstinence.

The evidence of impulsivity in substance dependence is not consistent, especially when we consider the different types of substance dependence (for a review, see Smith et al., 2014). However, there has been little research comparing groups with different dependencies within a single study and the majority of papers have fewer than 30 participants per group (Smith et al. 2014), only providing sufficient power to detect moderate effect sizes. Therefore, the aim of the present study was to investigate impulsivity measures across different modalities: self-report, behavioural and neuroimaging, in a large number of participants dependent on different substances. We hypothesised that AbDs would show increased impulsivity across all modalities and that this would be more marked in those with dependence on multiple substances compared to those dependent on alcohol alone.

## **Methods**

This study was conducted as part of the ICCAM Platform Study ([www.iccam.org.uk](http://www.iccam.org.uk)), details of which are reported by Paterson et al. (2015). The protocol was approved by the West London Research Ethics Committee (REC Ref: 11/H0707/9; PI: Prof D.J. Nutt). Non-imaging testing sessions were conducted at three sites: NIHR/Wellcome Trust Imperial Clinical Research Facility, NIHR/Wellcome Trust Cambridge Clinical Research Facility, and Clinical Trials Unit, Salford Royal NHS Foundation Trust. Imaging sessions were conducted in the adjoining centres at Imanova Limited (formerly the GSK Clinical Imaging Centre), Wolfson Brain Imaging Centre, Manchester Translational Imaging Unit (3T MRI Facility) respectively.

### *Participants*

Participants, including abstinent substance dependent individuals (AbDs) and controls, were recruited from local NHS addiction services and via advertising on social media, in job centres and libraries. Following written and informed consent, all participants were assessed using the Structured Clinical Interview for DSM-IV to assess for dependence history and checked by a psychiatrist. Exclusion criteria for all participants included lifetime history of psychotic disorder, neurological illness, neurodevelopmental disorder or traumatic head injury. Participants were between 20-65 years old and able to read and

write in English. To confirm abstinence on day of testing, all participants completed an alcohol breath test and urine drug screen. Participants were requested to refrain from cannabis use for at least seven days prior to each session but, given the long half-life of cannabinoid metabolites, positive results for cannabinoids were permitted if the participant was not intoxicated or in withdrawal (determined by the psychiatrist conducting the interview). AbDs were abstinent for at least two weeks prior to testing. Nicotine use was not an exclusion criterion in any group as the majority of substance dependent individuals smoke tobacco.

Of the 176 participants who completed the testing session across the three sites, 146 of these were eligible for inclusion in analyses based on exclusion criteria listed above. A further 32 participants were excluded (2 alcohol dependent, 17 polydrug, 13 controls, based on the flowchart in Supplementary Figure 1.1) in order to ensure the groups were matched on age, IQ and smoking status (Table 1.1). This left 114 participants (21.9% female, aged 27-64, mean 42.40, SD 8.38) comprising 46 control participants with no history of substance dependence (except nicotine), and 68 AbD participants. The majority of AbDs had experience with a large number of substances and many met criteria for dependence on multiple substances. For the purposes of this study, we defined two AbD groups: “alcohol dependent” participants who met DSM-IV criteria for dependence on alcohol (n=26) and “polydrug dependent” participants who met DSM-IV criteria for dependence on two or more substances, one of which was alcohol, cocaine or heroin (n=42; Table 1.2).

Three control participants did not complete the behavioural tasks, leaving 43 control participants in the behavioural analysis. Twelve participants were removed from the GNG imaging analysis due to excessive movement (defined as >20% volumes with >1mm movement) or low baseline performance on the GNG imaging task (<85% Go accuracy), leaving 42 control, 23 alcohol and 37 polydrug participants in the imaging analysis.

## *Assessment Procedure*

### *Clinical Variables*

Participants were interviewed to ascertain eligibility and group allocation. We also obtained data on their substances of dependence (excluding nicotine) and length of abstinence (Table 2.2). For alcohol dependent participants, length of abstinence was



calculated from their last use of alcohol to dependent levels. For polydrug dependent participants the multiple substances meant that length of abstinence could only be calculated from the most recent use of any substance of dependence.

#### *Self-Report Questionnaires*

Participants completed a battery of impulsivity questionnaires presented in computer format. These included the Barratt Impulsiveness Scale (BIS-11; Patton et al., 1995), Behaviour Inhibition/Activation System (BIS/BAS; Carver & White, 1994), the UPPS Impulsive Behaviour Scale (UPPS-P; Whiteside & Lynam 2003) and the Obsessive Compulsive Inventory Revised (OCI-R; Foa et al., 2002).

#### *Behavioural Tasks*

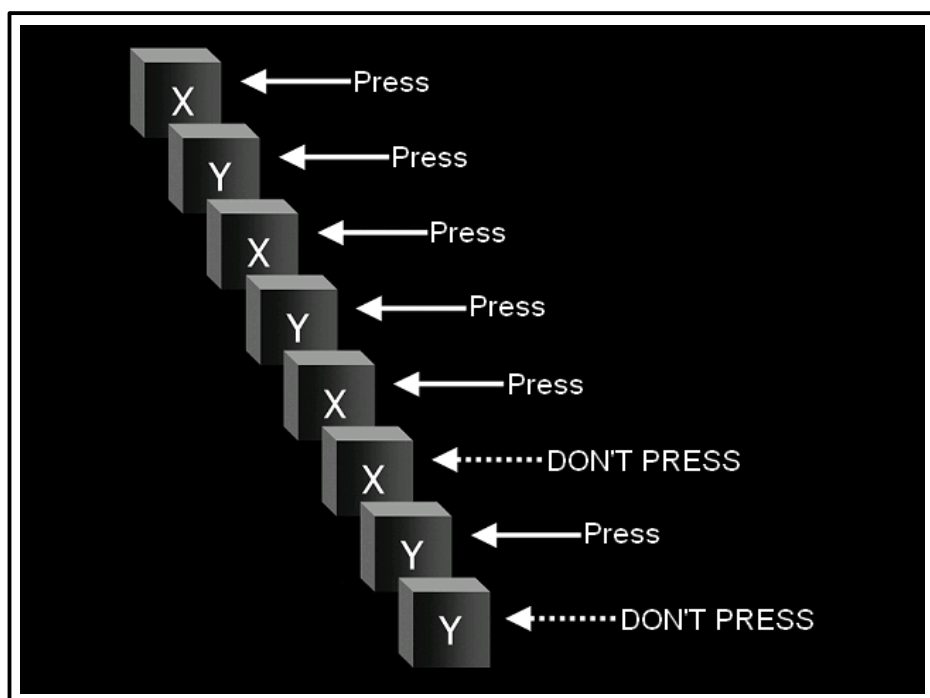
The Kirby test of delay-discounting (Kirby & Maraković, 1996) measures the discounting rate; the extent to which the present value of a future reward decreases as the delay to its receipt increases. Hypothetical immediate rewards of £11-80 and delayed rewards of £25-85, with delays of 7-186 days were used. A hyperbolic discount parameter ( $k$ ) score for each participant was generated from the proportion of immediate choices that were made over delayed choices using the method reported by Kirby (1999; 2000). Greater discounting, indexed by increasing  $k$  values, indicates higher levels of impulsivity.

Participants also completed the Stop Signal Task (SST) and the Intra-Extra Dimensional Set Shift (IED) task from the well-validated CANTAB neuropsychological test battery ([www.cambridgecognition.com/academic/cantabsuite/executive-function-tests](http://www.cambridgecognition.com/academic/cantabsuite/executive-function-tests)). The SST is a test of motor inhibition, specifically action cancellation (Dalley et al. 2011), at the presentation of an auditory stimulus. A full description is presented by Ersche and Sahakian (2007). The primary outcome is the “Stop-Signal Reaction Time” (SSRT), which is the time an individual requires to withhold a response.

The IED is derived from the Wisconsin Card Sorting Task and assesses rule acquisition and reversal, visual discrimination, attentional set formation, maintenance, shifting and flexibility of attention. Primary outcome measures are “total errors” (adjusted for any early terminations), “number of stages completed” and “number of errors at each stage”. A full description is presented in Downes et al. (1989).

### *Functional MR Imaging Tasks*

To investigate neural substrates of inhibitory control, participants performed a Go/NoGo (GNG) task whilst being scanned using fMRI (Figure 1.1). Participants were presented with a series of individual “X”s and “Y”s and asked to respond as quickly as possible to each letter by pressing a button (Go), except when it immediately repeated itself (NoGo). This was an event-related task carried out in two runs of 250 trials, each containing 220 Go trials and 30 NoGo trials. This ratio of frequent Go to rare NoGo trials was used as it is a stronger test of pure inhibition than equal Go:NoGo ratios (Smith et al. 2014). Each letter was presented for 900ms and followed by 100ms inter-stimulus interval of a blank screen. Each run began with a 12 second fixation and lasted for 262 seconds. Immediately before scanning participants completed 60 practice trials.



**Figure 1.1:** An instruction screen from the Go/NoGo task. Participants are asked to respond as quickly as possible to each letter “X” and “Y” that appears on the screen, except when the letter is the same as the one shown previously.

### *MR Image Acquisition*

Imaging was carried out at the three sites using a Siemens (Imperial and Cambridge) or a Philips (Manchester) 3T MR scanner. One hundred and thirty one volumes were acquired, comprising 33-36 axial slices of 3mm thickness, with a TR of 2000ms, TE of 32ms and a voxel size of 3 x 3 x 3mm. In order to maximise cerebral coverage while minimising slice thickness and susceptibility artefact, fMRI/EPI acquisition was at +30 degrees to the ACPC

line. A T1-weighted structural image was also acquired for use in spatial pre-processing and for examination of any structural abnormalities.

## *Data Analysis*

### *Self-Report and Behavioural Data Analysis*

Data were analysed using Statistical Package for Social Sciences (SPSS, version 22, [www.spss.com](http://www.spss.com)) firstly using multivariate analysis of variance (MANOVA) to assess overall group differences. Where significant main effects were found, these were explored with individual univariate analyses of variance (ANOVA), and finally Tukey's LSD post-hoc test when main effects from the univariate analyses were found. A Pearson's Chi-square test was used to assess group allocation, and Pearson's correlations to assess relationships between impulsivity variables and length of abstinence.

### *Image Analysis*

Imaging data were analysed using Statistical Parametric Mapping (SPM12; Wellcome Trust Centre for Neuroimaging, London, England, <http://www.fil.ion.ucl.ac.uk/spm/>), implemented in MATLAB (Mathworks, 2012). Images were realigned to correct for motion, using the first image as a reference. The structural (T1-weighted) and functional images were then coregistered, followed by spatial normalisation, and were smoothed using a Gaussian kernel filter of 8 x 8 x 8mm. First level analysis was performed on the contrasts of "Stops" (successful inhibitions) compared to a background of Go responding. Errors of commission were modelled as a contrast of no interest as there were too few for sufficient power. Also modelled as contrasts of no interest were "Sleep", where there were more than 10 consecutive errors of omission on Go trials, and "False Inhibitions" where successful inhibitions on NoGo trials were immediately preceded by an omitted Go trial.

The second level analysis used a region of interest (ROI) approach based on areas previously identified in the inhibitory control literature as being altered in substance dependence. The areas identified were the right and left inferior frontal gyri (IFG) and the anterior cingulate cortex (ACC), defined by Neuromorphometrics, Inc. ([www.neuromorphometrics.com](http://www.neuromorphometrics.com)), under academic subscription. We extracted the average value of the Stops contrast per person within each ROI and performed group comparisons using independent-samples t-tests in SPSS. Correlation analyses were conducted by performing one-way ANOVAs with the variables of "NoGo accuracy" and "length of

abstinence" entered as separate covariates ( $p < 0.05$ , Bonferroni corrected for three comparisons). To investigate the relationship with length of abstinence, the control group were removed from the analysis. One polydrug participant was also removed due to an outlying length of abstinence score (Table 1.2).

## Results

### *Demographics and Clinical Variables*

Participant group demographics can be seen in table 1.1, while additional dependencies and length of abstinence can be seen in table 1.2. One polydrug dependent participant was removed from the length of abstinence analysis due to an outlying length of abstinence of more than two standard deviations from the mean. There were no differences in length of abstinence between alcohol and polydrug dependent participants ( $t(65)=0.260$ ,  $p=0.777$ ).

**Table 1.1:** Demographic data for control, alcohol dependent and polydrug dependent participants.

	Control	Alcohol	Polydrug	F or $\chi^2$	df	p
<b>Age</b> (Mean, SD)	42.15 (8.33)	45.27 (8.16)	40.90 (8.31)	2.265	2, 111	0.109
<b>IQ</b> (Mean, SD)	106.24 (8.71)	104.38 (7.34)	103.24 (7.55)	1.574	2, 111	0.212
<b>% Female</b>	26.1	23.1	16.7	1.164	2	0.559
<b>% Smokers</b>	63.0	73.1	76.2	1.784	2	0.410

**Table 1.2:** Substance dependence data for control, alcohol dependent and polydrug dependent participant groups. Data exclude nicotine dependence.

		Control	Alcohol	Polydrug	Total
<b>Alcohol Dependence</b>	No	46	0	13	59
	Yes	0	26	29	55
<b>Cocaine Dependence</b>	No	46	26	10	82
	Yes	0	0	32	32
<b>Opioid Dependence</b>	No	46	26	15	87
	Yes	0	0	27	27

<b>Length of Abstinence</b> (months)		Alcohol	Polydrug	Polydrug (outlier removed)
	<b>Mean (SD)</b>	15.37 (18.11)	21.66 (-49.48)	14.29 (-12.98)
	<b>Median</b>	8.00	10.50	10.00
	<b>Range</b>	1.0-79.0	0.5-324.0	0.5-48.0

### *Normalisation of data*

Initial data screening using Q-Q plots highlighted non-normally distributed scores for the SST Stop Signal Delay, SST Mean Go Reaction Time, IED total errors, Kirby and OCI-R.

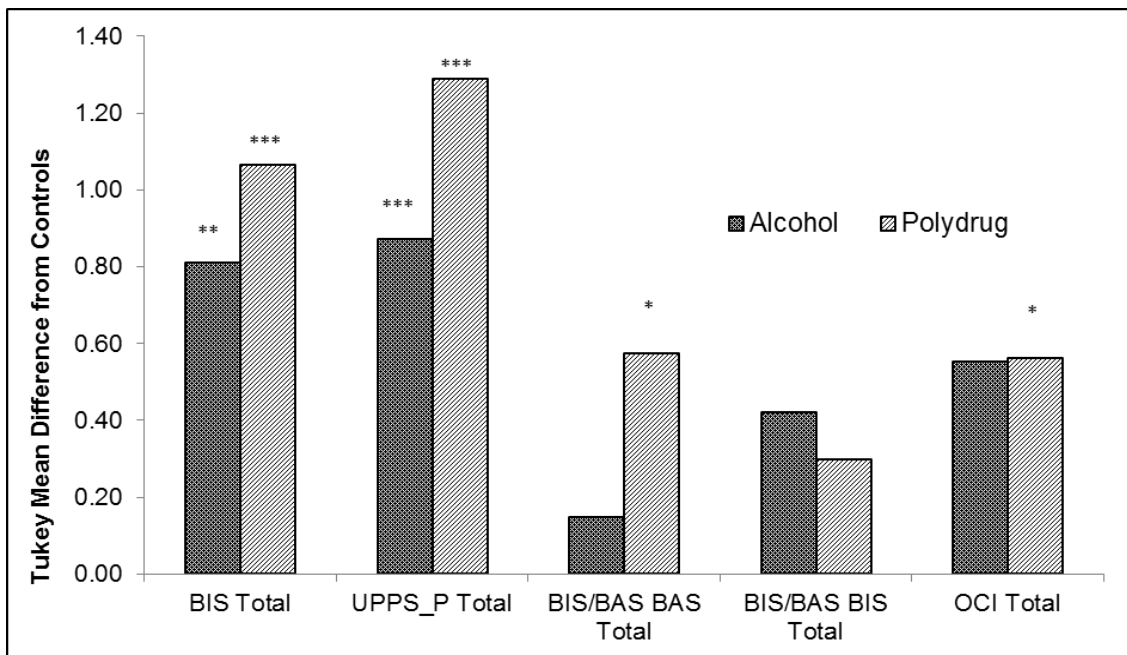
Therefore, these data were transformed using a log transformation, with the resulting Q-Q regressor plots showing normal distribution.

### *Self-report measures*

#### *Multivariate Analysis: Group Differences on Total Scores*

The effect of group (control, alcohol dependent, polydrug dependent) was analysed using a MANOVA conducted on total scores for each of the self-report measures of BIS-11, UPPS-P, BIS/BAS and OCI-R. Using Pillai's trace, a significant main effect of group was found ( $V=0.381$ ,  $F(10,216)=5.081$ ,  $p<0.001$ ).

This significant main effect allowed separate univariate ANOVAs to be performed post-hoc on each of the outcome variables. These revealed significant group differences on the total scores of BIS-11 ( $F(2,111)=17.240$ ,  $p<0.001$ ), UPPS-P ( $F(2,111)=27.895$ ,  $p<0.001$ ), BAS ( $F(2,111)=3.980$ ,  $p<0.05$ ) and OCI-R ( $F(2,111)=4.551$ ,  $p<0.05$ ). There was no main effect of group on BIS total ( $F(2,111)=1.786$ ,  $p=0.172$ ). Further post-hoc analysis using Tukey's LSD revealed that both alcohol and polydrug dependent groups scored significantly higher on the BIS-11 (alcohol  $p<0.01$ ; polydrug  $p<0.001$ ) and UPPS-P (alcohol  $p<0.001$ ; polydrug  $p<0.001$ ) total scores than controls, while only the polydrug dependent group scored significantly higher than controls on BAS ( $p<0.05$ ) and OCI-R ( $p<0.05$ ) total scores (Figure 1.2 and Table 1.3).



**Figure 1.2:** Total scores on self-report measures for alcohol and polydrug dependent groups plotted as their difference from control scores. \* $p<0.05$ , \*\* $p<0.01$ , \*\*\* $p<0.001$ .

**Table 1.3:** Mean total scores (and S.D.) for control, alcohol dependent and polydrug dependent participants on each of the self-report measures.

	Control		Alcohol		Polydrug	
<b>BIS-11 Total</b>	57.46	(9.61)	67.35	(12.25)	70.48	(10.98)
<b>UPPS_P Total</b>	114.46	(20.84)	137.77	(25.13)	148.90	(21.18)
<b>BIS/BAS BAS Total</b>	37.93	(5.60)	38.77	(6.13)	41.19	(5.03)
<b>BIS/BAS BIS Total</b>	18.76	(4.41)	20.62	(4.03)	20.07	(4.51)
<b>OCI Total</b>	7.83	(8.43)	13.81	(13.65)	13.90	(10.31)

#### *Group Differences on Sub-Scores*

A second MANOVA was conducted to assess for group differences on each of the questionnaire sub-scores. These included the BIS-11 (Attentional Impulsivity, Motor Impulsivity, Non-Planning Impulsivity), UPPS-P (Negative Urgency, Premeditation, Perseverance, Sensation Seeking, Positive Urgency), and BIS/BAS (Drive, Fun, Reward). Using Pillai's trace, a significant main effect of group was found ( $V=0.707$ ,  $F(28,198)=3.871$ ,  $p<0.001$ ), allowing for separate univariate ANOVAs to be performed.

These post-hoc ANOVAs revealed a significant group difference on BIS-11 Attentional Impulsivity ( $F(2,111)=14.725$ ,  $p<0.001$ ), Motor Impulsivity ( $F(2,111)=4.949$ ,  $p<0.01$ ), and Non-Planning Impulsivity ( $F(2,111)=9.152$ ,  $p<0.001$ ); UPPS-P Negative Urgency ( $F(2,111)=26.027$ ,  $p<0.001$ ), Premeditation ( $F(2,111)=6.771$ ,  $p<0.01$ ), Perseverance ( $F(2,111)=13.881$ ,  $p<0.001$ ), Sensation Seeking ( $F(2,111)=5.429$ ,  $p<0.01$ ), and Positive Urgency ( $F(2,111)=19.346$ ,  $p<0.001$ ); BIS/BAS Drive ( $F(2,111)=4.064$ ,  $p<0.05$ ). There was no main effect of group on BIS/BAS Reward ( $F(2,111)=1.665$ ,  $p=0.151$ ) or on BIS/BAS Fun ( $F(2,111)=2.735$ ,  $p=0.069$ ).

Further post-hoc analysis using Tukey's LSD revealed that both alcohol and polydrug groups scored significantly higher than controls on BIS-11 Attentional Impulsivity (alcohol  $p<0.01$ ; polydrug  $p<0.001$ ), Motor Impulsivity (alcohol  $p<0.01$ ; polydrug  $p<0.001$ ), and Non-Planning Impulsivity (alcohol  $p<0.01$ ; polydrug  $p<0.001$ ). Both alcohol and polydrug dependent groups scored significantly higher than controls on UPPS-P Negative Urgency (alcohol  $p<0.001$ ; polydrug  $p<0.001$ ), Perseverance (alcohol  $p<0.001$ ; polydrug  $p<0.001$ ), and Positive Urgency (alcohol  $p<0.001$ ; polydrug  $p<0.001$ ). Polydrug dependent participants

scored significantly higher than controls on UPPS-P Premeditation scores ( $p<0.01$ ), and BIS/BAS Drive scores ( $p<0.05$ ) and higher than both controls and alcohol dependent participants on UPPS-P Sensation Seeking (control  $p<0.01$ ; alcohol  $p<0.01$ ).

### *Correlations with clinical variables*

Exploratory correlation analyses were conducted on those measures which had a significant group difference to see if length of abstinence could explain variance. We performed separate analyses on the alcohol and polydrug dependent groups (Table 1.4). Shorter length of abstinence was associated with higher scores on BIS-11 Non-Planning Impulsivity ( $r=-0.44$ ,  $p<0.05$ ) and UPPS Negative Urgency ( $r=-0.41$ ,  $p<0.05$ ) within the alcohol dependent group and UPPS Positive Urgency ( $r=-0.36$ ,  $p<0.05$ ) in the polydrug dependent group.

**Table 1.4:** Correlation matrix for length of abstinence with measures of impulsivity. \*  $p<0.05$ , \*\*  $p<0.01$  (2-tailed).

		Alcohol Dependent	Polydrug Dependent
<b>BIS-11</b>	<b>Total</b>	-.353	-.067
	<b>Attention</b>	-.231	-.044
	<b>Motor</b>	-.230	-.156
	<b>Non-Planning</b>	<b>-.444*</b>	.026
<b>UPPS-P</b>	<b>Total</b>	<b>-.459*</b>	-.232
	<b>Negative Urgency</b>	<b>-.412*</b>	-.243
	<b>Premeditation</b>	-.383	-.031
	<b>Perseverance</b>	-.349	.035
	<b>Sensation Seeking</b>	-.056	-.100
	<b>Positive Urgency</b>	-.371	<b>-.315*</b>
<b>BIS/BAS</b>	<b>Drive</b>	-.260	.019
	<b>Fun</b>	-.384	.008
	<b>Reward</b>	-.211	-.061
	<b>BAS Total</b>	-.344	-.016
<b>OCI-R</b>	<b>Total</b>	.286	-.017

### *Behavioural Tasks*

The effect of group (control, alcohol dependent, polydrug dependent) was analysed using a MANOVA on the score outcome measures for each of the behavioural tasks; SSRT, IED total errors and Kirby  $k$  (Table 1.5). Using Pillai's trace, no significant effect of group was found ( $V=0.095$ ,  $F(8,206) = 1.283$ ,  $p=0.254$ ).

Additional exploratory analysis was performed on further outcome measures of the SST and IED in order to ensure these were not confounding the results. All participants did not differ on Stop Signal Delay ( $F[2,105]=0.662$ ,  $p=0.518$ ), Successful Stops ( $F[2,105]=0.549$ ,

$p=0.579$ ), or mean Go Reaction Times ( $F[2,105]=0.633$ ,  $p=0.533$ ). There were no significant group differences in the number of IED stages completed ( $\chi^2=11.802$ ,  $p=0.299$ ) nor number of errors at each stage.

**Table 1.5:** Mean (S.D.) scores for each of control, alcohol and polydrug groups on the three behavioural measures of impulsivity.

	Control		Alcohol Dependent		Polydrug Dependent	
<b>SSRT</b>	182.03	(33.84)	189.54	(48.87)	192.75	(44.93)
<b>IED Errors (adj.)</b>	1.26	(0.35)	1.38	(0.38)	1.37	(0.36)
<b>Kirby <i>k</i></b>	0.02	(0.02)	0.04	(0.05)	0.04	(0.05)

### *fMRI Analysis*

ANOVAs showed no significant group differences in Go accuracy ( $F[2,101]=2.196$ ,  $p=0.056$ ), NoGo accuracy ( $F[2,101]=0.298$ ,  $p=0.743$ ), or Go RT ( $F[2,101]=0.727$ ,  $p=0.486$ ). Key values are summarised in table 1.6.

**Table 1.6:** Mean (S.D.) performance scores for each group on GNG fMRI task.

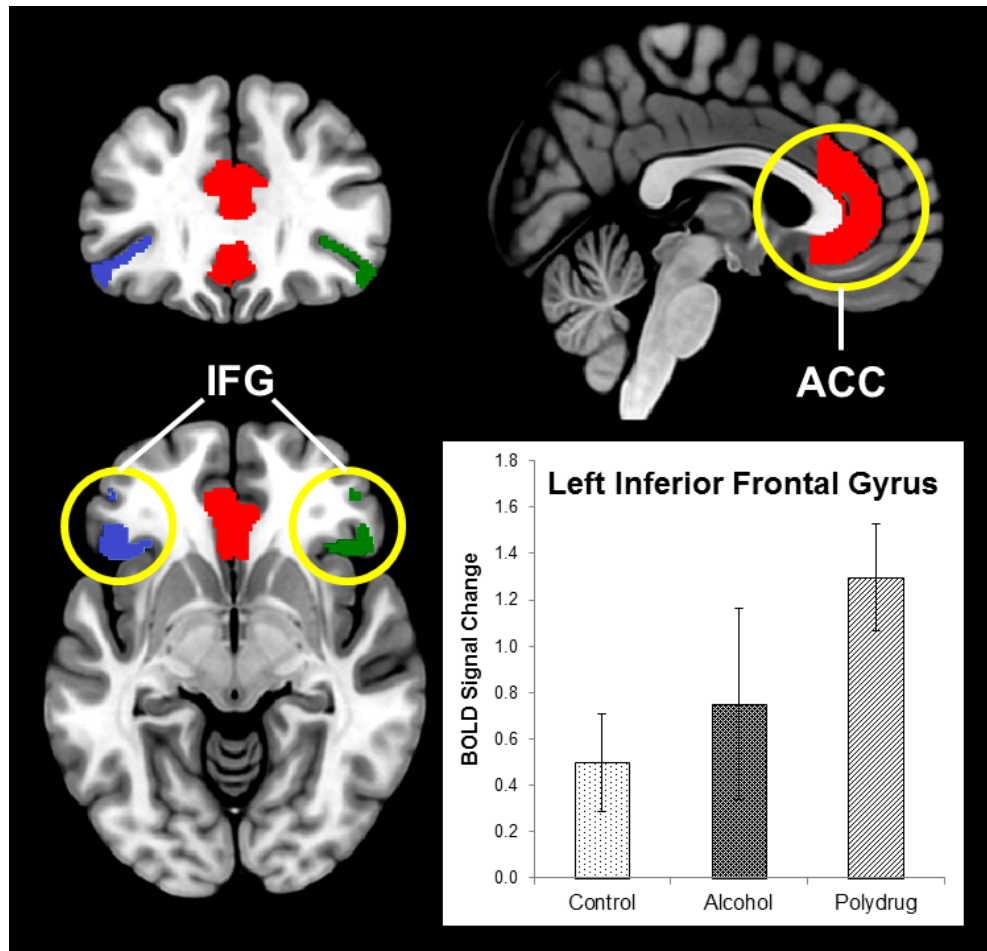
	Control		Alcohol Dependent		Polydrug Dependent	
<b>Go Accuracy %</b>	98.00	(3.76)	96.65	(6.42)	96.12	(4.74)
<b>NoGo Accuracy %</b>	67.98	(16.43)	65.67	(16.92)	64.88	(19.03)
<b>Go RT (ms)</b>	334.70	(65.88)	320.25	(63.74)	347.16	(83.76)

Independent t-tests between alcohol dependent vs control, polydrug dependent vs control and alcohol dependent vs polydrug dependent, identified significant hyperactivation in the pre-defined left IFG ROI in polydrug dependent group compared to controls ( $t(77)=-1.545$ ,  $p<0.05$ , Bonferroni corrected), but not between the alcohol dependent group and controls ( $t(32.4)=-0.675$ ,  $p=0.50$ , Bonferroni corrected; Figure 1.3 and Supplementary Figure 1.2). There were no other significant differences. Covariance analysis showed that neither NoGo performance, nor length of abstinence explained variance. The greater response in left IFG in polydrug dependent over control participants remained significant, even after controlling for NoGo performance.

### *Exploratory Regrouping of Polydrug Dependent Participants*

An exploratory MANOVA of the 42 polydrug dependent participants was conducted to assess whether a history of dependence on alcohol, opioids or stimulants alone was driving the difference from controls on some of the measures. However, since the numbers within





**Figure 1.3:** Region of interest masks, defined by Neuromorphometrics, Inc. ([www.neuromorphometrics.com](http://www.neuromorphometrics.com)), under academic subscription, including the anterior cingulate cortex (ACC), right and left inferior frontal gyri (IFG). Significantly greater response was found in the left IFG of polydrug dependent group compared to controls.

these divisions were small and unbalanced (see table 1.2), this analysis remains speculative. Using Pillai's trace, a significant main effect of stimulant dependence was found on total self-report scores ( $V=0.332$ ,  $F(5,36)=3.582$ ,  $p<0.01$ ). However, there was no effect of stimulant dependence on behavioural measures ( $V=0.032$ ,  $F(4,37)=3.582$ ,  $p=0.87$ ). There was also no effect of alcohol dependence on total self-report ( $V=0.214$ ,  $F(5,36)=1.963$ ,  $p=0.11$ ), or behavioural measures ( $V=0.031$ ,  $F(4,37)=0.298$ ,  $p=0.88$ ), and no effect of opioid dependence on either self-report ( $V=0.110$ ,  $F(5,36)=.888$ ,  $p=0.50$ ) or behavioural measures ( $V=0.073$ ,  $F(4,37)=0.731$ ,  $p=0.557$ ).

Following the significant effect of stimulant dependence on self-report scores, secondary ANOVAs were performed post-hoc on each individual measure. These revealed that those polydrug dependent participants with a history of stimulant dependence scored significantly higher than those with no history of stimulant dependence on the total scores

of BIS-11 ( $F(1,40)=6.224$ ,  $p<0.05$ ), UPPS-P ( $F(1,40)=6.737$ ,  $p<0.05$ ), BIS ( $F(1,40)=8.031$ ,  $p<0.01$ ) and OCI-R ( $F(1,40)=10.254$ ,  $p<0.01$ ), but not on BAS ( $F(1,40)=0.145$ ,  $p=0.706$ ).

The left IFG hyperactivation within the polydrug dependent participants no longer remained significant following regrouping by history of alcohol dependence ( $t(35)=0.388$ ,  $p=0.70$ ), opioid dependence ( $t(35)=0.203$ ,  $p=0.84$ ), or stimulant dependence ( $t(35)=0.157$ ,  $p=0.88$ ).

## Discussion

This investigation compared self-report, behavioural and neural measures of impulsivity in a large abstinent substance dependent (AbD) population. We found that AbD participants scored higher than controls on most self-report measures, but that alcohol and polydrug dependent groups did not differ from each other. We also identified a greater response in the left IFG of the polydrug dependent group compared to controls during performance of a motor inhibition task (GNG), suggesting this group may need to recruit additional brain regions in order to maintain normal levels of motor inhibitory control. In contrast, there were no group differences on any of the behavioural measures of impulsivity. These findings add to the growing literature on impulsivity in substance dependence and point to the need for more appropriate behavioural impulsivity measures for AbD individuals.

### *Self-Report Impulsivity*

Both alcohol and polydrug dependent groups were found to be more impulsive than controls across all self-report measures, except the Behaviour Inhibition Scale, in line with previous literature (Ersche et al., 2011; 2010; von Diemen et al.2008). Although the alcohol and polydrug dependent group scores were not significantly different, there was a trend for the polydrug group to score higher than the alcohol group, perhaps reflecting multiple dependencies.

The same pattern was also observed in the subscales of the self-report measures, with both AbD groups scoring significantly higher than control participants while not differing from each other. There was one notable exception, with polydrug dependent participants reporting more sensation seeking than both controls and alcohol dependent participants, while alcohol dependent participants were no different from controls. This may be a result of prevalent stimulant dependence history in the polydrug compared to the alcohol

dependent group. Stimulants such as cocaine and amphetamines produce alterations in the mesolimbic dopaminergic system (Volkow et al. 2011), which are associated with trait impulsivity (Dalley et al. 2011). Sensation seeking is particularly associated with stimulant use (Ersche et al., 2010; Mahoney et al., 2015), and the higher scores in polydrug dependent participants in our study could be consistent with their higher levels of stimulant use. This is supported by our exploratory post-hoc analysis that divided polydrug dependent participants by their specific dependencies, in which we found that only when stimulant dependence history, and not opioid or alcohol dependence history, was used as a grouping variable was there a significant difference on self-reported impulsivity. While this suggests that stimulant dependence is driving the increase in impulsivity, these findings should be taken with extreme caution due to the unbalanced groups and low power of this analysis.

Although sensation seeking has been highly related to substance dependence (Zuckerman 2007), there is relatively little evidence linking it directly to alcohol dependence (Noël et al. 2011). This is particularly notable in comparison to the wealth of evidence of elevated sensation seeking in stimulant dependence (e.g. Marusich et al. 2011; Mahoney et al. 2015; Ersche et al. 2010; Stoops et al. 2007; Kelly et al. 2006; Patkar et al. 2004). However, the literature seems to focus more on sensation seeking as a risk factor for heavy drinking in adolescence (e.g. Comeau et al. 2001; Shin et al. 2012; Gillespie et al. 2012). Additionally, impulsivity (specifically sensation seeking and lack of premeditation) were found to be more related to illicit substance use in young adults than was hazardous drinking (Shin et al. 2013). To the best of our knowledge there has not been an investigation comparing sensation seeking in stimulant and alcohol dependence within one study.

### *Neurocognitive Impulsivity*

While performing the fMRI GNG paradigm, the polydrug dependent group showed increased response in the left IFG to successful motor inhibition, which could not be explained by either performance or length of abstinence. This suggests a compensatory mechanism that requires additional brain activity to maintain normal levels of inhibitory control. These findings are in line with previous imaging studies of neural correlates of impulsivity, for example, siblings of stimulant dependent individuals showed greater activation in dorsal medial PFC (Morein-Zamir et al. 2013) while displaying the same level of performance as controls on the SST, suggesting they have a compensatory mechanism that

enables inhibitory control above that of their stimulant dependent siblings. This is further supported by Goldstein et al. (2001) who found greater OFC activation in chronic drug users while successfully performing the Stroop task. Additionally, imaging studies of decision making in current and former drug users have found significant hyperactivation in the left OFC compared to controls in the absence of behavioural group differences (Bolla et al., 2003; Ersche et al., 2005). This can also be explained by compensatory mechanisms and also links the left-sided hyperactivity seen in the present data with inhibitory control deficits, suggesting it may reflect additional response suppression that allows drug users to perform at the level of controls.

### *Behavioural Impulsivity*

There were no group differences on any of the behavioural measures of impulsivity. This suggests that the current set of self-report measures are more sensitive to detecting impulsivity in abstinent dependent individuals than these behavioural measures. One explanation would be that neurocognitive measures assess state impulsivity, which undergoes change during and after dependence, while self-report measures assess trait impulsivity that appears to be relatively impervious to such changes. While this conclusion is intuitively appealing, it is at odds with evidence of increased SST impulsivity in siblings of stimulant dependent individuals (Ersche et al., 2011) implicating cognitive impulsivity as an endophenotypic trait. It is also important to note that in the present study, length of abstinence was related to BIS-11 Non-Planning Impulsivity and UPPS Negative Urgency within the alcohol dependent group as well as Positive Urgency in the polydrug dependent group. Thus self-reported impulsivity decreased with extended abstinence, a pattern not entirely consistent with the hypothesis that self-reported impulsivity is a stable trait. Another consideration is that self-report measures of impulsivity are more susceptible to bias (Verdejo-García et al. 2008), intentional or otherwise, while behavioural tasks are much less prone to this bias. Therefore, this asks the question of whether this bias is driving the self-report impulsivity differences rather than “true impulsivity”.

### *Length of Abstinence*

Exploratory correlations with length of abstinence were conducted on measures where there was a group difference in impulsivity. More recent abstinence was associated with higher scores on BIS-11 Non-Planning Impulsivity and UPPS-P Negative Urgency within the

alcohol dependent group, as well as UPPS-P Positive Urgency within the polydrug dependent group.

Length of abstinence is an important point of variation between previous studies in this area and may provide a possible explanation for the lack of behavioural impulsivity differences found; participants in the present study had a longer length of abstinence than those in similar investigations. For example, Ersche et al.'s (2011) stimulant dependent individuals who showed increased impulsivity were not abstinent, while Naim-Feil et al. (2014) reported persisting impulsivity in abstinent alcohol dependent participants with a mean duration of abstinence of approximately six months. By comparison, mean length of abstinence in the present sample was in excess of 12 months. This additional abstinence duration may have allowed individuals time to recover lost, or improve on pre-existing, cognitive deficiencies. Although there is some evidence of improvement of inhibitory control with abstinence (Hopwood et al. 2011; Morie et al. 2014), including their neural circuits (Bell et al. 2014), there is also evidence of an improvement in executive functioning (Schulte et al., 2014; Stavro et al. 2013; Sullivan et al. 2000), into which inhibitory control can be included as a wider construct.

Alternatively, including only stably abstinent participants may have biased our sample towards individuals with lower cognitive impulsivity, for the most impulsive individuals prone to early relapse will have been excluded. Early relapse and poor treatment retention are associated with higher impulsivity in stimulant dependence, (Moeller et al. 2001; Patkar et al. 2004) and alcohol dependence (Evren et al. 2012), although not in opioid dependence (Passeti et al. 2008). Nevertheless, the correlations between self-report measures and length of abstinence were relatively weak and do not explain all of the variance. Self-reported impulsivity is thus elevated even in those with long-term abstinence.

### *Implications and Future Considerations*

The lack of corresponding group differences on these behavioural measures suggests that the tasks did not capture the most relevant aspects of impulsivity. For example, the SST and GNG, although used widely in the addiction literature, only measure motor impulsivity, which is just one aspect of this multifaceted construct. Cognitive flexibility (measured by the IED) and delay of gratification (measured by the Kirby task) were also unimpaired; however other aspects of impulsivity were not assessed here. For example, many self-

report methods measure how an individual reacts to emotional states, such as the UPPS-P Negative Urgency subscale, which is sensitive to differences between dependent individuals (Torres et al. 2013) as well as pathological gamblers (Clark et al. 2012). There is a need for validated behavioural measures that assess “affective impulsivity” in response to stress and anxiety, which are known to contribute significantly to risk for developing substance dependence (Andersen & Teicher, 2009; Woicik et al. 2009) as well as risk of later relapse (Koob & Le Moal 2001). The multidimensional nature of impulsivity (Evenden 1999; Bari & Robbins 2013) suggests that multiple tasks are required to assess the construct comprehensively and our findings highlight the need for more extensive cognitive impulsivity assessment in AbDs.

A limitation of this study is that the polydrug dependent participants were dependent on a wide range of substances with substantially different individual profiles of dependent and non-dependent use. While the cohort was representative of the substance-dependent population in the UK, this heterogeneity precluded systematic analysis of the contribution of different substances to the effects observed. For example, the specific contribution of a history of stimulant dependence to impulsivity was impossible to isolate. Poly-substance use is an important issue in addiction research, particularly the potential distinction of dependence on stimulants from other substances, with some studies suggesting that opioid dependence, for example, is behaviourally distinct from stimulant dependence (Badiani et al. 2011; Vassileva et al., 2014). Thus, for example high impulsivity in opioid use has been suggested to be a result of drug use rather than a risk factor in the development of dependence (Harty et al. 2011; Schippers et al. 2012), by contrast to stimulant dependence where high impulsivity is a well-established risk factor (Dalley et al., 2011; Ersche et al., 2010). In addition, a recent paper by Whelan et al. (2014) showed that impulsivity played a relatively minor role in the development of alcohol dependence. However, the clinical reality of drug addiction in the UK is a very high prevalence of poly-substance use and dependence; a meta-analysis by Smith et al. (2014) noted that there was little consistency across studies in the recording of the amount or length of drug use, pointing out that many findings need to be considered with caution. Thus, it is difficult to study single dependencies empirically and the practical clinical relevance of doing so is questionable, as polydrug dependency is the more common clinical challenge.

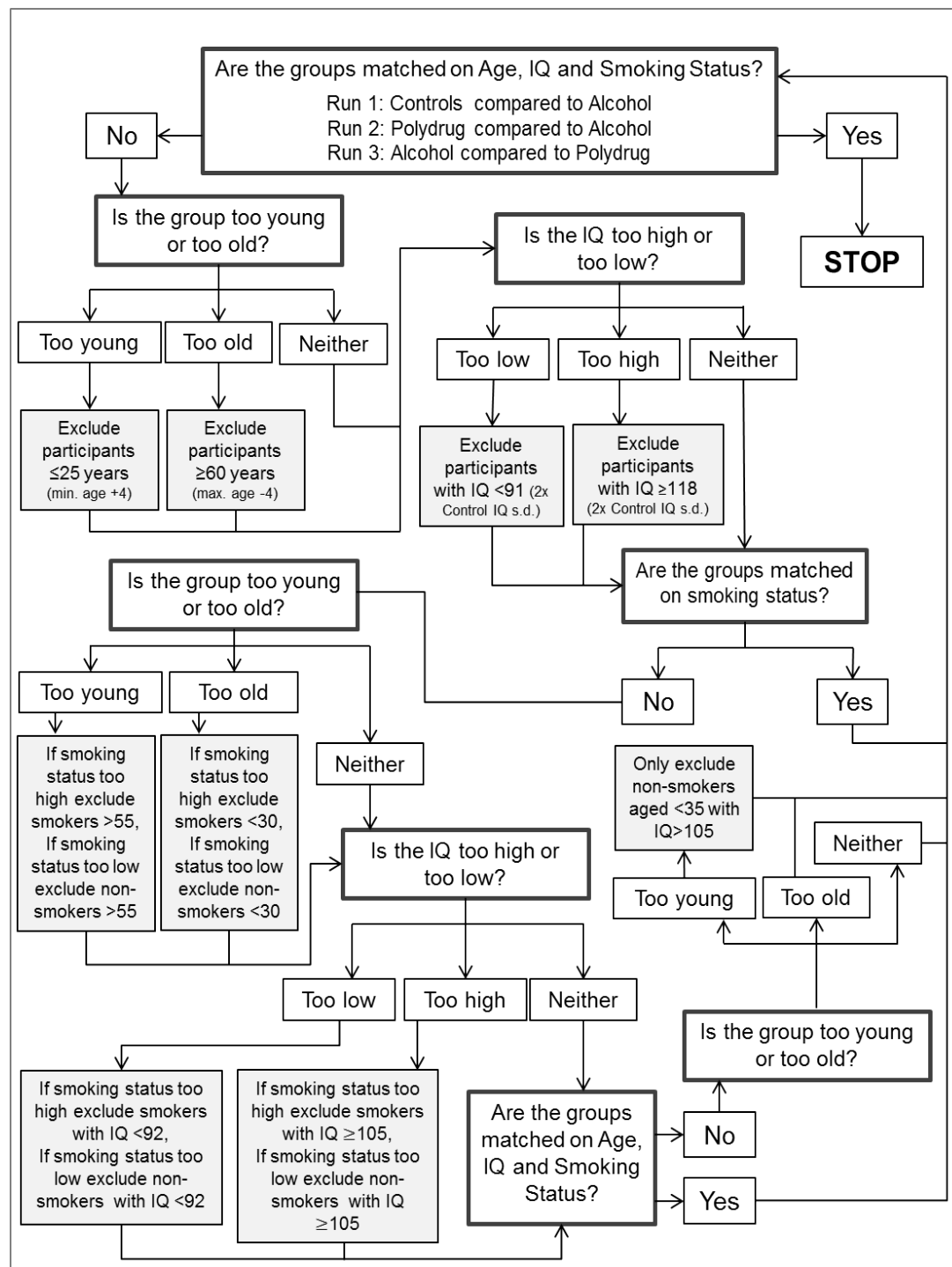
As a result of these difficulties in recruiting individuals with single dependencies (excluding nicotine), our alcohol group was relatively small ( $n=26$ ), only providing sufficient power to detect moderate effect sizes (Smith et al. 2014). It may be more valuable for future investigations to consider all AbD participants as one group and investigate their different profiles that are not based on the substances used.

Another limitation includes the upper age range of participants within this study (65 years) as this may have introduced an age-related bias in impulsivity. There is substantial evidence of brain atrophy with old age, for example the rate of cortical atrophy increases to 0.35% a year after the age of 52, compared to 0.12% in young adulthood, ventricle size expands at rate of 4.25% after 70 years compared to 0.43% in young adulthood, while the frontal lobes, which are involved in inhibitory control, show the steepest decline (for a review, see Dennis & Cabeza 2011). In addition, older adults show more compensation for poorer inhibitory control that declines with increasing age (Nielson et al. 2002), as well as poorer motor control (Levin et al. 2014). However, neither AbD group in the present study differed significantly in age from the control group, which means that any age-related decline in cognitive performance should have been balanced across the groups.

### *Conclusion*

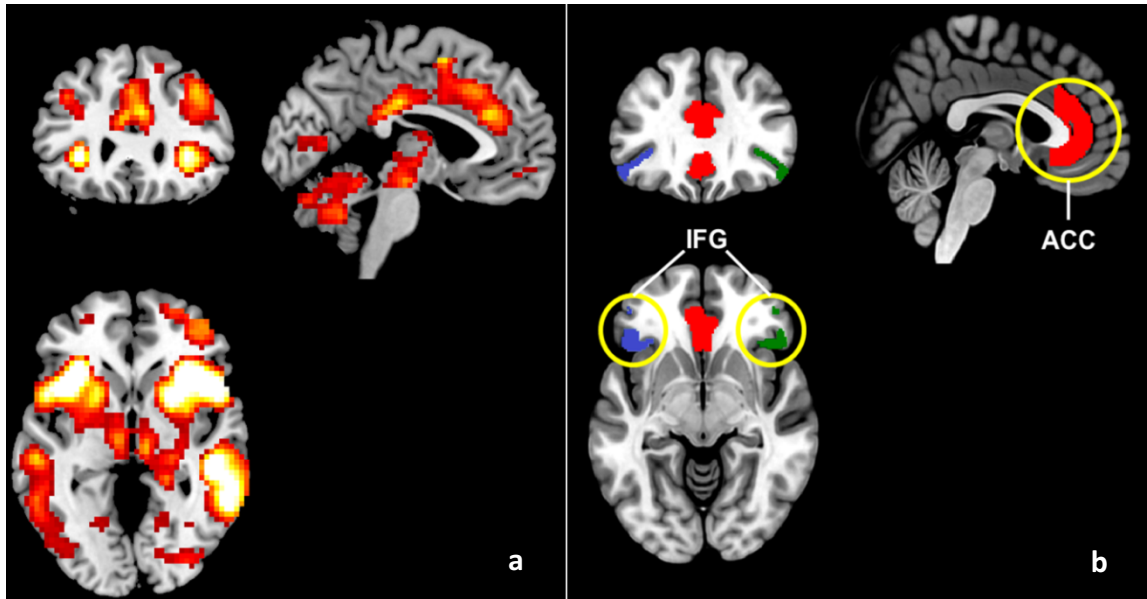
The present study suggests that the self-report measures used are more sensitive to detecting impulsivity in long-term abstinent individuals than the behavioural or neuronal measures. Our findings suggest the importance of developing behavioural measures that assess different aspects of impulsivity rather than simple motor response inhibition, alongside corresponding behavioural challenges to use in conjunction with fMRI. A complementary approach may be to reconsider the grouping of individuals in studies of dependence, with a shift of emphasis to cognitive endophenotypes rather than specific substances used. Such an approach would obviate the problem of categorising individuals with complicated drug use and dependence histories, and would have implications for optimising approaches to treatment and prevention based on cognitive profiles.

## Supplementary Materials



**Supplementary Figure 1.1:** Flowchart describing the process of matching participant groups. There are three runs through this process, the first compares the control group to the alcohol group, the second run compares the polydrug to the alcohol group, and the final run compares the alcohol group to both polydrug and control groups.





**Supplementary Figure 1.2:** a) Significant pattern of task-induced activation for successful inhibitions ( $p < 0.05$ , Family-wise error) b) Region of interest masks, defined by Neuromorphometrics, Inc. ([www.neuromorphometrics.com](http://www.neuromorphometrics.com)), under academic subscription, including the anterior cingulate cortex (ACC), right and left inferior frontal gyri (IFG).



## **2.2 Study 2: Reclassification of preconceived diagnostic categories for substance dependence**

### *Submission*

This paper has been prepared for submission to *Psychopharmacology* (<http://www.springer.com/biomed/neuroscience/journal/213>).

### *Individual contribution*

The data in this paper were collected as part of the ICCAM Platform Study, a multi-centre collaborative project shared between Imperial College, the University of Cambridge and the University of Manchester. I was one of two researchers who collected data at Manchester. The ideas behind the analysis of these data were my own and were separate from those of the ICCAM Platform Study. I conducted the analyses presented in this paper (with assistance from Dr Richard Emsley on the Latent Profile Analysis), and prepared the manuscript.

\*A full list of ICCAM Platform collaborators can be found in the Appendix.

## Reclassification of preconceived diagnostic categories for substance dependence

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**Rationale:** Addiction research classifies drug users on their primary substance of dependence. However, there is little agreement on how this should be conducted, potentially limiting our understanding of the disorder and thus its treatment.

**Objectives:** This study reclassified abstinent substance dependent (AbD) individuals based on personality risk factors and then compared the resulting groups to each other as well as a group of matched control participants. **Methods:** Firstly, Latent Profile Analysis was used to regroup AbD participants based on their scores on a number of self-report measures of impulsivity and affect. Secondly, differences on behavioural and neural measures of impulsivity and affect between these new groups were assessed. **Results:** A high-scoring and a low-scoring group of AbDs were identified. High AbDs scored significantly higher than both Low AbDs and controls on self-reported impulsivity, affect and childhood adversity. Low AbDs did not significantly differ from controls on the majority of measures. There were no group differences on cognitive behavioural measures. However, fMRI analysis found a significant positive correlation between increased length of abstinence and left IFG activation in response to GNG inhibition in High but not Low AbDs. **Conclusions:** This study highlights the utility of grouping participants by personality risk factors rather than on primary dependence. Our results draw particular attention to the involvement of childhood adversity in different profiles of substance dependence, which has important implications for improving treatment as well as further research. Future investigations should focus on different individual profiles of substance use and dependence that are not exclusive to primary dependence.

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## Introduction

Substance dependence is a remitting disorder that has huge economic and social costs. Despite successful detoxification and rehabilitation programs, relapse rates remain at 65-75% (Sinha 2011), with individuals frequently returning to treatment in repetitive cycles of detox and relapse. One potential barrier to better success rates is the current method for grouping substance dependent individuals into treatment categories based on their primary drug of dependence. While this approach is necessary for providing appropriate pharmacological care for safe detoxification and substitution therapy, it may be less helpful for psychological therapies. There is also little consensus on its utility for the purpose of research. For example, some studies categorise dependent individuals based on their preferred substance, others on the most consumed substance (which may not be the same). There is also huge variation in participant inclusion criteria for such studies, with no consistency in amount or length of drug use, or the inclusion or exclusion of comorbidities (for example, see a meta-analysis by Smith et al. 2014 for a discussion of this variation in studies of inhibitory control). This is complicated further by poly-substance dependence, which is widely observed clinically but often overlooked in research as many studies exclude individuals with multiple dependencies. There is also the issue that substance availability plays a substantial role in determining which drugs and how much are used. Using a “primary dependence” model may therefore hamper attempts to improve our understanding of mechanisms of addiction. Consequently, it may be appropriate to focus less on the specific substances used and more on the reasons for their use, which may relate more closely to the underlying mechanisms. The presence (or absence) of important risk factors for substance dependence, such as high impulsivity (for review see, de Wit 2009) and stress (for review see, Sinha 2008), may act as more effective grouping variables.

An alternative method for grouping substance dependent participants is one that considers the personality risk factors underlying the initial drug use. Becker and colleagues (2012) propose the existence of two routes into addiction that are driven by different personality types. The first is a sensation seeking route that is largely driven by positive reinforcement of the drug high, and represents individuals who are inclined to seek and use drugs in pursuit of their hedonic value. Impulsivity is involved in substance dependence through the inability to withhold this drug-seeking and using behaviour (Volkow et al. 2011) and the preference for immediate drug-related rewards at the cost of later negative outcomes (Bechara et al. 2001). Frequently associated with substance dependence, impulsivity is a

risk factor for development of dependence (Ersche et al. 2010; Hogarth 2011; Perry & Carroll 2008; Verdejo-García et al. 2008), a consequence of excessive drug use (Dallery & Locey 2005; Winstanley 2007), and a marker for poor treatment outcomes (Moeller et al. 2001; Patkar et al. 2004).

Becker's second, self-medicating route into addiction is driven by the negative reinforcement of relief from negative affective states. This reflects the individuals who take advantage of the anxiolytic and anti-depressant properties of many substances (Gilman et al. 2008; Lejuez et al. 2006) and is supported by the evidence that stress and anxiety contribute significantly to the risk of developing substance dependence (Andersen & Teicher 2009; Woicik et al. 2009), as well as later relapse (Koob & Le Moal 2001); as seen for heroin (Fatseas et al. 2011), alcohol (Sinha et al. 2009), and cocaine (Karlsgodt et al. 2003). In particular, adversity during childhood is also associated with the risk of substance dependence (Dube et al. 2003), as well as problems in later stages of dependence (Elton et al. 2015).

Becker and colleagues (2012) explain these two routes into addiction to account for sex differences in addiction vulnerability, with males more likely to engage in risky behaviours that include drug-seeking, and females more likely to self-medicate against negative emotional states. While the present study is not concerned with the sex differences, this model introduces the idea that personality risk factors may be extremely relevant to the understanding of addiction treatment and prevention. By grouping individuals on their primary substance we may be masking fundamental differences in drug users that are not only important for scientific investigation, but also have clinical implications, particularly with regard to polydrug dependence. A complementary approach to classification of substance dependent individuals may help shift the emphasis from specific substances towards cognitive endophenotypes of the disorder; circumventing the problem of complicated drug use and dependence histories in favour of optimising treatment and prevention.

In order to examine whether we can group participants based on their personality risk factors, the present study was divided into two parts. Firstly, we used latent profile analysis to regroup abstinent substance dependent (AbD) individuals based on their scores on a number of self-report measures of impulsivity and affect. Substances used were not

considered as a variable of interest in order to assess the utility of an approach that was “blind” to substances. Secondly, these reclassified AbD groups were then compared to controls on behavioural and neural measures of impulsivity and emotional processing to assess their value in terms of classification. We hypothesised that AbD participants would divide into two groups that would reflect Becker et al.’s (2012) two-route model: one group would score highly on impulsivity measures and low on affective measures, while the other group would show the opposite pattern.

## **Part 1: Regrouping Analysis**

### **Methods**

Both parts of this study were conducted as part of the ICCAM Platform Study ([www.iccam.org.uk](http://www.iccam.org.uk)), details of which are reported by Paterson et al. (2015). The protocol was approved by the West London Research Ethics Committee (REC Ref: 11/H0707/9; PI: Prof DJ Nutt). Non-imaging testing sessions were conducted at three sites: 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. Imaging sessions were conducted in the adjoining centres at Imanova Limited (formerly the GSK Clinical Imaging Centre), the Wolfson Brain Imaging Centre and the Manchester Translation Imaging Unit (3T MRI Facility) respectively.

### *Participants*

Eighty seven abstinent substance dependent (AbD) individuals were recruited as part of the screening sessions for the wider ICCAM Platform Study. Participants were the same cohort included in Taylor et al. (*in prep*, **Study 1**) with a mean age of 41.4 years (SD=9.2, 18.4% female). Our analysis approach treats these individuals as a single cohort and therefore there was no need to exclude individuals to create matching subgroups. All participants were abstinent from all substances of dependence (excluding nicotine) for at least two weeks prior to testing. To confirm abstinence on day of testing, all participants completed an alcohol breath test and urine drug screen. They were requested to refrain from cannabis use for at least seven days prior to the session, but positive results for cannabinoids were permitted given the long half-life of these metabolites.

## Self-Report Personality Measures for Generation of AbD Profiles

Participants completed a battery of self-report personality measures of impulsivity and affect presented in computer format (Table 2.1).

**Table 2.1:** Name, reference and details of each self-report measure included in the latent profiles analysis.

Name	Reference	Measures
Barratt Impulsiveness Scale (BIS-11)	(Patton et al., 1995)	Trait impulsivity with three subscales: attentional impulsiveness (inattention and cognitive instability); motor impulsiveness (spontaneous actions); and non-planning impulsiveness (lack of forethought).
UPPS Impulsive Behaviour Scale (UPPS-P)	(Cyders & Smith, 2007; Whiteside & Lynam, 2001, 2003)	Negative Urgency, (lack of) Premeditation, (lack of) Perseverance, Sensation Seeking and Positive Urgency
Behaviour Inhibition/Activation System (BIS/BAS)	(Carver & White, 1994)	Two aspects of self-regulation: aversive (BIS) and appetitive (BAS) motivation.
Obsessive Compulsive Inventory Revised (OCI-R)	(Foa et al., 2002)	Distress associated with common OCD symptoms: washing, checking, ordering, obsessing, hoarding and neutralising.
Beck Depression Inventory (BDI-II)	(Beck et al., 1996)	Sadness, pessimism, sense of failure, self-dissatisfaction, guilt, punishment, self-dislike, self-accusation, suicidal ideas, crying, irritability, social withdrawal, indecisiveness, work difficulty, insomnia, fatigability, loss of appetite, loss of libido, body image change, weight loss, somatic preoccupation.
The Spielberger State/Trait Anxiety Index (STAI)	(Spielberger et al., 1970)	State and trait anxiety. (Only the trait measures were used for this study)
Perceived Stress Scale (PSS-14)	(Cohen et al., 1983)	The degree to which situations in one's life are considered stressful.

## Data analysis

Latent Class Cluster Analysis (LCCA), including Latent Class and Latent Profile Analysis, is a model-based form of cluster analysis that is similar to factor analysis, but deals with cases or profiles rather than items. LCCA is based on the assumption that data are generated by a mixture of different probability distributions and thus provides probability estimates to determine classes objectively. Latent Profile Analysis identifies subtypes of related cases or individuals (Valmaggia et al. 2013) and is used to identify homogenous groups, or classes, from a set of categorical, ordinal and continuous multivariate data (Muthen & Muthen 2000).

The analysis was conducted in Mplus 7.11 (Muthen & Muthen 2013) using AbD participants' responses on self-report personality measures (Table 2.1) in order to determine the number and nature of personality risk factor profiles (classes) within this population. Maximum likelihood was estimated, followed by the assessment of the fit of



the two different models (two- and three-class model). We used several posterior fit statistics: Akaike information criterion (AIC), Bayesian information criterion (BIC) and sample-size-adjusted BIC (ssABIC). These are goodness-of-fit measures used to compare competing models to determine the optimum number of latent classes; lower observed values indicate better fit (Lin & Dayton 1997). Also used to help determine the selection were entropy measures, which determine the accuracy of participant classification, ranging from 0 (no predictive power) to 1 (perfect prediction). Each individual was assigned membership to their most likely class based on these posterior probabilities.

## Results

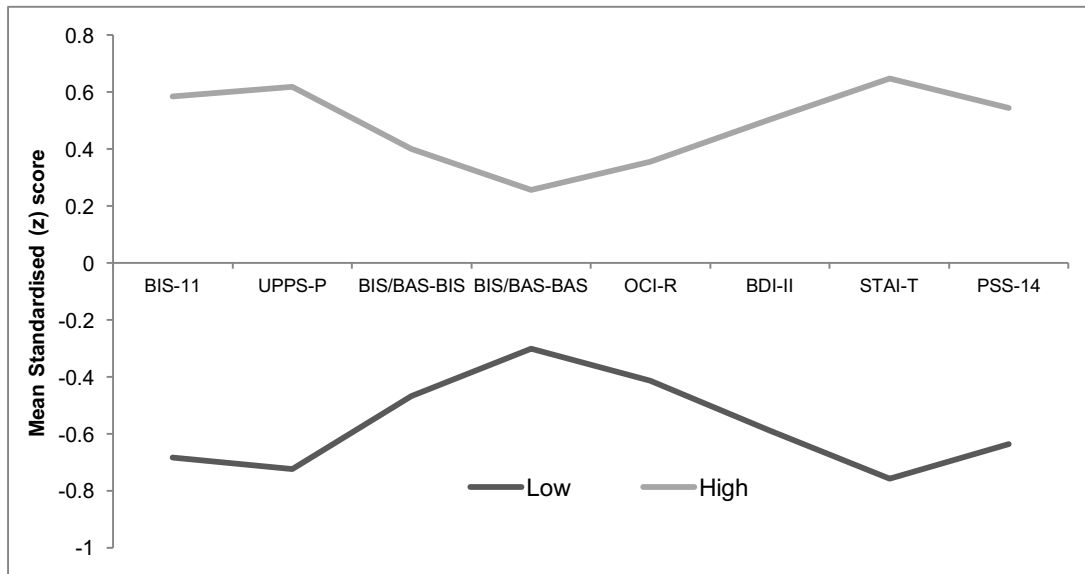
The analysis suggested a two- and a three-group model (Table 2.2). Although the model fit statistics suggest the three-group model is the better one, the second group within this model is not meaningful as it consists of only two participants. Therefore, we opted for the two group model, which identified a “high” and a “low” scoring group (Figure 2.1).

**Table 2.2:** Model fit statistics for the number of latent classes (upper panel). Mean (S.D.) self-report scores for controls and each of the latent classes (lower panel).

Number of Classes	2	3
Number of Free Parameters	25	34
Log Likelihood	-900.50	-858.58
Akaike Information Criteria (AIC)	1851.00	1785.16
Bayesian Information Criteria (BIC)	1912.65	1869.00
Sample-Size Adjusted BIC	1833.77	1761.72
Entropy	0.822	0.920
Number in Class	40/47	37/2/48

	Class 1: Low	Class 2: High	Overall Mean
<b>BIS-11</b>	61.00 (9.58)	76.91 (9.64)	69.60 (12.45)
<b>UPPS-P</b>	127.98 (18.43)	159.06 (15.99)	144.77 (23.10)
<b>BIS/BAS BAS</b>	38.68 (5.22)	41.62 (4.83)	40.26 (5.20)
<b>BIS/BAS BIS</b>	18.40 (3.88)	21.81 (3.75)	20.24 (4.16)
<b>OCI-R</b>	8.73 (9.85)	16.94 (10.76)	13.16 (11.08)
<b>BDI-II</b>	4.53 (4.18)	13.72 (8.63)	9.49 (8.31)
<b>STAI-T</b>	31.10 (6.21)	48.57 (10.03)	40.54 (12.17)
<b>PSS-14</b>	15.28 (5.10)	24.77 (6.53)	20.40 (7.57)



**Figure 2.1:** Mean response on self-report measures for two latent classes.

## Part 2: Group Differences

### Methods

#### Participants

Two groups comprising 40 Low AbDs and 47 High AbDs were identified in Part 1 of this study. We also included 46 control participants with no history of substance dependence (except nicotine) and were the same matched cohort included in Taylor et al. (*in prep*, **Study 1**). As in Part 1, all participants had completed an alcohol and drug screen to confirm abstinence on day of testing. The mean age of all participants was 41.6 (SD=8.9) with 21% female.

Three control participants did not complete the behavioural tasks, leaving 43 control participants in the cognitive analysis. Twelve participants were removed from the GNG imaging analysis; two controls, two Low AbD, and three High AbD participants due to excessive movement (defined as >20% volumes with >1mm movement), and an additional one control, one Low AbD and three High AbDs due to low baseline performance on the GNG imaging task (<85% Go accuracy). This left 43 control, 37 Low AbD and 41 High AbD participants in the GNG analysis. Nine participants were removed from the Evocative imaging analysis: two controls, three Low AbD, and four High AbD participants due to excessive movement (defined as >20% volumes with >3mm movement). This left 44 control, 37 Low AbD and 43 High AbD participants in the Evocative analysis. One substance dependent participant was excluded from analyses that involved length of abstinence as

they had an outlying length of abstinence of 324 months, which was more than two standard deviations from the mean of 19.16 months (SD=37.71; including outlier).

### *Cognitive Tasks*

Participants completed three cognitive tasks: the Kirby delay discounting task (Kirby & Maraković, 1996); the Stop Signal Task (SST) to measure inhibitory control; and the Intra-Extra Dimensional Set Shift (IED) to measure cognitive flexibility. The latter two tasks are part of the well-validated CANTAB neuropsychological test battery ([www.cambridgecognition.com/academic/cantabsuite/executive-function-tests](http://www.cambridgecognition.com/academic/cantabsuite/executive-function-tests)).

The Kirby requires participants to choose between hypothetical immediate rewards of £11-80 and delayed rewards of £25-85, with delays of 7-186 days. A “*k*” score for each participant is generated by calculating the proportion of immediate choices that were made over delayed choices (Kirby et al. 1999; Basar et al. 2010). The increasing value of *k* is an indication of higher levels of impulsivity (Herrnstein, 1981) represented by greater discounting of a future reward as the delay to that reward increases.

The SST measures motor inhibition at the presentation of an auditory stimulus; a full description is presented by Ersche and Sahakian (2007). The primary outcome is the time an individual requires to withhold a response: the “Stop-Signal Reaction Time” (SSRT).

The IED is a test of rule acquisition and reversal derived from the Wisconsin Card Sorting Task, featuring visual discrimination, attentional set formation maintenance, shifting and flexibility of attention. Primary outcome measures are “number of stages completed” and “total errors” (adjusted for any early terminations). A full description is presented in Downes et al. (1989).

### *Clinical Variables*

Data were obtained for length of abstinence, cumulative exposure and the total number of dependencies (excluding nicotine) in AbD participants. For those with a history of dependence on alcohol only, length of abstinence was calculated from their last use at dependent levels. For all other AbD participants, their dependence on multiple substances meant that length of abstinence could only be calculated from the most recent use of any substance of dependence.

A cumulative exposure variable was calculated for each of alcohol, cocaine or heroin, depending on the individual's dependence history. Exposure data for other substances of dependence was not recorded as a result of the original design of the ICCAM Platform Study (see Paterson et al. 2015). One year of alcohol exposure was recorded if >6 months in a 12 month period involved use of >50 units per week (men) and >35 units per week (women), or >8.75 units per day (men) and >7 units per day (women) for >3 days per week. One year of cocaine exposure was recorded if >6 months in a 12 month period involved >1 use per week of  $\geq 1$ g. One year of heroin exposure was recorded if >6 months in a 12 month period involved >1 use per week of any amount. For those with a history of multiple dependencies, exposure for each substance was summed to produce the cumulative variable. These definitions were devised and extracted from the interview data by Dr Remy Flechais MRCPsych.

### *Childhood Adversity*

Participants also completed the Childhood Trauma Questionnaire (CTQ; Bernstein et al. 1994), which measures physical, sexual and emotional abuse, as well as physical and emotional neglect.

### *Functional MR Imaging Tasks*

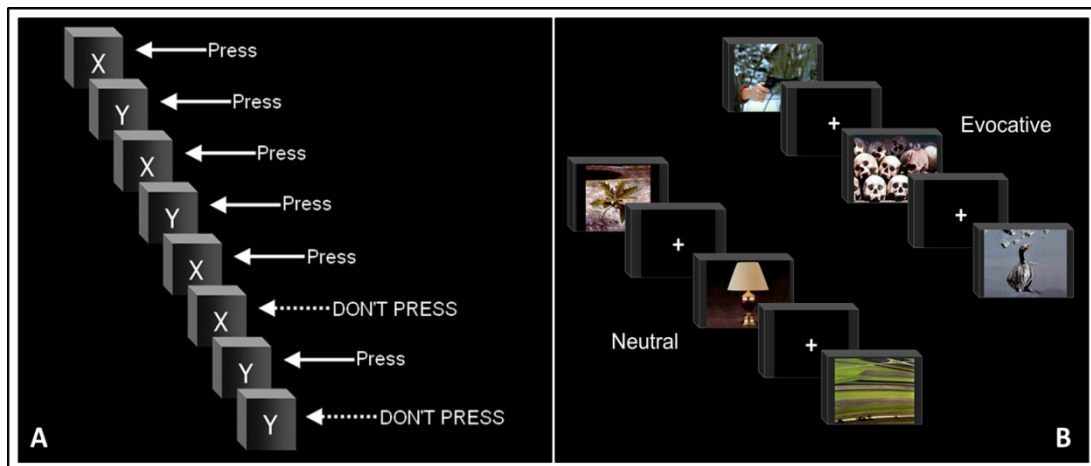
Participants completed two tasks while being scanned using fMRI. Participants completed practice versions of both tasks immediately before scanning to ensure they understood the instructions and were able to perform the tasks.

#### *Go/No-Go Task (GNG)*

To investigate neural substrates of impulsivity, participants performed a Go/NoGo (GNG) task. Participants were presented with a series of individual letter "X"s and "Y"s and asked to respond as quickly as possible to each with a button-press (Go), except when the letter immediately repeated itself (NoGo; Figure 2.2A). This was an event-related task carried out in two runs of 250 trials, each containing 220 Go trials and 30 NoGo trials. This ratio of frequent Go to rare NoGo trials was used as it is a stronger test of pure inhibition than equal Go:NoGo ratios (Smith et al. 2014). Each letter was presented for 900ms and followed by 100ms inter-stimulus interval of a blank screen. Each run began with a 12 second fixation and lasted for four minutes and 22 seconds.

### *Evocative Images Task (EIT)*

To assess stress-related emotional processing and negative reinforcement, participants performed the Evocative Images task (EIT), which evokes emotional distress with the presentation of aversive (evocative) compared to neutral images. Displaying both animate and inanimate objects, evocative images included scenes of injury or threat in the evocative category, but there were no drug-related images in either category. Images were from the International Affective Picture System (IAPS; <http://csea.php.ufl.edu/media/iapsmessage.html>) library and were counterbalanced for valence and arousal scores. The task was split into two runs of six minutes and 32 seconds; containing four blocks each of evocative images and neutral images, separated by a rest period of 15 seconds. Neutral blocks were presented first and followed by an evocative block; each consisting of six images presented in pseudo-randomised order and displayed for five seconds each with a 400ms inter-stimulus interval (Figure 2.2B). The second run contained the same images presented in a different order. Participants made a button-press response on the presentation of each image to ensure they were concentrating.



**Figure 2.2:** **A)** An example of the Go/No-Go task. Participants are asked to respond as quickly as possible to each letter “X” and “Y” that appears on the screen, except when the letter is the same as the one shown previously. **B)** An example of the Evocative Images task. Neutral or evocative images are presented in a block design. Participants are asked to look at each of the images displayed and make a button press response at each image presentation.

### *MR Image Acquisition*

Imaging was carried out at the three sites using a Siemens (Imperial and Cambridge) or a Philips (Manchester) 3T MR scanner. One hundred and thirty one volumes for the GNG and 196 for the EIT were acquired, comprising 33-36 axial slices of 3mm thickness, with a TR of 2000ms, TE of 32ms and a voxel size of 3 x 3 x 3mm. In order to maximise cerebral coverage while minimising slice thickness and susceptibility artefact, fMRI/EPI acquisition

was at +30 degrees to the ACPC line. A T1-weighted structural image was also acquired for use in spatial pre-processing and for examination of any structural abnormalities.

## *Data analysis*

### *Group Difference Analysis*

Data were analysed using Statistical Package for Social Sciences (SPSS, version 22, [www.spss.com](http://www.spss.com)). Multivariate analyses of variance (MANOVA) were used to assess group differences from controls on self-report and cognitive measures, followed by univariate analyses of variance (ANOVA) and Tukey's HSD post-hoc statistical test when main effects were found. IQ was entered into these as a covariate to control for the significant group differences in this variable.

Pearson's Chi-square test and independent t-tests were then used to assess whether any clinical or demographic variables significantly predicted AbD group allocation following latent profile analysis (Pickles & Croudace 2010). Pearson's correlations were used to assess whether the variation in CTQ scores was related to variables that predicted AbD group allocation.

### *Image Analysis*

Imaging data were analysed using Statistical Parametric Mapping (SPM12; Wellcome Trust Centre for Neuroimaging, London, England, <http://www.fil.ion.ucl.ac.uk/spm/>), implemented in MATLAB (Mathworks, 2012). Images were realigned to correct for motion, using the first image as a reference. The structural (T1-weighted) and functional images were then coregistered, followed by spatial normalisation, and were smoothed using a Gaussian kernel filter of 8 x 8 x 8mm.

First level analysis for the GNG task was performed on the contrasts of Stops (successful inhibitions) compared to a background of Go responding. Errors (of commission) were modelled as a contrast of no interest as there were too few for sufficient power. Also modelled as contrasts of no interest were "Sleep" where there were more than 10 consecutive errors of omission on Go trials, and "False Inhibitions" where successful inhibitions on NoGo trials were immediately preceded by an omitted Go trial. First level analysis for the EIT was performed and the key contrast of negative compared to neutral images (Evocative>Neutral) compared to a background of rest.

At the second level for both tasks we used region of interest (ROI) analysis based on areas previously identified as being associated with these two tasks in substance dependence. The ROIs were defined using Neuromorphometrics, Inc. ([www.neuromorphometrics.com](http://www.neuromorphometrics.com)), under academic subscription. Average values for each ROI were extracted for each contrast of interest: Stops (GNG) and Evocative>Neutral (EIT). ROIs were the anterior cingulate cortex (ACC) and bilateral inferior frontal gyri (IFG) for the GNG task (Chambers et al. 2009; Garavan et al. 2006; Simmonds et al. 2008); and bilateral hippocampi and bilateral amygdala for the EIT (LeDoux 2000; Baeken et al. 2010; Asensio et al. 2010; Vaisvaser et al. 2013; Supplementary Figure 2.1). Firstly, we performed an ANOVA to assess group differences (Control vs. Low AbD vs. High AbD) on both GNG and EIT tasks. IQ was entered into these as a covariate to control for the significant group differences in this variable. Secondly, we conducted correlation analyses to investigate the relationship between ROI activation from both tasks with the variables of length of abstinence and childhood trauma. The control group were excluded from length of abstinence analyses as they had no abstinence data.

## Results

### *Participant Demographics*

Analysis of participant demographics found that groups were significantly different in IQ, but did not significantly differ on age, sex, or smoking status (Table 2.3).

**Table 2.3:** Means (SD), proportions and group difference statistics on demographic and clinical variables for control participants and the two new AbD groups: High and Low.

	Control	Low AbD	High AbD	F or $\chi^2$	p
<b>Age</b> (Mean, SD)	42.15 (8.33)	42.13 (9.22)	40.77 (9.30)	0.358	0.700
<b>IQ</b> (Mean, SD)	106.24 (8.71)	101.00 (9.22)	101.38 (11.18)	3.987	<b>0.021*</b>
<b>% Female</b>	26.1	20.0	17.0	1.188	0.552
<b>% Smokers</b>	63.0	72.5	78.7	2.833	0.243

### *Normalisation of Data*

Initial data screening of all self-report and behavioural measures using Q-Q plots highlighted non-normally distributed scores for the IED Total Errors and the Kirby *k*. Therefore, these were transformed using a log transformation and resulted in normally-distributed Q-Q regressor plots.

## *Group Differences from Control Participants*

### *Self-Report Measures of Impulsivity and Affect*

We used a MANOVA to assess differences from controls on the total scores of each self-report measure (Table 2.1). Using Pillai's trace, a significant effect of group was found ( $V=0.721$ ,  $F(16,248)=8.746$ ,  $p<0.001$ ), which allowed separate univariate ANOVAs to be performed post-hoc on each of the self-report measures and revealed significant group differences on all measures. Further post-hoc analyses using Tukey's LSD revealed that that High AbDs scored significantly higher than both controls and Low AbDs on all self-report measures, while Low AbDs were no different from controls on any but the UPPS-P Impulsivity Scale (Supplementary Table 2.1 & Supplementary Figure 2.2).

### *Childhood Adversity*

An ANOVA was used to assess differences from controls on CTQ, and found a significant main effect of group ( $F(2,132)=13.944$ ,  $p<0.001$ ). Further post-hoc analyses using Tukey's LSD revealed that High AbDs scored significantly higher than both controls (mean difference=15.338,  $p<0.001$ ) and Low AbDs (mean difference=15.743,  $p<0.001$ ) on the CTQ, but that Low AbDs were not significantly different from controls (mean difference=0.405,  $p=0.993$ ).

### *Cognitive Tasks*

Differences from controls were analysed using a MANOVA on the score outcome measures for each cognitive task: SSRT, IED total errors, and Kirby *k*. Using Pillai's trace, a significant main effect of group was found ( $V=0.108$ ,  $F(6,252)=2.401$ ,  $p<0.05$ ), which allowed separate univariate ANOVAs to be performed post-hoc on each of the outcome scores. These revealed a significant group difference on Kirby *k* ( $F(2,127)=3.368$ ,  $p<0.05$ ), but not IED total errors ( $F(2,127)=2.555$ ,  $p=0.082$ ), or SSRT ( $F(2,127)=1.106$ ,  $p=0.334$ ). However, when we controlled for IQ (as a covariate), the group effect of Kirby *k* was no longer significant ( $F(2,126)=2.564$ ,  $p=0.081$ ), along with IED total errors ( $F(2,126)=1.515$ ,  $p=0.224$ ), and SSRT ( $F(2,126)=0.937$ ,  $p=0.395$ ; Supplementary Figure 2.3).

Additional exploratory analyses were performed on further outcome measures of the SST and IED to ensure these were not confounding the results. The groups did not differ on Stop Signal Delay ( $F[2,127]=0.467$ ,  $p=0.628$ ), Proportion of Successful Stops ( $F[2,127]=0.424$ ,  $p=0.655$ ), or mean Go Reaction Times ( $F[2,127]=0.070$ ,  $p=0.933$ ). There



were no significant group differences in the number of IED stages completed ( $\chi^2=12.818$ ,  $p=0.234$ ).

### *Differences between Abstinent Substance Dependent Groups*

We used Chi-square and t-tests to assess whether any demographic or clinical variables, as well as the original AbD groupings (Taylor et al., *in prep*, **Study 1**) or site of recruitment, significantly predicted group allocation from Part 1 (Table 2.4). These found that High AbDs were more likely to have a history of stimulant dependence ( $\chi^2=9.350$ ,  $p<0.01$ ), but not of alcohol ( $\chi^2=1.400$ ,  $p=0.330$ ), opioid ( $\chi^2=0.001$ ,  $p=1.00$ ), or nicotine dependence ( $\chi^2=0.457$ ,  $p=0.617$ ). Total number of dependencies (excluding nicotine) was a marginally significant contributor to High AbD allocation ( $t(85)=-1.983$ ,  $p=0.051$ ).

**Table 2.4:** Associations between latent classes and demographic factors and clinical variables, with significant results in red and marginally significant results in orange.

		Count ( $\chi^2$ ) or Mean (t)		$\chi^2$ or t	p
		Low	High		
Site	London	14	23		
	Cambridge	14	15	2.103	0.349
	Manchester	12	9		
Original Group	Alcohol	17	11	3.610	0.069
	Polydrug	23	36		
Age		42.13	40.77	0.682	0.497
IQ		101.00	101.38	-0.172	0.864
Sex	Male	32	39		
	Female	8	8	0.128	0.786
Smoking Status	Smoker	29	37		
	Non-Smoker	11	10	0.457	0.617
Stimulant Dependence	Yes	15	33	9.350	<b>0.003</b>
	No	25	14		
Alcohol Dependence	Yes	27	37	1.400	0.330
	No	13	10		
Opioid Dependence	Yes	18	21	0.001	1.000
	No	22	26		
Length of Abstinence		17.74	13.45	1.110	0.269
Cumulative Exposure		20.59	24.41	-1.439	0.154
Total Dependencies		1.73	2.17	-1.983	<b>0.051</b>
Childhood Trauma		39.73	55.47	-4.198	<b>&lt;0.001</b>

To assess whether childhood adversity could explain stimulant dependence history we performed an independent t-test across all AbD participants and found significantly higher CTQ scores in individuals with a history of stimulant dependence ( $t(85)=-2.520$ ,  $p<0.014$ ).

Also, to assess whether CTQ was related to the total number of dependencies, we performed a Pearson's correlation and found a moderate positive correlation between childhood adversity (CTQ) and total number of dependencies ( $r=0.367$ ,  $p<0.001$ ).

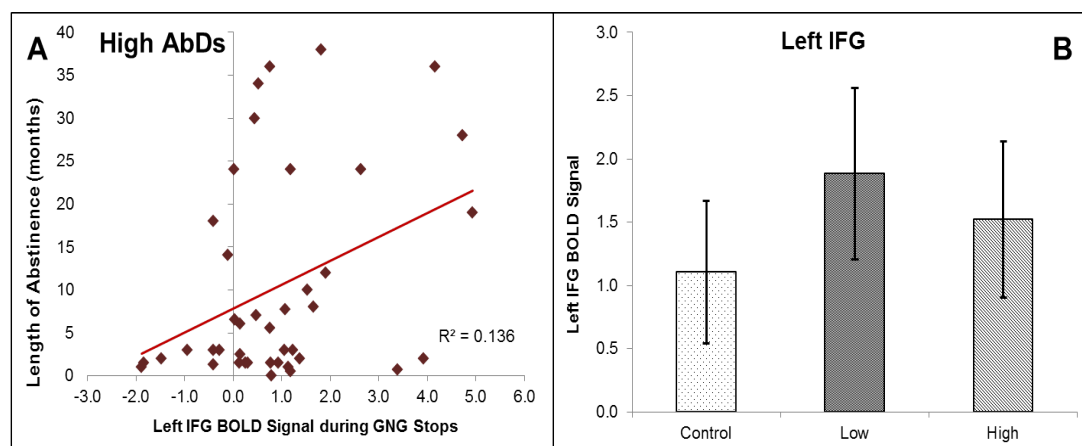
## Imaging Analysis

### Behavioural Performance

We assessed behavioural performance on the GNG task using ANCOVA, with IQ as the covariate to control for group differences on this variable. There were no significant group differences in NoGo accuracy ( $F(2,117)=0.261$ ,  $p=0.770$ ), Go accuracy ( $F(2,117)=2.783$ ,  $p=0.066$ ), or Go RT ( $F(2,117)=0.219$ ,  $p=0.804$ ; Supplementary Table 2.2). There was no performance data for the EIT.

### Go/NoGo (GNG) Task

An ANOVA did not identify any significant blood oxygen level dependent (BOLD) signal changes between groups at the voxel-level Family Wise Error (FWE) corrected threshold of  $p<0.05$ . We also used the predefined ROIs of right IFG, left IFG and ACC, none of which identified any significant group differences. For descriptive purposes only, additional effects at a  $p<0.001$  uncorrected threshold are displayed in Supplementary Table 2.3. Correlation analyses found no significant associations between activation and CTQ scores in either group. However, length of abstinence was found to show a positive correlation with left IFG activation in High AbDs ( $r=0.441$ ,  $p<0.05$ , Bonferroni corrected for 6 comparisons [3 regions in 2 groups]; Figure 2.3A) but this was not apparent in the Low AbDs ( $r=-0.064$ ,  $p=1.00$ ).



**Figure 2.3: A)** Left IFG BOLD activation during Stops contrast of Go/NoGo task within High AD participants is positively correlated with their length of abstinence; **B)** Mean beta values for each group in the left IFG at the peak -39, 26, -4 where the correlation was found.

### *Evocative Images Task (EIT)*

For the EIT we also conducted an ANOVA to assess group differences in activation, which did not identify any significant group differences in BOLD signal change at the FWE-corrected threshold  $p < 0.05$  level. We also used the predefined ROIs of the right and left hippocampus as well as the right and left amygdala, none of which identified any significant group differences. For descriptive purposes only, additional effects at the  $p < 0.001$  uncorrected threshold are displayed in Supplementary Table 2.3. Correlation analyses found no significant associations between activation and length of abstinence or CTQ.

## **Discussion**

This study used Latent Profile Analysis to classify abstinent substance dependent (AbD) participants based on their personality risk factors determined by their responses on a number of self-report measures of impulsivity and affect, rather than based on their primary substance of dependence. We sought to test a hypothesis, based on Becker et al.'s (2012) two-route theory of addiction, that the analysis would identify two groups; one characterised by high impulsivity and one by high stress. Contrary to our hypothesis, our reclassification method identified a group of AbD participants that scored high and another that scored low across all the self-report measures.

Investigation of the role of clinical and demographic variables, as well as childhood adversity, in these reclassified groups found that higher childhood trauma scores (CTQ) and a history of stimulant dependence were the only significant predictors of group allocation. We also found that CTQ scores were significantly higher in individuals with a history of stimulant dependence, and were positively correlated with the number of dependencies (excluding nicotine). While Low AbDs did not differ from controls on any but one self-report measure, High AbDs scored significantly higher than both controls and Low AbDs on all self-report measures. A positive correlation was also found between length of abstinence and GNG left IFG activation in High but not Low AbDs.

We found that the Low AbDs were no different from controls on specific measures of impulsivity and affect. Previous studies have found substantial evidence of increased impulsivity (Dallery & Locey 2005; Ersche et al. 2010; Hogarth 2011; Perry & Carroll 2008; Verdejo-García et al. 2008; Winstanley 2007), and higher rates of affective disorders in substance dependence (Conway et al. 2006). In our cohort, when all AbD participants are

grouped together or when they are grouped by substance of dependence, they show a significant increase in these measures compared to controls (see Taylor et al., *in prep*, **Study 1**), consistent with the literature. However, the analysis performed here, using a data-driven grouping method, reveals two distinct groups. Our study suggests that previous findings of increased impulsivity and affective disturbance in substance dependence may be driven by a distinct subgroup (approximately 50% in our sample) with high scores rather than a general elevation of scores.

Analysis of the GNG fMRI data found that length of abstinence was positively correlated with left IFG activation in High AbDs only. The IFG (especially right sided) is associated with inhibitory control tasks, such as the GNG and SST, along with the ACC and dorsolateral prefrontal cortex (dlPFC, Garavan et al. 2006; Simmonds et al. 2008; Chambers et al. 2009). These regions are usually associated with reduced activations that are related to poorer inhibitory control in substance users (with current substance use or up to an average of seven weeks length of abstinence) compared to controls (Kaufman et al. 2003; Hester & Garavan 2004; Li et al. 2008; Li et al. 2009; Forman et al. 2004; Fu et al. 2008). Interestingly, the left IFG activation correlation with length of abstinence is only present in the High AbD group. This is in accordance with the finding of greater activation of the same region acting as a compensatory mechanism in polydrug dependent individuals who show control-level performance (Taylor et al., *in prep*, **Study 1**), although there was not a significant difference in length of abstinence between High and Low AbD groups.

Evidence of compensatory inhibitory control mechanisms are also seen in siblings of stimulant dependent individuals who showed greater activation in dorsal medial (dm)PFC (Morein-Zamir et al. 2013) while displaying the same level of performance as controls on the SST. This suggests the siblings are recruiting additional mechanisms to enable the control-levels of behavioural inhibitory control, which is above that of their inhibitory control-deficient stimulant dependent siblings. Similarly, these compensation mechanisms are also reported in executive control tasks, such as the Stroop task; chronic drug users showed behavioural performance comparable to controls, but greater orbitofrontal cortex (OFC) activation (Goldstein et al. 2001). Compensation is also seen in substance users compared to controls within the left OFC during decision making tasks (Bolla et al., 2003; Ersche et al., 2005). The positive correlation in High AbDs with length of abstinence in light of a lack of group differences in abstinence duration would suggest that this ability to

compensate for deficient inhibitory control is something acquired during extended abstinence in the High group. Notably the Low AbDs have (non-significantly) higher left IFG responses than either High AbDs or controls (Figure 2.3B), possibly suggesting that compensatory mechanisms are in place at an earlier stage in these individuals rather than developing with extended abstinence.

The High and Low AbD groups did not differ significantly from controls on cognitive behavioural measures of the SST, IED, or Kirby delay discounting. The AbD groups also did not differ from controls in responses to evocative images on the EIT. This may reflect greater sensitivity to differences of self-report measures than of neurocognitive measures (Taylor et al., *in prep*, **Study 1**), which also appear to be the case in the present study and suggests that neurocognitive tasks assess constructs that are more vulnerable to external influences.

Our central finding is that High AbDs differed from Low AbDs and controls on most questionnaire measures, while the Low AbDs were no different from controls on the majority of measures. We propose two possible explanations for these differences between High and Low AbDs. The first relates to the relatively long length of abstinence in both AbD groups. While there is no difference in abstinence duration, the Low AbD group may have “recovered” to control levels on these measures during their abstinence, whereas the High AbD group have not fully done so.

The second potential explanation for the difference between AbD groups is that the Low group may never have differed from controls on these measures. If this is the case, our alternative classification method has revealed a distinct sub-group of substance dependent individuals who score comparably to controls on a number of measures of impulsivity and affect. The latter suggestion is supported by the assumption that the self-report measures (on which the groupings were based) are trait measures that are relatively resistant to change (Taylor et al., *in prep*, **Study 1**), and thus should not be affected by recovery during abstinence. More importantly, the groups did differ significantly on childhood adversity, which appears to be a crucial variable driving the difference between the groups. Furthermore, we also found that CTQ scores were related to the number of dependencies and with stimulant dependence history. This suggests that individuals who experienced

more adversity during childhood are more likely to develop dependence to multiple substances; the more adversity the more substances.

There is substantial evidence that childhood adversity is a risk factor for developing substance dependence (Dube et al. 2003; Sorocco et al. 2015), as well as being a negative influence on the progression of dependence and recovery (Elton et al. 2015). Childhood adversity is thought to alter prefrontal and limbic function (Andersen & Teicher 2009; Chocyk et al. 2013), with the result that individuals with high adversity show blunted physiological responses to stress (Matthews & Robbins 2003; Lovallo et al. 2012), poor cognitive function and more impulsive behaviour (Lovallo et al. 2013), as well as more negative affect and poorer affective regulation (Sorocco et al. 2015). As such, these individuals may resort to substance use as an alternative means to compensate for these deficiencies (Koob & Le Moal 2008; Andersen & Teicher 2009). This is in line with the present findings that High AbDs have higher self-report impulsivity and affect scores as well as significantly higher CTQ scores than controls and Low AbDs.

High AbDs also were significantly more likely to have a history of stimulant dependence, but this was not seen for alcohol or opioid dependence. This importance of stimulant dependence in reclassification of drug users is particularly interesting as this study used a grouping method that was blind to substance. This is supported by evidence of increased impulsivity and depression in individuals dependent on cocaine and methamphetamine (Mahoney et al. 2015) compared to controls. Substances with a stimulant effect, such as cocaine and amphetamines, directly affect the mesolimbic dopaminergic system (Volkow et al. 2011), a system that is highly associated with trait impulsivity (Dalley et al. 2011). However, this division by stimulant dependence is not a perfect split as there were individuals with a history of stimulant dependence in the Low AbD group, and other drivers, particularly childhood adversity that also appear to be important. Indeed, it seems likely that childhood adversity is the most important influence in this classification of AbDs, as it almost certainly predated any clinical variables. In addition, CTQ scores were significantly higher in those with a history of stimulant dependence, although we are unable to determine if individuals actively seek out stimulants as a result of their high levels of childhood adversity from the present cross-sectional data.

### *Limitations*

Potential limitations of the study include the use of only self-report measures to group AbDs. Such measures are reliant on individual honesty and insight as well as being susceptible to bias (Verdejo-García et al. 2008). However, all these measures are frequently used in addiction research and are well-validated. A second limitation is that, inevitably, there are other measures, including their sub-scales, that may provide wider scope for more accurate grouping. In relation to this, latent profile analysis gives more robust outcomes with greater numbers of variables. While the present sample of 87 AbDs is relatively large for behavioural and especially for imaging investigations, it is comparatively small for use with Latent Class Cluster Analysis, which in turn limited the number of variables on which the separate classes were based.

Further limitations include the significant group difference in IQ. Although we co-varied for this in all analyses possible, the higher IQ of the control group may have confounded our findings. There was also an unequal representation of gender, with only approximately 20% female participants. However, this reflects the general population of substance dependent individuals, in which there is a greater prevalence of men (e.g. Compton et al 2007). In addition, the design of the ICCAM Platform Study (Paterson et al. 2015) may have introduced a sampling bias by recruiting participants who were relatively stable in their abstinence and thus may have excluded individuals who are more prone to early relapse, creating a selection bias. In addition, participants were recruited from treatment services, meaning that individuals who become abstinent without clinical assistance are not represented in this sample. If this regrouping technique was to be repeated in newly abstinent individuals we would predict to see a higher proportion in the High group and to observe an elevated risk of relapse in this group. As a result, it is likely that Low AbDs are overrepresented in the current sample.

### *Unanswered Questions and Future Research*

Future research should investigate this regrouping method across the spectrum of substance use and dependence; ideally from vulnerable individuals, through harmful use and dependence, to recent and sustained abstinence on all substances. By looking at these different stages of substance use and dependence we can investigate whether the same divisions are identified at each stage, or if there are particular aspects that have impact at certain stages more than at others.

While other studies have used data-driven methods to identify alternative groupings of substance dependent individuals, this is the first study (to the best of our knowledge) to use personality risk factors alone. The majority of other studies group users based on drug classes and patterns of use (e.g. Agrawal et al. 2007; Monga et al. 2007; Reboussin et al. 2006; Scheier et al. 2008; Patra et al. 2015; Kuramoto et al. 2011; Trenz et al. 2013; Harrell et al. 2014; Dias et al. 2015). Although Harrell et al. (2014) investigated cognitive performance, they used demographics to group their participants (such as age, years of education etc.) and then assessed group difference in cognitive performance.

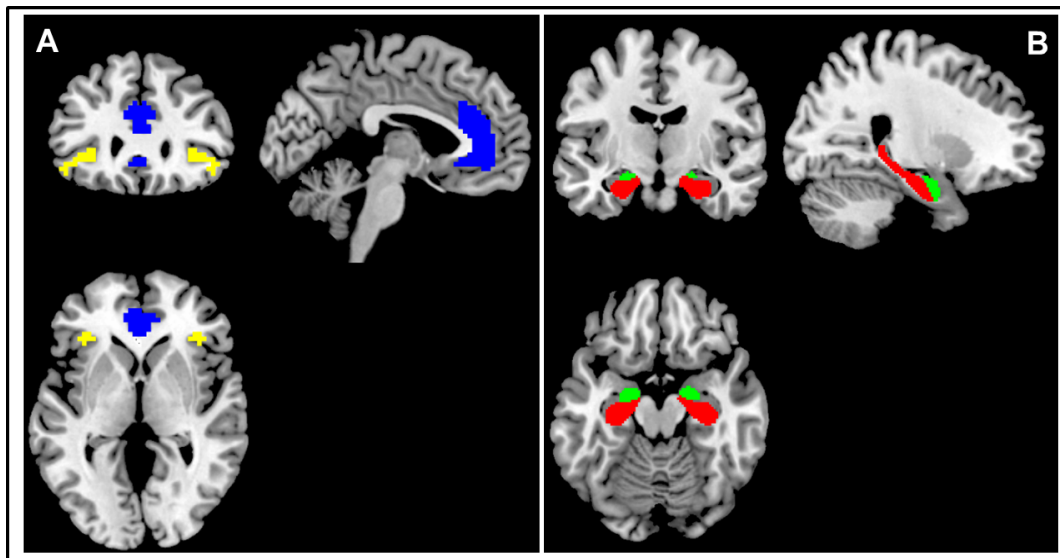
This method using personality risk factors may also improve understanding of problems such as “hopping” to other substances or behavioural addictions (e.g. gambling). We may better understand these problems by regarding addiction as one disorder (Shaffer et al. 2004) with a number of different profiles that can be treated accordingly. This is particularly important in the case of poly-substance dependence and of co-morbidities with other psychiatric conditions.

### *Conclusions and Implications*

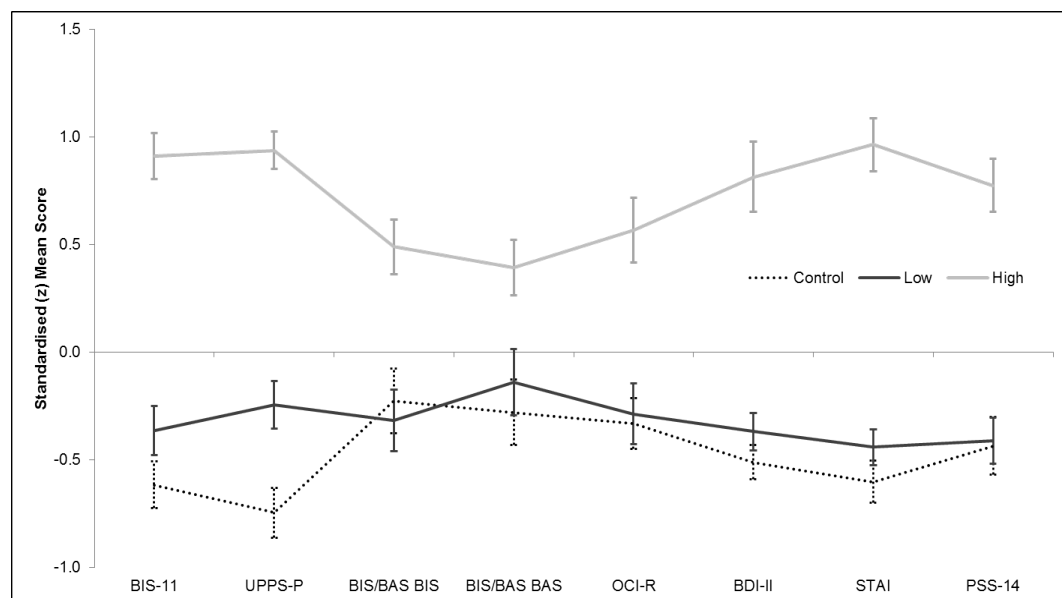
This study introduced an alternative way to group substance dependent participants that does not focus on the primary dependence. We identified a group of AbD individuals who did not differ from controls on measures of impulsivity and affect, and another with significantly higher scores on these measures as well as greater incidence of childhood adversity and stimulant dependence. The fact that childhood adversity occurs before initial drug use highlights this as a fundamental factor that should be considered in addiction research, as well as in treatment and prevention. Future research should investigate reclassification of substance users based on their personality risk factors at the different stages from vulnerability through to long-term stable abstinence.



## Supplementary Materials



**Supplementary Figure 2.1:** Region of interest masks, defined by Neuromorphometrics, Inc. ([www.neuromorphometrics.com](http://www.neuromorphometrics.com)), under academic subscription. **A)** For the Go/NoGo task these are the anterior cingulate cortex (ACC; blue) and bilateral inferior frontal gyri (IFG; yellow); **B)** for the Evocative Images Task these are the bilateral amygdala (green) and bilateral hippocampi (red).



**Supplementary Figure 2.2:** Mean standardised (z) scores for Control, Low AbD and High AbD participants on each of the self-report measures.

**Supplementary Table 2.1:** Mean (SD) scores for each Self-Report measure of Impulsivity and Affect for Control, Low AbD and High AbD participants

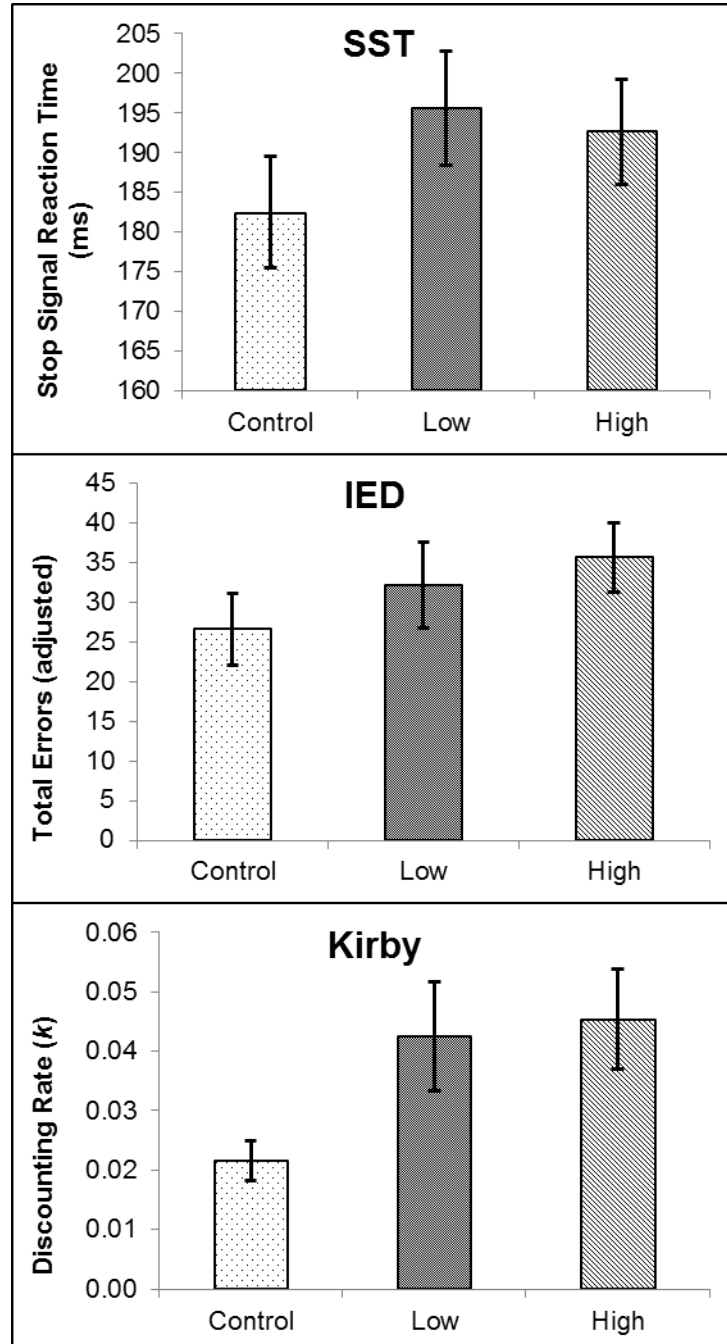
	Control	Low AbD	High AbD
<b>Barratt Impulsiveness Scale</b>	57.46 (9.61)	60.70 (9.31)	77.17 (9.42)
<b>UPPS Impulsive Behaviour Scale</b>	114.46 (20.84)	127.80 (18.33)	159.21 (15.78)
<b>Behaviour Inhibition System</b>	37.93 (5.60)	38.70 (5.25)	41.60 (4.82)
<b>Behaviour Activation System</b>	18.76 (4.41)	18.38 (3.88)	21.83 (3.73)
<b>Obsessive Compulsive Inventory</b>	7.83 (8.43)	8.30 (9.40)	17.30 (10.81)
<b>Beck Depression Inventory</b>	3.48 (4.46)	4.58 (4.28)	13.68 (8.63)
<b>Spielberger Trait Anxiety Index</b>	29.37 (8.03)	31.33 (6.41)	48.38 (10.26)
<b>Perceived Stress Scale</b>	15.24 (7.04)	15.43 (5.24)	24.64 (6.62)

**Supplementary Table 2.2:** Go/NoGo and Evocative accuracy mean (S.D.) for each group.

	Control	Low	High
<b>Go Accuracy %</b>	98.51 (2.27)	96.67 (3.73)	97.22 (3.43)
<b>NoGo Accuracy %</b>	68.64 (15.85)	66.32 (16.39)	64.80 (19.75)
<b>Go RT (ms)</b>	330.23 (65.51)	341.52 (65.33)	333.51 (78.45)

**Supplementary Table 2.3:** Uncorrected whole brain effects of Successful Inhibitions (Stops) on the Go/NoGo task and for Evocative>Neutral Images on Evocative Images Task.

Go/NoGo Task						
Cluster size (voxels)	Z	x	y	z	Hemisphere	Region
21	3.519	48	-55	11	R	Middle Temporal Gyrus
	3.386	18	5	-10	R	Ventral Striatum
	3.351	-15	5	-13	L	Ventral Striatum
	3.319	-12	26	29	L	Anterior Cingulate Cortex
Evocative Images Task						
Cluster size (voxels)	Z	x	y	z	Hemisphere	Region
16	3.215	21	-49	20	R	Precuneus



**Supplementary Figure 2.3:** Mean scores (with standard error bars) on the Stop Signal Task (SST), Intra-Extra Dimensional Set Shift (IED), and Kirby Delay Discounting tasks.



## **2.3 Study 3: Stress, Alcohol-Approach Bias and Avoidance Behaviour in Heavy Drinkers**

### *Submission*

This paper has been prepared for submission to *BMC Psychology* (<http://www.biomedcentral.com/bmcpsychol>). Please note that the reference style is consistent with the rest of the thesis and will be updated to that required by the journal before submission.

### *Individual contribution*

The data in this paper were collected as part of a protocol that I designed for Studies 3 (p. 101) and 4 (p. 127). I collected the data, completed all the analyses presented, and prepared the manuscript.

# Stress, Alcohol-Approach Bias and Avoidance Behaviour in Heavy Drinkers

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**Rationale:** Heavy alcohol use is prodromal for alcohol dependence. Through the processes of positive and negative reinforcement, automatic approach and avoidance mechanisms are thought to be involved in the development of dependence. Stress is also implicated in this transition to dependence.

**Objectives:** The present study assessed the effect of stress induction on automatic alcohol-approach behaviours and avoidance of aversive stimuli in heavy drinking individuals.

**Methods:** Twenty-eight heavy drinking participants and 29 controls completed an Alcohol Stimulus-Response Compatibility Task measuring automatic alcohol-approach behaviour, and an Active-Passive Avoidance Task measuring avoidance of an aversive non-alcohol-related stimulus, before and after stress induction. Measures of behavioural inhibitory control (Stop Signal Task) and self-report impulsivity and affect were also collected.

**Results:** Contrary to the hypotheses, there was no differential effect of stress on heavy drinkers on either Alcohol Approach-Bias or avoidance of an aversive non-alcohol related stimulus.

**Conclusions:** Findings are interpreted in light of the relatively older age of the present heavy drinkers compared to those recruited in other studies. We suggest that these older heavy drinkers are more similar to alcohol dependent participants who show no Alcohol-Approach Bias compared to controls. The importance of investigating behaviours related to addiction across the whole spectrum of substance use and dependence is highlighted.

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## Introduction

Harmful alcohol use is responsible for 5.1% of the global burden of disease and injury, with 11.1 % of people in the UK suffering from alcohol use disorders (WHO 2014). Excessive alcohol consumption is also known to be prodromal for alcohol dependence (Kranzler et al. 1990; Dawson & Aecher 1993). Stress, as well as the negative affective states it produces, contributes significantly to the risk for developing alcohol use disorders (Heilig & Koob 2007; Wand 2008; Hägele et al. 2014), as well as later relapse following detoxification (Koob and Le Moal 2001; Garland, Franken, and Howard 2012). Particular stressors, such as childhood trauma, have also been identified to play a significant role in the development of substance use disorders within a subset of individuals (Taylor et al., *in press*, **Study 2**). To investigate the role of stress in the development of alcohol use disorders, we studied its influence on motivation towards alcohol cues in heavy drinking individuals, focussing on how approach and avoidance behaviours are altered following stress induction.

Approach and avoidance behaviour are mediated by two different processes: positive reinforcement and negative reinforcement, respectively. Positive reinforcement strengthens behaviour by its association with the presentation of a pleasant event, while negative reinforcement strengthens behaviours that enable avoidance of unpleasant outcomes. These reinforcement processes are involved in substance use; reflected in the approach of the drug high (positive reinforcement) and in the avoidance of withdrawal (negative reinforcement).

Through the process of positive reinforcement, incentive motivation is assigned to a substance as a result of the pleasant feelings that accompany its intake. Substance-related cues are also assigned this incentive salience by the process of classical conditioning, whereby they are paired with the substance that evoked the positive outcome (Robinson & Berridge 1993; 2003; 2008). This incentive salience is thought to be behind the attentional bias that is seen for alcohol-related cues in heavy social drinkers (Field et al. 2004; Townshend and Duka 2001), as well as other substance-related cues in dependence (for a review, see Field & Cox 2008). Repeated exposure to substances and their cues through the process of attentional bias strengthens their incentive salience further, which in turn increases the attentional bias. Incentive salience of alcohol-related cues also initiates automatic behavioural approach towards these cues (Field et al. 2008; 2011) and continues

the cycle of exposure, salience, and attentional bias; increasing the risk of developing dependence (Robinson and Berridge 2008; Wiers et al. 2007).

Negative reinforcement is also influential in assigning incentive motivation towards drugs and their cues through the removal of aversive events. In substance use this can be the removal of withdrawal symptoms, or drug use as “self-medication” to ameliorate pre-existing negative affective states (Koob and Le Moal 2008; Becker, Perry, and Westenbroek 2012). For example, depression and anxiety are associated with dependence (Heilig & Koob 2007; Wand 2008; Hägele et al. 2014) and can be relieved with the anxiolytic and anti-depressant effects of many substances, including alcohol. Alcohol use as self-medication is also seen in adolescents and young adults who drink heavily; those who report drinking as a coping mechanism were more likely to have alcohol-related problems (Kuntsche et al. 2005). Additionally, a systematic review by Snelleman, Schoenmakers, and van de Mheen (2014) found a relationship between stress and sensitivity to alcohol cues. The avoidance of negative affective states with the use of substances is a form of negative reinforcement (Koob, 2009), and thus assigns incentive salience to substances and their cues. Consequently, it is important to understand the impact of these negative affective states on automatic approach behaviours to see how they alter an individual’s behaviour towards substances and their cues.

To the best of our knowledge there are no published studies investigating the effect of stress on automatic approach responses to alcohol cues. However, there is evidence of an increase in attentional bias following stress induction: in heavy drinkers compared to controls (Field and Powell 2007; Grant, Stewart, and Birch 2007); in high scorers on the “drinking to cope” subscale of the Drinking Motives Questionnaire (Birch et al., 2004; Field & Quigley, 2009); and in high compared to low “escape drinkers” (Forestell et al. 2012). Physiological measures of stress are also associated with alcohol attentional bias in alcohol dependent individuals during stress-primed alcohol cue-exposure (Garland et al. 2012). Furthermore, negative mood induction increases subjective alcohol craving (Cooney et al. 1997; Willner et al. 1998), which is associated with attentional bias for alcohol cues (for a meta-analysis, see Field, Munafo, and Franken 2009). This suggests that attentional bias, and with it automatic approach responses, may be affected by individual differences in stress reactivity.



How an individual acts on these influences of positive and negative reinforcement when under stress is dependent on a number of other factors. One factor strongly associated with substance dependence is impulsivity (Dallery & Locey 2005; Ersche et al. 2010; Hogarth 2011; Perry & Carroll 2008; Verdejo-García et al. 2008; Winstanley 2007). Related to the evaluation of response options, including cognitive and emotional assessment of possible behavioural outcomes, high impulsivity is also associated with alcohol dependence and earlier onset of alcohol use in adolescents as measured by the Barratt Impulsiveness Scale (BIS-11; von Diemen et al. 2008). Additionally, general inhibitory control deficits are reported in the face of extreme positive or negative emotion (Cyders & Smith 2008), such as that caused by stress, and are also seen in alcohol dependence (Whiteside & Lynam 2003).

In addition, dual process models (Stacy & Wiers 2010) suggest there are two factors contributing to alcohol use disorders: first the motivational cycle of attentional bias and automatic approach behaviour; and second, when this motivation is combined with poor cognitive control, the individual is no longer able to suppress automatic appetitive processes. Both sensitivity to reinforcement and levels of experienced stress can influence processes involved in impulsive behaviour. Referred to as “affective impulsivity”, this relates to the ability to control behaviour in the face of extreme positive or negative affect (Whiteside & Lynam, 2001). Consequently, dysfunctions in impulsivity combined with stress mechanisms are likely to contribute to the abnormal approach-avoidance behaviours seen in heavy drinking individuals.

In light of this evidence, we hypothesised that heavy drinking individuals are more likely to show automatic alcohol approach and avoidance of aversive stimuli, perhaps resorting to drinking alcohol to avoid the negative affective states induced by stress. In order to investigate approach and avoidance behaviour in heavy drinking individuals, we used two previously-validated behavioural tasks. The first task, an Alcohol Stimulus-Response Compatibility Task (ASRC; Field et al. 2008), assessed the extent to which individuals automatically approached alcohol-related images. This task has found that automatic approach behaviour is heightened in heavy drinkers compared to controls, and has been used as a predictor of hazardous drinking (Kersbergen et al. 2015). The second task, an Active-Passive Avoidance Task (APA; Levita et al 2012; 2015), assessed non-alcohol related avoidance behaviour in the form of active and passive avoidance of an aversive auditory

stimulus. As yet this task has only been used in healthy controls, although nucleus accumbens (NAcc) response was associated with individual levels of self-reported anxiety (Levita et al. 2012). It is important to have both alcohol- and non-alcohol-related tasks to establish whether or not the effects of stress on motivation are alcohol-specific. We then repeated these tasks following stress induction to investigate if and how these alcohol-approach and avoidance behaviours changed in response to stress.

We investigated two hypotheses: first that heavy drinkers will show greater alcohol approach-bias than controls, as seen in previous studies (Field et al. 2008; Field et al. 2011), while also showing more avoidance of aversive stimuli; secondly that there will be a differential effect of stress on alcohol-approach behaviour and avoidance of aversive stimuli between heavy drinking and control individuals. A third task, the Stop Signal Task (SST), assessed motor inhibitory control, which, along with self-report measures of impulsivity, personality and affect, were included to assess their relation to the effect of stress on automatic approach and avoidance behaviour in heavy drinking individuals.

## **Methods**

The protocol was approved by the North West, Greater Manchester East Research Ethics Committee (REC Ref: 13/NW/0650). Sessions were conducted at the Neuroscience and Psychiatry Unit, University of Manchester.

### *Participants*

Sixty-six participants were recruited from the Greater Manchester area via posters and online advertising. Participants were included into either a “heavy drinking” group if they self-reported consumption of 30+ (male) or 22+ (female) UK units of alcohol per week (one UK unit = 8g alcohol), or a “control” group if they reported consuming <20 (male), or <15 (female) units of alcohol per week. These limits were based on UK Government advice on alcohol consumption (as of October 2013), which was to consume no more than 2-3 (female) or 3-4 (male) units of alcohol per day with two alcohol-free days a week (House of Commons Science and Technology Committee 2012). This equates to a maximum of 20 (male) or 15 (female) units of alcohol per week, which is the control upper limit for this study, while 1.5 times these guidelines was the lower limit for inclusion in the heavy drinking group.

Following consent, participants were assessed using the Structured Clinical Interview (SCID) for DSM-IV. Exclusion criteria included: use of psychoactive prescription medications, such as those with anti-depressant or anxiolytic properties; a history or presence of a neurological diagnosis; clinically significant head injury; neuroendocrine disorder, including impaired thyroid function and steroid use; current or past substance dependence (although current alcohol dependence was allowed in the heavy drinking group); current or past psychosis, bipolar disorder or eating disorder; and any current axis I or II disorder, including depression and anxiety.

Three participants were excluded due to past substance dependence, three due to past or current eating disorders, two with weekly alcohol consumption between the group limits and one who did not drink alcohol. This left fifty-seven participants who were eligible for inclusion in the analyses: 29 controls and 28 heavy drinkers, aged 22-53 years old (mean age = 32.2, S.D = 7.9, 49.1% female). Three heavy drinkers were assessed to have current mild alcohol dependence. Participants completed an alcohol breath test and urine drug screen to confirm abstinence on day of testing, but positive results for cannabinoids were allowed given the long half-life of these metabolites. No participants were excluded due to positive drug or alcohol screens, although two participants were rescheduled due to positive results for cocaine and alcohol respectively. On return they completed another drug and alcohol screen to ascertain abstinence before the testing session. Nicotine use was not an exclusion criterion for either group, with 27.6% of all participants reporting current or recent (within the last two weeks) smoking.

### *Cognitive Tasks and Self-Report Measures*

Participants completed a battery of computer-based neuropsychological tasks and self-report personality measures. All cognitive tasks, except for the Stop Signal Task (SST), as well as self-report measures were programmed in PsychoPy2 (version 1.78.01; Peirce 2007) and presented on 1366x768 or 1280x800 pixel screen laptop computers with a separate key board and mouse by which participants made their responses.

Following consent and SCID assessment, participants completed the first run of the cognitive battery, which involved the Alcohol Stimulus-Response Compatibility task (ASRC), immediately followed by the Active-Passive Avoidance Task (APA). Participants then completed the SST, followed by the self-report measures. At this point participants were

offered a break before commencing the second run of the cognitive battery. After the practice block of the stress induction task, they completed the experimental block of this task and then a second ASRC and APA. These tasks were exactly the same as before stress, presented in the same order as the first run. However, each experimental run of the ASRC and the APA were separated by a block of 30 stress induction trials.

#### *Alcohol Stimulus-Response Compatibility Task (ASRC)*

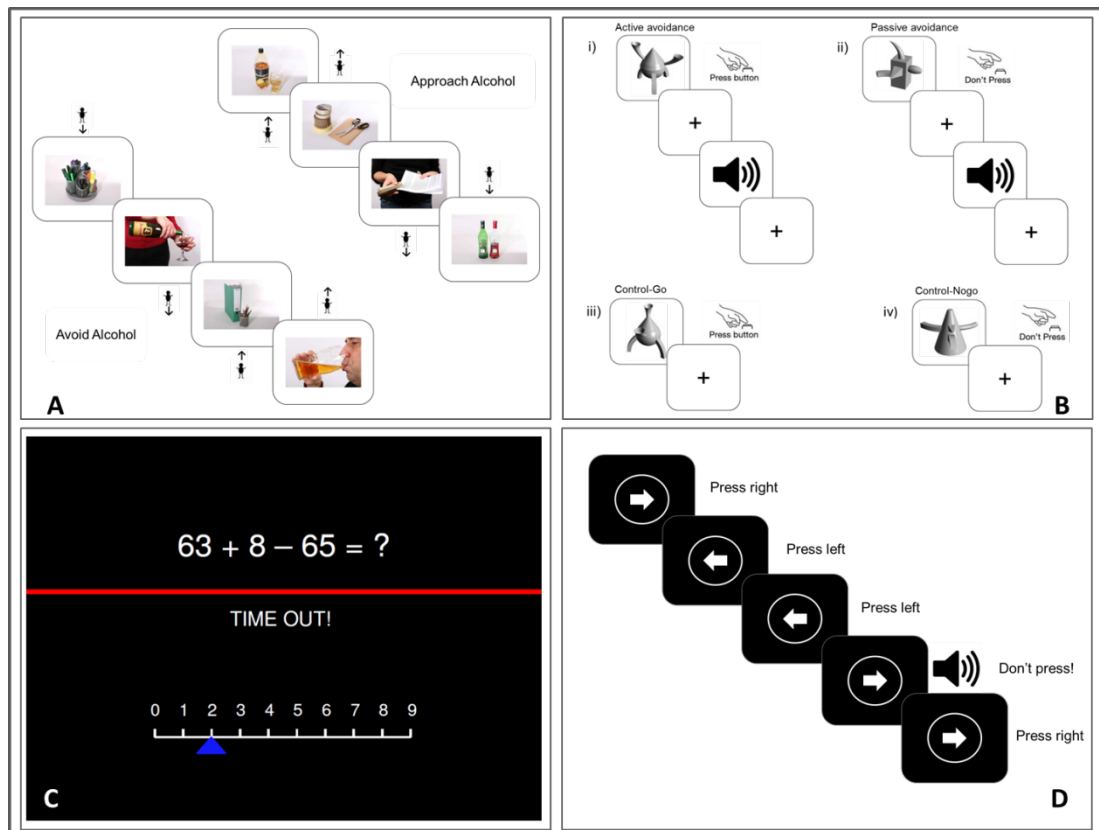
The ASRC was a relevant-feature stimulus response compatibility task used by Field et al. (2008). The task required participants to distinguish between alcohol-related and neutral images using an “approach” or “avoid” response, represented by the movement of a small manikin figure (match stick man) either toward (approach) or away (avoid) from images. Approach-Alcohol blocks consisted of approaching alcohol and avoiding neutral (stationery) images, while the reverse was required for Avoid-Alcohol blocks.

The task consisted of four blocks, two blocks each of Approach-Alcohol and Avoid-Alcohol, presented in alternate order. There were four blocks instead of the original two to allow for regular stress induction blocks during the second run (after stress) of the task. Each block contained 28 trials with two presentations each of seven alcohol and seven neutral images, presented in random order. Images were those employed in previous studies using this task (Field et al. 2008; 2011; Kersbergen, Woud, and Field 2015). During each of the trials, the manikin was presented either directly above or directly below each picture until the participant made a response by pressing keyboard “up” or “down” arrow buttons as quickly as possible (Figure 3.1A). A correct response would move the manikin in the specified direction (1000ms), followed by an inter-trial interval (500ms). An incorrect response would produce a large red “X” in the centre of the screen (1000ms) followed by the same fixation cross before the start of the next trial. Instructions and a practice block of eight trials (four each of neutral and alcohol images) were presented at the beginning of each block. The task was counterbalanced so that equal numbers of participants in each group were presented with either Approach or Avoid blocks first.

#### *Active-Passive Avoidance Task (APA)*

The APA was adapted from that used by Levita et al. (2012; 2015), involving emitting (Active) or omitting (Passive) a button-press response to a visual warning cue in order to avoid an aversive auditory stimulus (unconditioned stimulus, US) presented through

headphones. The auditory stimulus and visual cues were provided by Liat Levita, Department of Psychology, University of Sheffield (<http://levita-lab.group.shef.ac.uk>), used in a number of previous studies (Levita et al. 2009; 2012; 2015). The visual cues were presented in greyscale. The auditory stimulus was a combination of a 1000Hz tone and white noise with the intensity tiered for smooth onset and offset, played through Lenco HP-080 headphones at 95dB for 2000ms.



**Figure 3.1:** Examples of tasks: **A)** Alcohol Stimulus Response Compatibility task (ASRC); **B)** Active-Passive Avoidance task (APA); **C)** Stress-Inducing Task (SIT); **D)** Stop Signal Task (SST).

Two of the visual cues presented during the task acted as warning stimuli (WS) since they predicted the presentation of an aversive sound (the US, 2000ms). Participants were told that they could avoid the US by making a button press while the WS was visible on the screen (1000ms). Participants learned that one of the cues required a button press response in order to avoid the aversive US (Active Avoidance; Figure 3.1Bi), whereas the other cue required participants to not press the button (omit an action) in order to avoid the aversive US (Passive Avoidance; Figure 3.1Bii). Correct avoidance responses were followed by a fixation cross (1000ms) before moving on to the next trial, while an incorrect response was followed by a blank screen and the presentation of the aversive auditory stimulus (1000ms) and then an inter-stimulus-interval (1000ms). The task also included two

control cues (Figure 3.1Biii, iv). Participants were told that these cues were not associated with an aversive outcome, but were there to ensure that they were paying attention throughout the task. The Control-Go and -NoGo trials controlled for potential differences between the two groups in attentional and motor-preparation processes. The Active, Passive and Control trials were presented in a pseudorandom order, with the same stimulus not being presented more than twice consecutively. The four visual cues used were counterbalanced between participants so that each of the four cues acted as either Control-Go or -NoGo, and Passive or Active warning stimuli.

Participants first learned the task contingencies during a practice run of 20 trials (five presentations of each of the four trial types), in which participants learnt (by trial and error) which response (“press” or “don’t press”) was required for each of the warning stimuli. This was followed by three experimental runs, each consisting of 60 trials with 15 presentations of each of the four cues. Cues were displayed for up to 1000ms but could be ended sooner by a button press response.

#### *Stress-Inducing Task (SIT)*

The Stress-Inducing Task (SIT) was a mildly stressful numeracy task, adapted from the Montreal Imaging Stress Task (MIST; Dedovic et al., 2005) in which participants are required to solve a number of mental arithmetic problems in a limited amount of time. Participants first completed a practice block of 30 trials during which they were encouraged to solve each problem as quickly as possible. Unknown to them, their average correct response time on these practice trials was recorded. The following experimental block of 60 trials had a time limit, calculated by deducting 10% of the average correct solve time from the practice block. Three consecutive correct responses reduced the time limit by a further 10%, while three consecutive incorrect or time limit exceeded responses increased the time limit by 10% so that the task was only just beyond participants’ ability.

Arithmetic problems consisted of three one or two-digit numbers paired with the actions of plus or minus, while the solutions were always an integer between 0 and 9. Responses were made by moving a blue cursor to the correct answer on a fixed number display at the bottom of the screen by using the “left” and “right” arrow keys, and “down” to select the answer. Elapsed time was displayed by a red horizontal progress bar across the screen, while appropriate feedback was given on trial completion (“Correct”, “Incorrect” or “Time

Out”). Figure 3.1C shows an example of the display with, from top to bottom, the mental arithmetic problem, progress bar, feedback and the solution display.

#### *Stop Signal Task (SST)*

The Stop Signal Task (SST) is from the well-validated CANTAB neuropsychological test battery (details at [www.cambridgecognition.com/academic/cantabsuite/executive-function-tests](http://www.cambridgecognition.com/academic/cantabsuite/executive-function-tests)). Participants made speedy responses to the presentation of an arrow in the centre of the computer screen, pressing the correct button for the direction of the arrow, but withholding this response following an auditory “Stop Signal” (a “beep”, Figure 3.1D). There were more Go-trials (no beep) than Stop-trials (beep) to make the stopping response difficult, while the timing of the Stop Signal was manipulated by a tracking algorithm so that the “Stop Signal Reaction Time” (SSRT), the time required to withhold a response, could be estimated. A full description is presented by Ersche and Sahakian (2007).

#### *Visual Analogue Scale (VAS)*

Participants also completed a visual analogue scale (VAS), which consisted of three trials at four time points throughout the testing session. A mouse click was used to report feelings on a 100mm line scaled Happy-Sad, Proficient-Incompetent, and Tense-Relaxed. These were completed once at the start of cognitive battery, immediately before the practice SIT, immediately after the experimental SIT, and on completing the test battery.

#### *Self-Report Personality Measures*

Participants completed seven self-report personality measures presented in random order. Measures were the Beck Depression Inventory (BDI-II; Beck, Steer, Ball, & Ranieri, 1996), Spielberger State/Trait Anxiety Index (STAI; Spielberger, Gorsuch, & Lushene, 1970), Barratt Impulsiveness Scale (BIS-11; Patton, Stanford, & Barratt, 1995), Behaviour Inhibition/Activation System (BIS/BAS; Carver & White 1994), Zuckerman Sensation Seeking Scale (SSS; Zuckerman 1994), Big Five Inventory (BFI; John et al. 2008), and the UPPS Impulsive Behaviour Scale (UPPS-P; Cyders & Smith 2007; Whiteside & Lynam 2001; 2003).

#### *Data analysis*

Data were analysed using Statistical Package for Social Sciences (SPSS, version 22, [www.spss.com](http://www.spss.com)) using t-tests and Pearson’s Chi-Square tests to assess group differences on demographic and clinical variables, multivariate analysis of variance (MANOVA) for self-

report measures, and then mixed-measures analysis of variance (ANOVA) for behavioural tasks. Where significant main effects were found, these were explored with ANOVA, Tukey's LSD post-hoc tests, independent- or paired-samples t-tests where appropriate. Additional Pearson's correlation analyses were used to assess relationships between variables. A Wilcoxon Signed Ranks Test was used on the APA accuracy data as it was not normally distributed.

## Results

### *Demographics*

Analysis of participant demographics found that groups did not significantly differ on age (although this was marginal), IQ, sex, smoking status or daily cigarette consumption (Table 3.1). Heavy drinking participants consumed significantly more alcohol units per week than controls ( $t(28.39)=-10.863$ ,  $p<0.001$ ). Median alcohol consumption for control participants was 5.0 units per week and ranged from 1.0-14.0 units/week (males) and 1.0-13.1 units/week (females), while the heavy drinking group had a median alcohol consumption of 53.5 units per week that ranged from 31.0-125.2 units/week (males) and 24.3-105.5 units/week (females).

**Table 3.1:** Demographic details for control and heavy drinking participants.

	Control	Heavy	Difference		
	Mean (SD)		t	df	p
<b>Age</b>	30.21 (5.88)	34.25 (9.14)	-1.978	45.8	0.054
<b>IQ</b>	111.00 (5.15)	111.21 (5.15)	-0.149	55	0.882
<b>Cigarettes/day</b>	0.65 (1.78)	2.02 (4.23)	-1.591	36.1	0.120
<b>Alcohol units/week</b>	6.42 (4.08)	58.26 (24.93)	-10.863	28.4	<b>&lt;0.001</b>
	Count		$\chi^2$	df	p
<b>Sex</b>					
Male	15	14	0.017	1	0.896
Female	14	14			
<b>Smoking Status</b>					
Non-Smoker	23	18	1.593	1	0.207
Smoker	6	10			

### *Data Normality*

Initial screening using Q-Q plots highlighted one outlying score on each of the ASRC (control) and APA (heavy drinker) reaction times, which were removed. Apart from APA



accuracy scores, which were analysed using a Wilcoxon Ranked Signed Test, all other data were normally distributed.

### *Self-Report Affect and Personality Results*

To examine differences between heavy drinkers and controls on self-report measures of affect and impulsivity, a MANOVA was conducted. Using Pillai's trace, this revealed a significant main effect of group ( $V=0.734$ ,  $F(24,32)=2.074$ ,  $p<0.05$ ), which allowed separate post-hoc ANOVAs to be performed on each of the outcome variables (Table 3.2). These revealed that heavy drinkers scored significantly higher than controls on the measures of

**Table 3.2:** Mean (SD) self-report scores for control and heavy drinking participants on each of the self-report measures and their sub-scales. Significant ( $p<0.05$ ) results are marked with an asterisk.

	Control		Heavy		ANOVA	
	Mean	SD	Mean	SD	F	p
<b>Beck Depression Inventory</b>						
Total	3.90	4.23	7.21	6.18	5.63	0.021*
<b>Spielberger State/Trait Anxiety Index</b>						
Trait	37.00	11.98	35.43	10.82	0.269	0.606
State	35.10	9.95	35.61	8.27	0.043	0.837
<b>UPPS Impulsive Behaviour Scale</b>						
Total	129.03	18.30	139.64	22.70	3.786	0.057
Negative Urgency	2.23	0.58	2.46	0.56	2.314	0.134
Premeditation	2.01	0.46	2.38	0.55	7.707	0.008*
Perseverance	1.97	0.36	2.19	0.57	2.974	0.090
Sensation Seeking	3.02	0.50	2.86	0.59	1.193	0.279
Positive Urgency	1.73	0.55	1.98	0.62	2.575	0.114
<b>Barratt Impulsiveness Scale</b>						
Total	61.66	9.93	70.29	12.08	8.713	0.005*
Attentional	15.62	3.42	17.14	4.21	2.257	0.139
Motor	22.86	3.53	26.21	4.98	8.648	0.005*
Non-Planning	23.17	4.54	26.93	5.25	8.357	0.005*
<b>Behaviour Inhibition/Activation System</b>						
BIS Total	20.14	3.43	19.64	3.91	0.259	0.613
BAS Total	40.28	5.58	39.11	5.47	0.637	0.428
Drive	10.97	2.63	10.54	2.81	0.357	0.553
Fun-Seeking	12.21	2.11	12.50	2.22	0.261	0.611
Reward Responsiveness	17.10	1.86	16.07	1.88	4.334	0.042*
<b>Big Five Inventory</b>						
Total	152.31	12.95	151.71	16.22	0.024	0.878
Extraversion	27.76	6.18	29.57	4.47	1.601	0.211
Agreeableness	34.52	6.06	34.18	5.28	0.051	0.823
Conscientiousness	32.59	6.21	30.43	6.66	1.600	0.211
Neuroticism	20.62	5.91	21.36	6.45	0.202	0.655
Openness	36.83	6.09	36.18	7.64	0.126	0.724
<b>Sensation Seeking Scale</b>						
Total	22.10	6.26	23.36	6.37	0.562	0.457
Disinhibition	5.34	2.09	7.04	1.86	10.394	0.002*
Boredom Susceptibility	2.90	2.35	3.89	2.20	2.725	0.104
Thrill/Adventure Seeking	7.03	2.21	5.54	2.90	4.836	0.032*
Experience Seeking	6.83	2.28	6.89	2.30	0.012	0.915

depression (BDI-II;  $F(1,55)=5.632, p<0.05$ ), Premeditation (UPPS-P;  $F(1,55)=7.707, p<0.01$ ), Impulsiveness Total (BIS-11;  $F(1,55)=8.713, p<0.01$ ), Motor Impulsiveness (BIS-11;  $F(1,55)=8.648, p<0.01$ ) and Non-Planning Impulsiveness (BIS-11;  $F(1,55)=8.375, p<0.01$ ), as well as Sensation Seeking Disinhibition (SSS;  $F(1,55)=10.394, p<0.01$ ). These also revealed that controls scored higher than heavy drinking participants on measures of Reward Responsiveness (BIS/BAS;  $F(1,55)=4.334, p<0.05$ ) and Sensation Seeking Thrill/Adventure Seeking (SSS;  $F(1,55)=4.836, p<0.05$ ).

### *Behavioural Results*

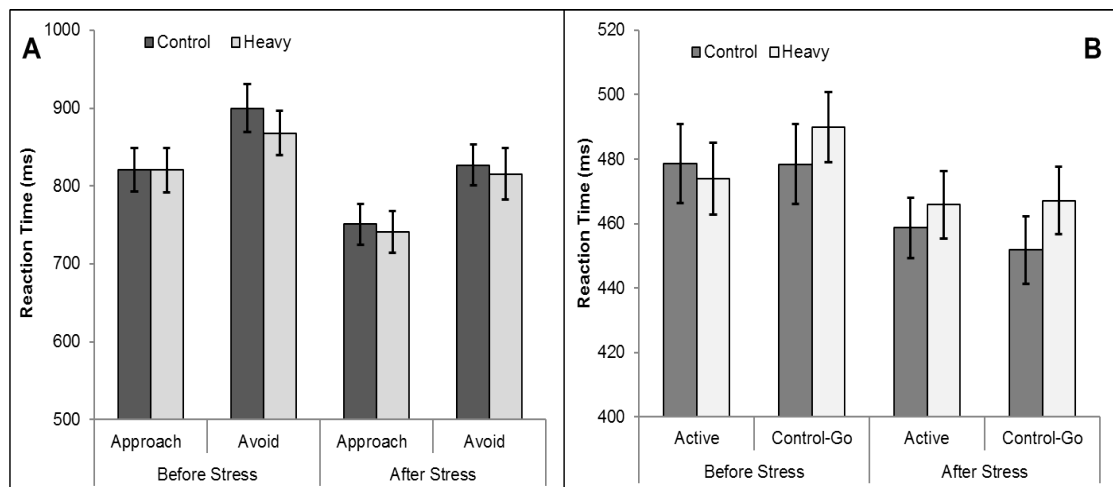
Performance on the ASRC, APA and SST were assessed before conducting the main analysis. Participant data were removed from analyses if accuracy was below 80%; as a result, three control participants were excluded from the APA analysis only. In addition, individual reaction times (RTs) were removed from the ASRC that were  $<200\text{ms}$ ,  $>2000\text{ms}$  or  $>3\text{xSD}$  above the participant mean, which excluded 1.8% of the data. One control participant was excluded from the SST due to a negative Stop Signal Delay.

#### *Alcohol Stimulus-Response Compatibility Task (ASRC)*

As with previous studies (e.g. Field et al. 2008) using this task, a separate mean reaction time (RT) was calculated for each movement block ("Approach-Alcohol" vs. "Avoid-Alcohol") as well as an "Approach-Bias" score for each participant by subtracting the mean Approach-Alcohol RT from the mean Avoid-Alcohol RT.

To assess the effects of stress and group, a mixed three-way repeated measures ANOVA was conducted with movement (Approach-Alcohol vs. Avoid-Alcohol) and stress (before vs. after) as within-subjects factors and group (control vs. heavy) as the between-subjects factor. This found significant main effects of stress ( $F(1,54)=57.951, p<0.001$ ) and movement ( $F(1,54)=171.795, p<0.001$ ). Contrary to predictions, there was no effect of group ( $F(1,54)=0.120, p=0.731$ ), nor significant interactions of stress x group ( $F(1,54)=0.074, p=0.786$ ), movement x group ( $F(1,54)=2.401, p=0.127$ ), stress x movement ( $F(1,54)=1.302, p=0.259$ ), or stress x movement x group ( $F(1,54)=2.056, p=0.157$ ). Investigation of the main effects of stress and movement were conducted using paired-samples t-tests and indicated

that RTs were faster after than before stress ( $t(55)=7.677$ ,  $p<0.001$ ) and for Approach than Avoid blocks ( $t(55)=-12.943$ ,  $p<0.001$ ; Figure 3.2A).



**Figure 3.2:** Group differences for controls vs. heavy drinking participants on ASRC and APA tasks before and after stress. A) Mean reaction times before and after stress for Approach-Alcohol blocks and Avoid-Alcohol blocks in controls and heavy drinkers; B) mean reaction times for Active Avoidance and Control-go cues, before and after stress in controls and heavy drinkers.

Although the group  $\times$  stress interaction was non-significant, we also conducted two-way repeated ANOVAs on each of the movement (Approach vs. Avoid) and group (control vs. heavy) comparisons separately for before and after stress. Before stress there was a main effect of movement ( $F(1,54)=72.779$ ,  $p<0.001$ ), but not of group ( $F(1,54)=0.156$ ,  $p=0.695$ ), although there was a significant movement  $\times$  group interaction ( $F(1,54)=4.500$ ,  $p<0.05$ ). Investigation of the main effect of movement using a paired-samples  $t$ -test indicated that RTs were faster for approach than avoid blocks ( $t(55)=-8.272$ ,  $p<0.001$ ). To investigate the movement  $\times$  group interaction we performed separate paired-tests on each of the groups and found that both controls ( $t(27)=-7.151$ ,  $p<0.001$ ; mean difference 79.14ms) and heavy drinkers ( $t(27)=-4.803$ ,  $p<0.001$ ; mean difference 47.62ms) were faster to approach than avoid alcohol images. After stress there was a main effect of movement ( $F(1,55)=99.934$ ,  $p<0.001$ ), but not of group ( $F(1,55)=0.170$ ,  $p=0.682$ ) or a significant movement  $\times$  group interaction ( $F(1,55)=0.002$ ,  $p=0.964$ ). Investigation of the main effect of movement using a paired-samples  $t$ -test again indicated that RTs were faster for Approach than Avoid blocks ( $t(55)=-10.132$ ,  $p<0.001$ ). However, as the group  $\times$  stress interaction was non-significant, this should be use for descriptive purposes only.

### *Active-Passive Avoidance Task (APA)*

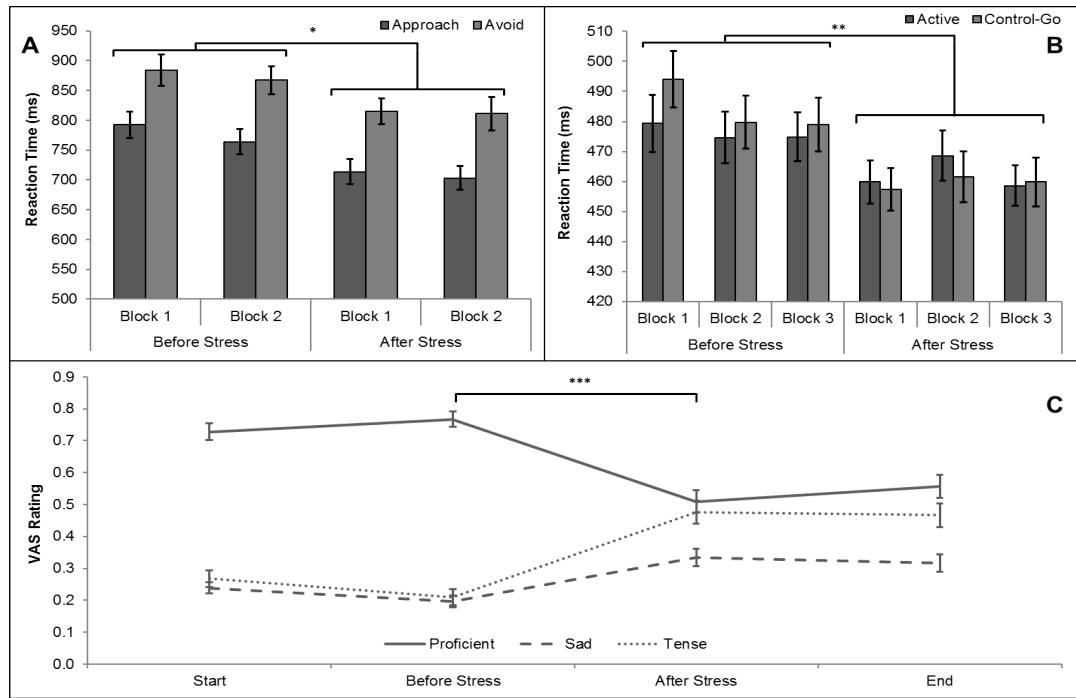
As with previous studies (e.g. Levita et al. 2012) using this task, a mean RT for correct responses to cues (Active Avoidance, Control-Go) and percentage accuracy were calculated for each cue (Active Avoidance, Passive Avoidance, Control-Go, Control-NoGo). As response accuracy data were non-normally distributed, we used a Wilcoxon Signed Ranks test, which indicated that participants made the same number of errors during Active and Passive Avoidance trials ( $Z=-.363$ ,  $p=0.717$ ), but significantly more errors during Control-Go than Active Avoidance trials ( $Z=-2.540$ ,  $p<0.05$ ), Control-NoGo than Passive Avoidance trials ( $Z=-4.192$ ,  $p<0.001$ ), and during Control-NoGo than Control-Go trials ( $Z=-2.335$ ,  $p<0.05$ ). Analysis of the accuracy data before and after stress found that accuracy on all cues increased following stress: Active Avoidance ( $Z=-6.334$ ,  $p<0.001$ ), Passive Avoidance ( $Z=-2.693$ ,  $p<0.01$ ), Control-Go ( $Z=-6.334$ ,  $p<0.001$ ) and Control-NoGo ( $Z=-3.139$ ,  $p<0.01$ ).

To assess the effect of stress induction and group on RTs, a mixed three-way repeated measures ANOVA was conducted with cue type (Active Avoidance vs. Control-Go) and stress (before vs. after) as within-subjects factors, and group (control vs. heavy) as the between-subjects factor. This found a significant main effect of stress ( $F(1,51)=13.630$ ,  $p<0.01$ ), which was investigated using paired-samples t-tests and indicated that RTs were faster after than before stress ( $t(52)=3.695$ ,  $p<0.01$ ; Figure 3.2B). Contrary to predictions, there were no main effects of group ( $F(1,51)=0.280$ ,  $p=0.599$ ) or cue ( $F(1,51)=0.489$ ,  $p=0.487$ ), or significant interactions of stress x group ( $F(1,51)=0.549$ ,  $p=0.462$ ), cue x group ( $F(1,51)=2.867$ ,  $p=0.096$ ), stress x cue x group ( $F(1,51)=0.984$ ,  $p=0.326$ ; Figure 3.2B). There was, however, a significant interaction of stress x cue ( $F(1,51)=6.923$ ,  $p<0.05$ ), which when investigated by conducting individual paired-samples t-tests, found that a marginally significant difference between Active Avoidance and Control-Go cues before stress ( $t(52)=-1.974$ ,  $p=0.054$ ) was no longer present after stress ( $t(52)=0.626$ ,  $p=0.534$ ).

### *Stress Induction Effects versus Practice Effects*

As a result of the task design, it is not clear whether the significant main effects of stress found in both tasks were confounded by time, which would mean that the decrease in observed RTs could be due to a practice effect rather than to stress induction. In order to investigate this we used the mean RTs from each block of both tasks (ASRC: two before and two after stress; APA: three before and three after stress) to see if there was a steady improvement across the blocks (which would indicate a practice effect) or a single shift in

RTs following stress induction (which would indicate an effect of stress). Firstly, we conducted a three-way repeated measures ANOVA on the ASRC with stress (before vs. after), movement (Approach-Alcohol vs. Avoid-Alcohol) and block (block 1 vs. block 2) as within-subjects factors. This found significant main effects of stress ( $F(1,54)=6.917, p<0.05$ ) and movement ( $F(1,54)=68.563, p<0.001$ ), but not of block ( $F(1,54)=2.597, p=0.113$ ). There were no significant interactions of stress x block ( $F(1,54)=0.173, p=0.679$ ), stress x movement ( $F(1,54)=0.223, p=0.637$ ), block x movement ( $F(1,54)=0.759, p=0.387$ ), or stress x block x movement ( $F(1,54)=0.085, p=0.772$ ). Investigation of the main effects using a paired-samples t-test identified that RTs were significantly faster after stress than before stress ( $t(55)=2.63, p<0.05$ ; Figure 3.3A). The main effect of movement was not investigated as it was not relevant for this question.



**Figure 3.3:** **A)** Mean block reaction times for Approach Alcohol and Avoid alcohol in the ASRC task before and after stress; **B)** Mean block reaction times for Active Avoidance and Control-go cues in the APA before and after stress; **C)** Mean visual analogue scale ratings for all participants at the start of testing, before and after stress paradigm, and at the end of testing. (\* $p<0.05$ , \*\* $p<0.01$ , \*\*\* $p<0.001$ ).

Secondly, we conducted a three-way repeated measures ANOVA on the APA, with stress (before vs. after), cue (Active Avoidance vs. Control-Go) and block (block 1 vs. block 2 vs. block 3) as within-subjects factors. This found a significant main effect of stress ( $F(1,52)=13.649, p<0.01$ ), but not of cue ( $F(1,52)=0.516, p=0.476$ ) or block ( $F(1,52)=1.073, p=0.346$ ). There were also significant interactions of stress x block ( $F(2,104)=3.303, p<0.05$ ) and stress x cue ( $F(1,52)=7.027, p<0.05$ ), but not of block x cue ( $F(2,104)=1.211, p=0.302$ ) or

stress x block x cue ( $F(2,104)=1.203$ ,  $p=0.304$ ). Investigation of the main effect of stress using a paired-samples t-test revealed that RTs were significantly faster after than before stress ( $t(52)=3.695$ ,  $p<0.001$ ). Investigation of the stress x block interaction using separate paired t-tests revealed that active avoidance RTs were significantly faster in the first block after stress than last block before stress ( $t(52)=2.731$ ,  $p<0.01$ ), which then slowed in block two after stress ( $t(52)=-2.011$ ,  $p<0.05$ ), and then reduced again for block three after stress ( $t(52)=2.138$ ,  $p<0.05$ ). Control-Go RTs were significantly decreased from block one before stress to block two before stress ( $t(52)=2.107$ ,  $p<0.05$ ), and also the last block before stress to the first block after stress ( $t(52)=2.856$ ,  $p<0.01$ ; Figure 3.3B). The stress x cue interaction was not investigated as it was not relevant for this question. Taken together, these results tentatively suggest that the effects observed were a result of stress induction rather than a practice effect, although these should be taken with caution.

#### *Validation of the Stress Induction Procedure*

To assess the validity of the Stress Induction Task (SIT) and whether there was a differential group effect, we conducted a mixed two-way repeated measures ANOVA on the Visual Analogue Scale (VAS) scores. The within-subjects factor was stage (start, before stress, after stress, end) and group (control vs. heavy) was the between-subjects factor. There was no effect of group ( $F(1,55)=0.897$ ,  $p=0.348$ ) nor a stage x group interaction ( $F(3,165)=1.067$ ,  $p=0.365$ ). However, there was a significant effect of stage ( $F(3,165)=7.142$ ,  $p<0.001$ ), which when explored with individual paired-samples t-tests found no difference between start and before stress scores ( $t(56)=-1.598$ ,  $p=0.116$ ), or between after stress and end scores ( $t(56)=0.697$ ,  $p=0.489$ ), but there was a significant change in scores from before stress to after stress ( $t(56)=4.600$ ,  $p<0.001$ ). We then explored this change from before stress to after stress for each of the scales using separate paired-t-tests. Following stress there was a significant decrease in proficiency ( $t(56)=-7.086$ ,  $p<0.001$ ), while there was a significant increase in sadness ( $t(56)=6.166$ ,  $p<0.001$ ) and tension ( $t(56)=7.918$ ,  $p<0.001$ ). This indicates that the Stress Induction Task (SIT) significantly increased feelings of sadness and tension, while reducing feelings of proficiency in participants (Figure 3.3C).

#### *Stop Signal Task*

To assess group differences in inhibitory control, we analysed the Stop Signal Task (SST) using an independent measures ANOVA. This found no significant group differences on Stop Signal Reaction Time (SSRT;  $F(1,54)=0.460$ ,  $p=0.501$ ; Table 3.3). Additional exploratory

ANOVAs were performed on further outcome measures of the SST to ensure these were not confounding the results. Groups did not differ significantly on Stop Signal Delay (SSD; (1,54)=0.445,  $p=0.508$ ), Proportion of Successful Stops (1,54)=0.819,  $p=0.369$ ), Number of Direction Errors (1,54)=0.206,  $p=0.652$ ), or Mean Go Reaction Times ( $F(1,54)=2.696$ ,  $p=0.106$ ). We also used Pearson's correlation to assess whether inhibitory control mediated the performance on either ASRC or APA tasks. We found that SSRT was not significantly correlated with Alcohol-Approach Bias (Before Stress,  $r=0.066$ ,  $p=0.626$ ; After Stress  $r=0.100$ ,  $p=0.464$ ) or with Active-Avoidance RTs (Before Stress,  $r=-0.086$ ,  $p=0.542$ ; After Stress  $r=0.062$ ,  $p=0.661$ ).

**Table 3.3:** Stop Signal Task performance measures

	Control		Heavy		Differences	
	Mean	SD	Mean	SD	F	p
<b>SSRT</b>	177.77	45.52	186.33	48.92	0.460	0.501
<b>Go Reaction Time</b>	355.04	41.19	378.14	62.04	2.696	0.106
<b>Direction errors</b>	5.50	5.62	6.29	7.24	0.206	0.652
<b>Proportion of successful stops</b>	0.49	0.08	0.47	0.05	0.819	0.369
<b>Stop Signal Delay</b>	177.28	72.51	191.82	89.78	0.445	0.508

### *Exploratory Correlational Analyses*

As there were no group differences on behavioural tasks, we investigated whether the wide variation in weekly alcohol consumption within the heavy drinking group accounted for any variation in these scores. Therefore, we conducted exploratory correlational analyses between weekly alcohol consumption and both behavioural and self-report scores within heavy drinkers but found no significant correlations (Supplementary Table 3.1).

## **Discussion**

The present study investigated avoidance behaviour in heavy drinking individuals by assessing the extent to which automatic approach of alcohol images and avoidance of a non-alcohol related aversive stimulus were influenced by the induction of stress. There was not a differential group effect of stress on reaction times (RTs) in either the ASRC or APA tasks, although these were significantly reduced by the induction of stress. The findings were contrary to our hypotheses that heavy drinking individuals would show more of an Alcohol-Approach Bias and more avoidance of the negative stimulus than control participants, as we found no group differences on either the ASRC or APA before or after stress induction. There were also no group differences on the SST indicating no differences in impulse control nor moderation of ASRC or APA performance. However, some group

differences were identified on the self-report personality measures; heavy drinkers scored significantly higher than controls on the measures of depression (BDI-II), UPPS Premeditation, BIS-11 Motor and Non-Planning Impulsiveness, as well as Sensation Seeking (SSS) Disinhibition. Interestingly, controls scored higher than heavy drinking participants on measures of BIS/BAS Reward Responsiveness and marginally higher on SSS Thrill/Adventure Seeking. Despite the wide range in weekly alcohol units consumed by heavy drinkers, exploratory correlational analyses found no relationship between weekly alcohol consumption and any of the behavioural or self-report measures within the heavy drinking group.

### *Alcohol Stimulus-Response Compatibility Task (ASRC)*

All participants demonstrated an Alcohol-Approach Bias (faster RTs to approach than avoid alcohol images), although heavy drinkers showed no difference to controls, contrary to previous studies that find that heavy, but not light drinkers, are faster to approach than avoid alcohol images (Christiansen, Cole, Goudie, & Field, 2012; 2011; Field et al., 2008; Kersbergen et al., 2015). Alcohol-Approach Bias is also associated with self-reported alcohol craving (Field et al. 2008) and hazardous alcohol consumption (Christiansen et al. 2012). While the present study found no difference in Alcohol-Approach Bias between controls and heavy drinkers, Barkby et al. (2012) have also reported no difference between controls and alcohol dependent patients.

A notable difference between the heavy drinkers in previous studies using this task and those in the present sample is their age; the latter are more than a decade older (mean age 34.3 years) than previous samples (e.g. Field et al. 2008, mean age = 23.3 years; Field et al. 2011, mean age = 23.6 years). Although we can only make this assumption, as lifetime exposure was not recorded in either study, it is probable that heavy drinkers in their mid-thirties have had greater alcohol exposure than those in their early twenties. The average weekly alcohol intake of the present heavy drinking sample (mean = 58.26 units/week) was almost twice that of Field et al.'s heavy drinkers (mean = 30.37 units/week), indicating the likelihood that the older heavy drinkers will have been exposed to much more alcohol with their higher intake over additional years.

This evidence would imply that abnormal alcohol-approach behaviour is present in late adolescence and early adulthood, when drinking motives are driven by positive



reinforcement, but normalises once heavy drinking habits are well established. Here is perhaps where secondary effects of negative reinforcement also begin to play a role, as the symptoms of withdrawal (either physiological, psychological or both) are avoided by repeated alcohol consumption. Barkby et al. (2012) found no difference in Alcohol-Approach Bias in alcohol dependent participants compared to controls on the same task, suggesting that the present sample of heavy drinkers, at least in terms of automatic alcohol-approach, behave more like alcohol dependent participants than the younger heavy drinking participants in previous studies. A possible interpretation is that the current heavy drinkers are further along the trajectory of alcohol use towards dependence than the younger ones in previous studies and that alcohol-approach tendencies are not consistent across the different stages of alcohol use.

However, Barkby et al. (2012) did find that the strength of Alcohol-Approach Bias was positively correlated with the amount of alcohol consumed prior to the study; an effect not detected in the present study. Also, Spryut et al. (2013) found an Alcohol-Avoidance Bias in alcohol dependent individuals with longer abstinence than in Barkby et al., suggesting a reversal of bias in abstinence. The nature of the ASRC task means that the alcohol-approach measure is calculated relative to the alcohol-avoidance, so we cannot detect which is the driver in any of these studies. Baker, Dickson and Field (2014) used a modified version of the ASRC that was able to differentiate alcohol-approach from alcohol-avoidance. While they found no evidence of an Alcohol-Approach Bias in heavy drinkers, they had no control comparison group, meaning their findings are not comparable to those of the present study. Future research should investigate the different roles of alcohol-approach and avoidance at the different stages of alcohol use and dependence.

### *Active-Passive Avoidance (APA) Task*

All participants were faster to respond to Active Avoidance than Control-Go cues, but again there were no significant group differences, nor a differential effect of stress. The faster RTs for Active Avoidance cues compared to Control-Go cues are consistent with previous studies (e.g. Levita et al. 2015). However, as with the ASRC, it is likely that we may see greater differences in younger adult heavy drinkers who are more prone to reward-based and risky decisions (Ernst & Fudge 2009; Somerville et al. 2010). We may also find that those with clinical levels of anxiety or depression may push this trend for avoidance differences to a significant one; the present sample were all below clinical levels of both

anxiety and depression, although the heavy drinking group did report higher BDI-II scores than the control group and there was no correlation with avoidance behaviour and BDI-II scores. Since this task has not yet been used in substance-using populations, this is only speculation.

### *Stop Signal Task (SST)*

Despite evidence showing increased SSRTs in alcohol dependence (for meta-analysis see, Smith et al. 2014), the present study did not find any difference between controls and heavy drinkers. This is in line with previous studies of SST in heavy drinkers (for meta-analysis see, Smith et al. 2014) despite their inability to display executive control over automatic alcohol-approach behaviour. In this respect, the heavy drinkers are not the same as alcohol dependent participants, and it may be this inhibitory control that sets them apart. However, the Smith et al (2014) meta-analysis finds a small effect size for the association between SSRT and alcohol intake in non-dependent drinkers, which would imply that small studies (including the present one) would not reliably detect the association. While there were no group differences on the SST, this tendency for self-report measures to detect group differences that are not seen in behavioural tasks has also been found with measures of impulsivity in abstinent substance dependent participants (Taylor et al., *in prep*, **Study 1**). Additionally, only risk-taking measures but not inhibitory control or delay discounting measures predicted unique variance in alcohol use of a young adult social drinking population (Ferne et al. 2010).

### *Self-Report Measures of Impulsivity and Affect*

Self-report measures of impulsivity and affect found that heavy drinkers scored significantly higher than controls on measures of depression (BDI-II), UPPS-P Premeditation, BIS-11 Motor Impulsiveness and Non-Planning Impulsiveness, as well as Sensation Seeking (SSS) Disinhibition. Higher BDI-II scores in heavy drinkers are consistent with evidence that heavy alcohol use disorders are highly linked with mood disorders (Kuntsche et al. 2006). However, while the present sample of participants did show a group difference in depression scores, all of them were well below clinical levels. Higher scores on UPPS-P Premeditation, BIS-11 Motor Impulsiveness and Non-Planning Impulsiveness, as well as SSS Disinhibition are in line with previous studies that also report such measures to be related to alcohol use in adolescents (Shin et al. 2012) and adults (Fischer & Smith, 2008; Papachristou et al., 2012; and for a meta-analysis see Sharma et al. 2014). These subscales

measure very similar aspects of impulsivity and relate to the non-emotional characteristics of the trait.

Conversely, the finding that measures of BIS/BAS Reward Responsiveness, and marginally of SSS Thrill/Adventure Seeking, were higher in controls than heavy drinkers raises some questions. These questions can also be addressed with that of why there were no group differences found on the remaining measures, particularly Positive Urgency, Negative Urgency and Sensation Seeking (UPPS-P), which are associated with alcohol-related problems in young adults (mean age 21.9 years; Shin et al. 2012). As is the case with the behavioural tasks, it is likely that the present sample of older well-established heavy drinkers are less likely to be influenced by affective impulsivity. It is interesting that these heavy drinkers who score highly on BDI-II, but are not susceptible to negative urgency as a way of managing these negative affective states; perhaps because they are further along the pathway towards dependence whereas coping mechanisms that relate to positive and negative affect only feature at the very beginning of alcohol use, becoming inconsequential with greater and habitual alcohol exposure.

The SIT appeared to be successful in its induction of stress as indicated by VAS ratings, which only changed after stress. The effect of stress was also seen in the increased RTs on the ASRC and APA in the secondary block analysis of both tasks, which indicated that RTs improved following stress induction. The step change in RT after stress in the absence of a block-by-block improvement suggests that this was not a practice effect. However, we hypothesised that stress induction would show a differential effect on heavy drinking participants compared to controls, and this was not observed. One explanation is that the task is not sufficiently stressful to be detrimental to performance, but nevertheless fits with the Yerkes-Dodson law of a U-shaped relationship between arousal and cognitive performance (Mendl 1999); there is an optimal amount of stress that improves performances, while more than this results in a reduction in performance. It is likely that the performance improvement seen in the present study after stress induction has not passed the optimal stress level, and so we do not see a disadvantageous influence on their behaviour. Future investigations could use more rigorous stress induction to pass the optimal stress level, which may illuminate the differences in automatic avoidance behaviour in heavy drinkers compared to controls that we hypothesised. On the other hand, Snelleman et al (2014) highlight the difference between psychological stress, that is

induced by emotional stressors (such as thinking about or looking at evocative images), and physical stress, that is induced by cognitive tasks. They suggest that the former is more related to increased cue sensitivity than the latter, and thus, would also explain why we did not see a negative impact of stress on the tasks in the present study.

### *Age and Alcohol Exposure in Heavy Drinkers*

Another important point to consider is the age of the heavy drinkers in question. Younger heavy drinkers are found to be more reward-driven (Nees et al. 2011), report higher levels of sensation seeking and poorer inhibitory control (Shin et al. 2013; Moreno et al. 2012), as well as alcohol use as a coping mechanism for poor mood regulation (Kuntsche et al. 2006). They also appear to be more prone to automatic alcohol-approach behaviour (Field et al. 2008; Field et al. 2011) that was not found in the older heavy drinkers in the present study, or in recently abstinent alcohol dependent individuals (Barkby et al. 2012). While there is some question of the robustness of these findings, given that not all studies using this task have found an Alcohol-Approach Bias in relation to alcohol consumption (for a review, see Kersbergen et al. 2015), those studies that are comparable to this one that do not find an Alcohol-Approach Bias are conducted in older participants. In view of this, we tentatively suggest that this is due to the relative immaturity of certain brain regions during late adolescence and early adulthood, particularly the prefrontal cortex (Ernst & Fudge 2009; Somerville et al. 2010), which is responsible for executive control and thus would elicit control over automatic alcohol-approach behaviours (Sharbanee et al. 2014). Since much of the literature on heavy drinking is conducted in a relatively young population, often university-age adults (e.g. Ihssen et al. 2011; Nederkoorn et al. 2009; Field et al. 2008), it is not surprising they show less control over automatic alcohol-approach behaviours. We thus speculate that while heavy drinking individuals are young and impulsive, they are driven by automatic alcohol-approach tendencies. Once drinking becomes more established and prefrontal maturity is reached, however, this automatic approach behaviour is balanced out by an equally strong alcohol-avoidance tendency created by a conflict between the guilt, or need, to cut down alcohol consumption with the desire to continue drinking. These older heavy drinkers appear to behave in a similar way to alcohol dependent individuals who do not show an abnormal Alcohol-Approach Bias (Barkby et al. 2012), suggesting that being a heavy drinker in your mid-thirties is a more reliable prodrome for the development of alcohol dependence than heavy drinking in your early twenties.

### *Conclusions and implications*

The present study investigated what differentiates heavy drinking individuals from controls. The primary question was to assess whether they have a dysfunctional approach-avoidance system, and if so, whether it was specific to alcohol itself, or if it was a more general abnormality in instrumental action selection mechanisms for the avoidance of harm. We found that these behavioural tasks do not distinguish heavy drinkers from controls. We propose the suggestion that older, well-established heavy drinkers are less prone to the risky behaviours and emotional and incentive-driven behaviour that is reported in much of the literature conducted on young adult heavy drinking individuals. We also highlight the possibility of separate stages of alcohol use disorders that differ in terms of cognitive mechanisms from young heavy drinkers to older heavy drinkers, to alcohol dependence, and then to stable abstinence in recovery.

## Supplementary Materials

**Supplementary Table 3.1:** Correlation coefficients for each of the behavioural and self-report measures with weekly alcohol consumption in heavy drinking participants.

ASRC

Before Stress

Approach Alcohol

Avoid Alcohol

Approach Bias

.034

.087

.300

.120

.661

.864

After Stress

Approach Alcohol

Avoid Alcohol

Approach Bias

.091

.099

.055

.645

.617

.782

Before Stress

Active Avoidance RT

.096

.628

Control-Go RT

.096

.626

Active Avoidance

Accuracy

-.358

.061

Control-Go

Accuracy

-.103

.603

Passive Avoidance

Accuracy

-.209

.287

Control-NoGo

Accuracy

.097

.622

APA

Before Stress

Active Avoidance

Accuracy

-.358

.061

Control-Go

Accuracy

-.103

.603

Passive Avoidance

Accuracy

-.209

.287

Control-NoGo

Accuracy

.097

.622

After Stress

Active Avoidance

Accuracy

-.021

.915

Control-Go RT

.004

.982

Passive Avoidance

Accuracy

-.025

.898

Control-Go

Accuracy

.023

.908

Passive Avoidance

Accuracy

.057

.774

Control-NoGo

Accuracy

.236

.227

After Stress

Active Avoidance

Accuracy

-.021

.915

Control-Go RT

.004

.982

Passive Avoidance

Accuracy

-.025

.898

Control-Go

Accuracy

.023

.908

Passive Avoidance

Accuracy

.057

.774

Control-NoGo

Accuracy

.236

.227

SSRT

Start

Before Stress

After Stress

End

-.004

.196

.263

.222

.983

.318

.177

.255

VAS

Start

Before Stress

After Stress

End

-.004

.196

.263

.222

.983

.318

.177

.255

Self-Report Measures

Beck Depression Inventory

Trait

State

Total

Extraversion

Agreeableness

Conscientiousness

Neuroticism

Openness

.040

-.029

-.076

-.079

.021

-.005

-.184

-.070

.043

.840

.885

.701

.690

.915

.979

.349

.723

.828

Sensation Seeking Scale

Disinhibition

Boredom Susceptibility

Thrill/Adventure Seeking

Experience Seeking

.250

.159

.119

.218

.176

.199

.418

.547

.264

.371

BIS Total

BAS Total

BAS Drive

BAS Fun Seeking

BAS Reward Responsiveness

-.131

.282

.266

.209

.172

.286

.176

.370

Behaviour Inhibition/Activation Scale

BIS Total

BAS Total

BAS Drive

BAS Fun Seeking

BAS Reward Responsiveness

-.131

.282

.266

.209

.172

.286

.176

.370

UPPS-P Impulsive Behaviour Scale

Negative Urgency

Premeditation

Perseverance

Sensation Seeking

Positive Urgency

Total

Attentional Impulsivity

Motor Impulsivity

Non-Planning Impulsivity

.277

.279

-.003

-.018

.256

.317

.163

-.126

.313

.179

.154

.151

.987

.928

.189

.100

.407

.523

.104

.361

Barratt Impulsiveness Scale

Attentional Impulsivity

Motor Impulsivity

Non-Planning Impulsivity

-.126

.313

.179

## **2.4 Study 4: Neural Correlates of Automatic Approach and Avoidance Behaviours in Heavy Drinkers**

### *Submission*

This paper has been prepared for submission to *Alcoholism & Clinical Experimental Research* (<http://onlinelibrary.wiley.com/journal/10.1111/%28ISSN%291530-0277>). Please note that the reference style is consistent with the rest of the thesis and will be updated to that required by the journal before submission.

### *Individual contribution*

The data in this paper were collected as part of a protocol that I designed for Studies 3 (p. 101) and 4 (p. 127). The imaging data collection was shared between myself and Elly McGrath, while I completed all the analyses presented, and prepared the manuscript.

# Neural Correlates of Automatic Approach and Avoidance Behaviours in Heavy Drinkers

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**Rationale:** Heavy alcohol consumption is a stage along a spectrum of alcohol use that is prodromal for the development of alcohol dependence. Automatic approach and avoidance mechanisms related to positive and negative reinforcement are thought to be involved in the transition to dependence.

**Objectives:** The present study investigated the neural mechanisms of automatic alcohol-approach behaviours as well as avoidance of aversive stimuli in heavy drinking individuals.

**Methods:** Twenty heavy drinking participants and 20 controls completed an Alcohol Stimulus-Response Compatibility Task measuring automatic alcohol-approach behaviour, and an Active-Passive Avoidance Task measuring avoidance of an aversive non-alcohol-related stimulus, during fMRI.

**Results:** Despite no behavioural differences in Alcohol-Approach Bias, heavy drinking participants compared to controls showed greater deactivation of the right dlPFC during alcohol-approach. There were no differences between controls and heavy drinkers in behaviour or brain responses to avoidance of an aversive stimulus. However, there was a significant positive correlation between right insula response to Active Avoidance and trait anxiety scores in heavy drinking participants only.

**Conclusions:** These findings suggest that heavy drinkers show less control when approaching alcohol cues, and that there is a link between avoidance of aversive stimuli and anxiety in heavy drinkers. These functional differences were found in the face of no behavioural group differences on these measures and highlight the importance of using multiple levels of measurement.

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## Introduction

Models of addiction are based on operant conditioning in which reinforcement drives behaviour; strengthening an action when it is paired with either a pleasant outcome (positive reinforcement) or removal of an unpleasant one (negative reinforcement). These processes of reinforcement are apparent in substance use as the drug serves both to elicit a high (positive) and remove symptoms of withdrawal (negative). Incentive motivational properties that are assigned to the substances are also assigned to predictive cues associated with drug reinforcement through classical conditioning (Robinson & Berridge 1993; 2003; 2008). Theories of incentive salience suggest these incentive motivational properties are a driving force behind the attentional bias for drug-related cues (for a review, see Field & Cox 2008), including alcohol cues (Field et al. 2004; Townshend & Duka 2001), as well as those of other substances.

Attentional bias triggers automatic approach-biased responses to drug-related cues, as seen in heavy drinkers (Field et al. 2008; Field et al. 2011), smokers (Mogg et al. 2005) and cannabis users (Cousijn et al. 2012). Substance approach biases are thought to be important in the development of dependence (Robinson & Berridge 2008; Wiers et al. 2007) due to repeated exposure to the substances and their cues that further condition biases, creating a vicious cycle whereby an increase in attentional bias exacerbates substance approach and worsens the attentional bias further. Dual process models (e.g. Stacy & Wiers 2010) suggest that repeated substance use increases automatic processing of substance-related cues, such as that seen in attentional bias and automatic approach behaviour, which individuals are unable to suppress due to poor cognitive control.

There is also evidence for greater deficits in impulse control that are related to extreme positive or negative affective states (Cyders & Smith 2008), and which have been linked to alcohol dependence (Whiteside & Lynam 2003). Such evidence is consistent with the suggestion that substance use may be a form of unconscious “self-medication” to ameliorate negative affective states (G. E. Koob & Le Moal 2008; Becker et al. 2012) and is supported by the contribution that affective disorders make to the development of substance dependence (Heilig & Koob 2007; Wand 2008; Hägele et al. 2014). In addition, negative affective states are associated with increased attentional bias to alcohol cues in

heavy drinkers generally (Field and Powell 2007; Grant, Stewart, and Birch 2007), and in heavy drinkers who “drink to cope” more specifically (Field and Quigley 2009; Birch et al. 2004). Substance use to avoid negative affective states produces negative reinforcement and strengthens avoidance behaviour. Furthermore, Becker et al. (2012) theorise that individuals who develop dependence as a result of a desire to self-medicate against negative affective states do so more rapidly than those driven by positive reinforcement.

The nucleus accumbens (NAcc) is particularly implicated in avoidance behaviour via its bivalent response to both rewarding and aversive stimuli (Becerra et al. 2001; Jensen et al. 2003; Reynolds & Berridge 2001; Levita et al. 2009). It is thought to be responsible for gating motivational and emotional signals from the prefrontal cortex (PFC), amygdala and hippocampus to produce appropriate adaptive behavioural responses (Levita et al. 2009), and modulating goal-directed behaviour to detect both aversive and rewarding stimuli in the environment (Cardinal et al. 2002). Human and rodent studies show a critical role for the NAcc in active avoidance of aversive stimuli (Ammassari-Teule et al. 2000; Hoebel et al. 2007; Levita et al. 2002; Schwienbacher et al. 2004). Left NAcc activation is seen during active avoidance of aversive visual stimuli in humans, while right NAcc deactivation is seen during passive avoidance (Levita et al. 2012), indicating involvement of this region in the preparation of appropriate motor action responses (fight or flight). Furthermore, higher anxiety scores were associated with activation changes during avoidance (Levita et al. 2012), suggesting inputs from anxiety structures may control information input to the NAcc. These anxiety structures influence motivation appropriate to the situation at hand (Nestler & Carlezon 2006) and modulate action to gain reward and avoid harm (Levita et al. 2012).

The NAcc has also shown specific responses to alcohol cues in alcohol dependent individuals (Braus et al. 2001; Wrase et al. 2007; Heinz et al. 2009). In conjunction with regions of the PFC (Goldstein & Volkow 2011), it forms the executive system of the fronto-limbic circuit, which is responsible for the regulation of substance approach motivation (Robinson & Berridge 2003; 2008; Wiers et al. 2007; Koob & Volkow 2010). The medial (m)PFC and anterior cingulate cortex (ACC) are associated with the attribution of salience to alcohol cues (Grüsser et al. 2004), and the mPFC is also involved in goal-directed decision

making (Hare et al. 2009; Kahnt et al. 2010; Park et al. 2011). In addition, the amygdala is thought to encode salient associations between positive drug rewards and drug-cues (Baler & Volkow 2006; Heinz et al. 2009), and thus encourages automatic approach behaviour (Robinson & Berridge 2003; 2008).

Previous imaging studies investigating automatic drug-approach behaviour have identified activation during approach responses in alcohol dependent participants compared to controls in the NAcc and mPFC using functional magnetic resonance imaging (fMRI; Wiers et al. 2014) and in the orbitofrontal cortex (OFC) using near-infrared spectroscopy (Ernst et al. 2014). Wiers et al. (2014) also found that self-reported craving was positively correlated with amygdala activation. Cousijn et al. (2012) investigated automatic approach tendencies in heavy cannabis users compared to controls using fMRI, finding that greater activation in the dorsolateral (dl)PFC and ACC during cannabis-approach trials was associated with reduced cannabis use at six month follow up. Further support for frontal region involvement in automatic substance-approach behaviour is seen in frontal activation during passive viewing of alcohol cues (for a systematic review, see Schacht et al. 2013) and, along with the insula, during attentional bias to substance-related compared to neutral cues (for a review, see Field et al. 2014).

Heavy alcohol use is known to be prodromal for dependence (Kranzler et al. 1990; Dawson & Aecher 1993) and is part of a spectrum of alcohol use and dependence that we need to understand in order to reduce alcohol harms. Many studies of heavy drinking individuals have sampled students who “binge-drink”, a pattern of alcohol use that is a societal norm in the UK. Continuing to drink heavily after the early 20s is a less common pattern and may represent a higher risk of later dependence. Therefore, this study investigated the automatic alcohol-approach response of heavy drinking individuals over the age of 21, as well as their response to avoidance of an aversive non-alcohol-related stimulus. While the first task assessed alcohol-specific behaviour, the non-alcohol-specific second task was able to assess whether this bias reflected heightened avoidance behaviour. Those who use alcohol as a coping mechanism are likely to show greater avoidance of aversive events and an “Alcohol-Approach Bias”. We hypothesised that heavy drinkers would show greater approach-bias to alcohol-related cues than controls as well as increased avoidance of an

aversive stimulus. We also hypothesised that neural correlates of these approach biases and avoidance behaviours would correspond to those identified in previous studies, reflected in differential responses within the mPFC, dlPFC, ACC and NAcc during alcohol-approach, and in the NAcc and amygdala during avoidance of aversive stimuli.

## **Methods**

The protocol was approved by the North West, Greater Manchester East Research Ethics Committee (REC Ref: 13/NW/0650). Sessions were conducted at the Wellcome Trust Clinical Research Facility, Magnetic Resonance Imaging Facility, Central Manchester University Hospital NHS Foundation Trust.

### *Participants*

Forty participants aged 22-53 years old (mean age = 31.8, S.D = 7.6, 50% female) were recruited from a linked behavioural study (Taylor et al., **Study 3**) who had consented to take part in additional imaging sessions and were recruited if they fulfilled MR safety regulations. Participants were included in either a “heavy drinking” group if they self-reported consuming 30+ (male) or 22+ (female) units of alcohol per week, or a “control” group if they reported consuming <20 (male), or <15 (female) units of alcohol per week. These limits were based on current (as of October 2013) UK Government advice on alcohol consumption which is to consume no more than 2-3 (female) or 3-4 (male) units of alcohol per day with two alcohol-free days a week (House of Commons Science and Technology Committee 2012). This equates to a maximum of 15 (female) or 20 (male) units of alcohol per week, which is the control upper limit for this study, while 1.5 times these guidelines was the lower limit for inclusion in the heavy drinking group.

Six participants were removed from the Alcohol Stimulus-Response Compatibility (ASRC) task and four from the Active-Passive Avoidance (APA) task due to excessive movement (defined as >20% voxels with >1mm movement) or poor performance (<80% accuracy on either task), leaving 16 controls and 18 heavy drinkers in the ASRC analysis, and 17 controls and 19 heavy drinkers in the APA analysis.

### *Procedure*

Following consent, participants were assessed using the Structured Clinical Interview (SCID) for DSM-IV and completed the Spielberger State/Trait Anxiety Index (STAI; Spielberger, Gorsuch, & Lushene, 1970). Exclusion criteria included: use of psychoactive prescription medications, such as those with anti-depressant or anxiolytic properties; a history or presence of a neurological diagnosis; clinically significant head injury; neuroendocrine disorder, including impaired thyroid function and steroid use; current or past substance dependence (although current alcohol dependence was allowed in the heavy drinking group); current or past psychosis, bipolar disorder or eating disorder; and any current axis I or II disorder, including depression and anxiety. No heavy drinking participants had a history of alcohol dependence, although two were assessed to have current mild alcohol dependence.

Before scanning participants also completed an alcohol breath test and urine drug screen to confirm abstinence on day of testing, although positive results for cannabinoids were allowed given the long half-life of these metabolites. No participants were excluded due to positive drug or alcohol screens, although one session was rescheduled for the following week due to a positive amphetamine result. On return, the individual completed another drug and alcohol screen to ascertain abstinence before the testing session. Nicotine use was not an exclusion criterion for either group and was matched between groups so that the overall percentage of smokers was 27.5%.

### *Functional MR Imaging Tasks*

Participants completed a counterbalanced version of each task so that it was not a repeat of that completed in the behavioural arm of the study (see Taylor et al., **Study 3**); for example, if they had performed Avoid-Alcohol blocks first in the behavioural study, they completed Approach-Alcohol blocks first this time. Tasks were programmed in PsychoPy2 (version 1.78.01; Peirce 2007) and presented on laptop computers with either a 1366x768 pixel screen or a 1600x900 pixel screen, which were then projected onto a screen positioned at participants' feet and reflected on mirrors attached to the head coil. Participants made their responses on an MR-compatible button box that was held in the

right hand, using the right index finger to press the buttons. Scanning sessions were completed on a separate day to the behavioural testing sessions.

#### *Alcohol Stimulus-Response Compatibility (ASRC) Task*

This task was adapted for fMRI from a relevant-feature stimulus response compatibility task used by Field and colleagues (Field et al. 2008; 2011; Barkby et al. 2012) and a similar fMRI study of automatic approach to cannabis cues by Cousijn et al. (2012). The task involved distinguishing between alcohol-related and neutral images using an “Approach” or “Avoid” response, represented by the movement of a small manikin figure (match stick man) either toward (Approach) or away from (Avoid) images. Approach-Alcohol blocks consisted of approaching alcohol and avoiding neutral (stationery) images, while Avoid-Alcohol blocks were the reverse. There were also baseline and motor-control blocks, which involved non-alcohol images only. Baseline blocks involved the same approach and avoid discrimination as the alcohol blocks, but used the categories of tools and cosmetics in the place of alcohol and stationery. Motor control blocks only required the indication of the manikin’s position: either above or below the image (Figure 4.1A).

There were two runs of 10 blocks; two each of Approach-Alcohol, Avoid-Alcohol, Baseline, Motor and Rest. The sequence of blocks presented was either Approach-Baseline-Avoid-Motor-Rest or Avoid-Baseline-Approach-Motor-Rest, repeated four times across both runs. Each block consisted of 12 trials preceded by an instruction screen lasting 5000ms and then a fixation cross for 500ms. There were six images in each category for the alcohol-related (both Approach- and Avoid-Alcohol) and Baseline blocks, and 12 neutral images in the Motor blocks. Each image was presented for a maximum of 2000ms, with the manikin either directly above or below the image. Responses were made by pressing either the “up” or “down” button on an MR compatible button box. For blocks involving category discrimination, correct responses would move the manikin in the specified direction for 1000ms, followed by a fixation cross for 500ms. An incorrect response (including no response within the allowed time of 2000ms) would produce a large red “X” in the centre of the screen for 1000ms followed by the fixation cross before the start of the next trial. For correct responses to motor-control trials, the manikin would turn red and remain in its starting position for a further 1000ms, while incorrect responses were the same as for the

category discrimination trials. Rest blocks lasted 20 seconds. Each run began with a 12 second fixation and lasted for 8 minutes 28 seconds.

There were 16 alcohol-related and 64 neutral images. Neutral images consisted of 16 pictures of tools, 16 of cosmetics and 16 of stationery; the remaining 32 images were used only for Motor blocks, consisting of a mixture of additional images of tools, cosmetics, stationery, or kitchen utensils. Images were matched as close as possible on perceptual characteristics (e.g. complexity and brightness) and were presented in landscape, measuring 590x394 pixels. Participants completed a practice run of the task outside the scanner that consisted of four blocks of eight trial, with four images of each category.

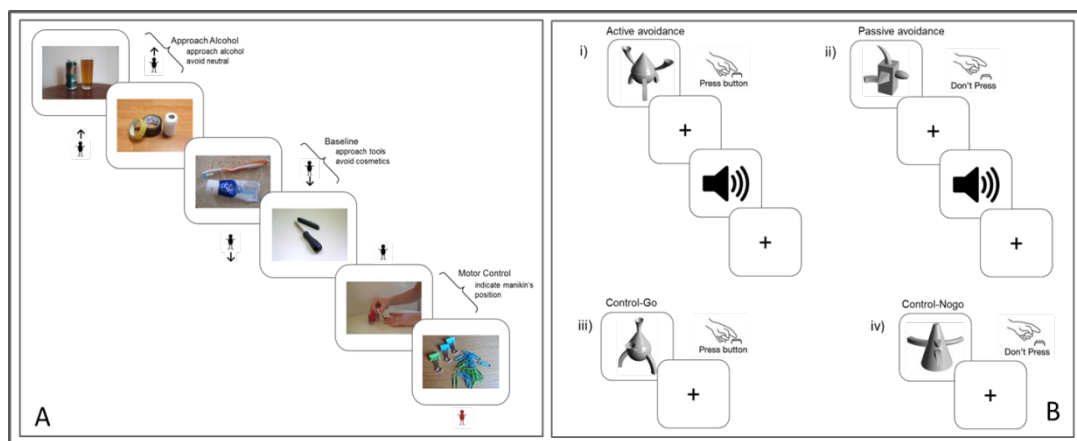
#### *Active-Passive Avoidance (APA) Task*

This task was adapted from Levita et al. (2012) using an aversive auditory stimulus from Levita et al. (2015) as seen in a behavioural version by Taylor et al. (**Study 3**). Participants were required to emit (Active) or omit (Passive) a button-press response to a visual target in order to avoid an aversive auditory stimulus presented through headphones. Two cues acted as warning stimuli (WS; Figure 4.1B i & ii) and predicted the presentation of an aversive auditory sound (the unconditioned stimulus, US); one required a button press response (Active Avoidance) and the other a withheld response (Passive Avoidance). Correct avoidance responses were followed by a fixation cross before moving on to the next trial, while an incorrect response was followed by a blank screen and the presentation of the aversive auditory stimulus for 1000ms and then an inter-stimulus-interval. There were also two control cues that were not followed by the US; one required a button press (Control-Go) and the other a withheld response (Control-NoGo; Figure 4.1B iii & iv). The Active, Passive and Control trials were presented in a pseudorandom order, with the same stimulus not being presented more than twice consecutively. The four visual cues used were counterbalanced between participants so that each of the four cues acted as either Go- or NoGo-Control, and Passive or Active WS. Participants learnt these associations in a practice run of 20 trials outside the scanner.

This was an event-related task carried out in two runs of 40 trials, containing 10 of each Active Avoidance, Passive Avoidance, Control-Go and Control-NoGo cues. Each cue was

presented for a maximum of 2000ms and followed by an inter-stimulus interval of a blank screen that was jittered to ensure that each trial lasted between 12-14 seconds (including the cue presentation and aversive stimulus if it was presented). Each run began with a 12 second fixation and lasted for an average of 8 minutes and 52 seconds.

The auditory stimulus and visual cues were provided by Liat Levita, Department of Psychology, University of Sheffield (<http://levita-lab.group.shef.ac.uk>) and were those used by herself and colleagues (Levita et al. 2009; 2012; 2015). The auditory stimulus was a combination of a 1000Hz tone and white noise with the intensity tiered for smooth onset and offset, played for 2000ms and delivered using a MR compatible noise-cancelling headphone unit developed by MR Confon (<http://www.mr-confon.de/>).



**Figure 4.3:** An example of each task: **A)** Alcohol Stimulus-Response Compatibility Task, ASRC; **B)** Active Passive Avoidance Task, APA.

## MR Image Acquisition

Imaging was carried out using a Philips 3T MR scanner. 202 volumes were acquired for the ASRC and 214 for APA, both comprising 27 axial slices of 4mm thickness, with a TR of 2500ms, and a voxel size of 3 x 3 x 4mm. A T1-weighted structural image was also acquired for use in spatial pre-processing and for examination of any structural abnormalities.

## Data Analysis

### Behavioural Data Analysis

Behavioural data were analysed using Statistical Package for Social Sciences (SPSS, version 22, [www.spss.com](http://www.spss.com)). For the ASRC a separate mean reaction time (RT) for each movement



block (“Approach-Alcohol” vs. “Avoid-Alcohol”) was calculated. We used a mixed two-way repeated measures analysis of variance (ANOVA) with block (Approach-Alcohol, Avoid-Alcohol, Baseline, Motor) as the within-subjects factor and group (control vs. heavy) as the between-subjects factor. An “Alcohol-Approach Bias” score was generated for each participant by subtracting their Approach-Alcohol RT from that of Avoid-Alcohol, which was assessed for group differences using independent t-tests. For the APA a mean RT for correct responses to cues (Active Avoidance, Control-Go) was calculated. We used a mixed two-way repeated measures ANOVA with cue (Active Avoidance vs Control-Go) as the within-subjects factor and group (control vs. heavy) as the between-subjects factor. Significant main effects were investigated with separate paired-samples t-tests.

### *Image Analysis*

Imaging data were analysed using Statistical Parametric Mapping (SPM12; Wellcome Trust Centre for Neuroimaging, London, England, <http://www.fil.ion.ucl.ac.uk/spm/>), implemented in MATLAB (Mathworks, 2012). Images were realigned to correct for motion, using the first image as a reference. The structural (T1-weighted) and functional images were then coregistered, followed by spatial normalisation, and were smoothed using a Gaussian kernel filter of 9 x 9 x 12mm.

For the Alcohol Stimulus-Response Compatibility (ASRC) task, first level analysis was performed on the contrasts of Approach-Alcohol > Baseline and Avoid-Alcohol > Baseline. The primary contrast of interest was for Approach-Bias, which was specified as Approach-Alcohol > Avoid-Alcohol, both compared to baseline ([Approach-Alcohol > Baseline] > [Avoid-Alcohol > Baseline]). For the APA, first level analysis was performed on the contrasts of Active-Avoidance > Control-Go and Passive-Avoidance > Control-NoGo. Errors on Avoidance (Active and Passive) and Control (Control-Go and Control-NoGo) trials were modelled separately as contrasts of no interest as they would confound motor action.

For both the ASRC and APA tasks we first performed whole brain analyses on all participants as there were no clinical patient groups. These were performed on the contrasts of interest (detailed above) using the Family Wise Error (FWE) threshold of  $p < 0.05$ . Additional effects at the  $p < 0.001$  uncorrected threshold were also included for

descriptive purposes only, although no conclusions were drawn from these liberal thresholds. The central part of our analyses relied on small volume correction (SVC) analyses of regions previously identified in studies using these tasks (Cousijn et al. 2012; Wiers et al. 2014; Levita et al. 2009; 2012). The regions used for SVC were a sphere of 5, 10, or 15mm radius depending on the size of the region of interest (e.g. the dlPFC is relatively large, so required a radius of 15mm, whereas the NAcc is relatively small, so required a radius of 5mm), centred on coordinates from previous studies (Table 4.1). Regions of interest identified were the NAcc, mPFC, bilateral dlPFC and bilateral ACC (ASRC), as well as bilateral NAcc and amygdala (APA).

To assess the effect of group in both tasks, we used the Flexible Factorial module to specify a mixed-effects repeated measures ANOVA using the SPM non-sphericity correction to estimate a unique covariance structure per group. In order to use the correct error term (either within-subject or between-subject) for our contrasts, two models were fitted. For all between-subject main effects and interactions we specified a basic t-test model after averaging over the repeated measurements for each subject. For the within-subject main effects and interactions we used the full repeated measures ANOVA model specified using the Flexible Factorial module.

For the ASRC, condition (Approach-Alcohol > Baseline vs. Avoid-Alcohol > Baseline) was the within-subjects factor and group (heavy drinkers vs. controls) the between-subjects factor. Approach-Bias activations were first compared between heavy drinkers and controls and then a condition x group interaction was specified. For the APA, condition (Active Avoidance > Control-Go vs. Passive Avoidance > Control-NoGo) was the within-subjects factor and group (heavy drinkers vs. controls) the between-subjects factor. Passive and Active Avoidance activations were first compared between heavy drinkers and controls and then a condition x group interaction was specified. These contrasts were small volume corrected (SVC; Table 4.1) for the regions previously associated with Alcohol Approach-Bias (ASRC; Cousijn et al. 2012; Wiers et al. 2014) and with Active and Passive Avoidance of aversive stimuli (APA; Levita et al. 2009; 2012). Significant main effects were investigated with separate paired-samples t-tests for within-groups effects, and independent t-tests for between-groups effects.

For both tasks, Pearson's correlations were used to assess relationships between blood oxygen level dependent (BOLD) activation in heavy drinkers with their weekly alcohol use. We also assessed the relationship between BOLD activation and trait anxiety (STAI-T) scores within the APA task. These correlations were SVC for the same regions used for the group analysis (Table 4.1).

**Table 4.1:** Regions of interest and their coordinates based on previous findings for both the Alcohol Stimulus-Response Compatibility (ASRC) and Active-Passive Avoidance (APA) tasks.

Region	Hemisphere	MNI Coordinates			Reference
		x	y	z	
Approach-Avoid Alcohol					
Nucleus Accumbens	R/L	15	5	-8	Wiers et al (2014)
Medial Prefrontal Cortex	R/L	0	59	7	
Amygdala	R/L	30	-7	-11	
Dorsolateral Prefrontal Cortex	R	36	32	36	Cousijn et al (2012)
Anterior Cingulate Cortex	R/L	-8	42	18	
Active-Passive Avoidance					
Nucleus Accumbens	L	-13	-4	-5	Levita et al (2009) [converted from Talairach coordinates]
Amygdala	L	-27	3	-20	
Amygdala	R	21	5	-21	

## Results

### Demographics

Heavy drinking participants consumed significantly more alcohol units per week than controls ( $t(38)=-9.067$ ,  $p<0.001$ ). Median alcohol consumption for control participants was 7.0 units per week and ranged from 1.6-12.2 units/week (male) and 1.0-13.1 (female), while the heavy drinking group had a median alcohol consumption of 47.4 units per week that ranged from 31.0-125.3 units/week (males) and 24.3-80.0 units/week (females). Groups did not significantly differ on age, IQ, sex, smoking status or daily cigarette use (Table 4.2).

### Behavioural Analysis

#### Alcohol Stimulus-Response Compatibility (ASRC) Task

A mixed two-way repeated measures ANOVA found a main effect of block ( $F(3,96)=185.305$ ,  $p<0.001$ ), which indicated that all participants were faster to respond to Approach blocks than Avoid blocks ( $t(33)=-5.551$ ,  $p<0.001$ ), and to Approach blocks than

Baseline ( $t(33)=-4.897$ ,  $p<0.001$ ), but not to Avoid than Baseline blocks ( $t(33)=1.596$ ,  $p=0.120$ ). Participants were also faster to respond to Motor control blocks than Approach ( $t(33)=17.232$ ,  $p<0.001$ ), Avoid ( $t(33)=16.691$ ,  $p<0.001$ ), and Baseline blocks ( $t(33)=16.618$ ,  $p<0.001$ ). Contrary to our hypotheses, there was no effect of group ( $F(1,32)=0.021$ ,  $p=0.886$ ), and no group x block interaction ( $F(3,96)=1.042$ ,  $p=0.378$ ).

**Table 4.2:** Demographic data for control and heavy drinking participants.

	Control	Heavy	Differences		
	Mean (SD)	Mean (SD)	t	df	p
<b>Age</b>	30.20 (5.86)	33.30 (8.82)	-1.309	38	0.198
<b>Alcohol units/wk</b>	6.70 (3.67)	53.14 (22.61)	-9.067	38	<b>0.000*</b>
<b>Cigarettes/day</b>	0.68 (1.88)	2.16 (4.74)	-1.296	24.81	0.207
<b>IQ</b>	112.10 (3.89)	112.25 (5.05)	-0.105	38	0.917
Count			$\chi^2$	df	p
<b>Sex</b>					
Male	11	9	0.400	1	0.530
Female	9	11			
<b>Smoking Status</b>					
Non-Smoker	16	13	1.129	1	0.290
Smoker	4	7			

#### *Active-Passive Avoidance (APA) Task*

A mixed two-way repeated measures ANOVA found no significant effects of cue ( $F(1,34)=0.093$ ,  $p=0.762$ ), group ( $F(1,34)=0.128$ ,  $p=0.722$ ) or cue x group interaction ( $F(1,34)=0.425$ ,  $p=0.519$ ).

### *Imaging Analysis*

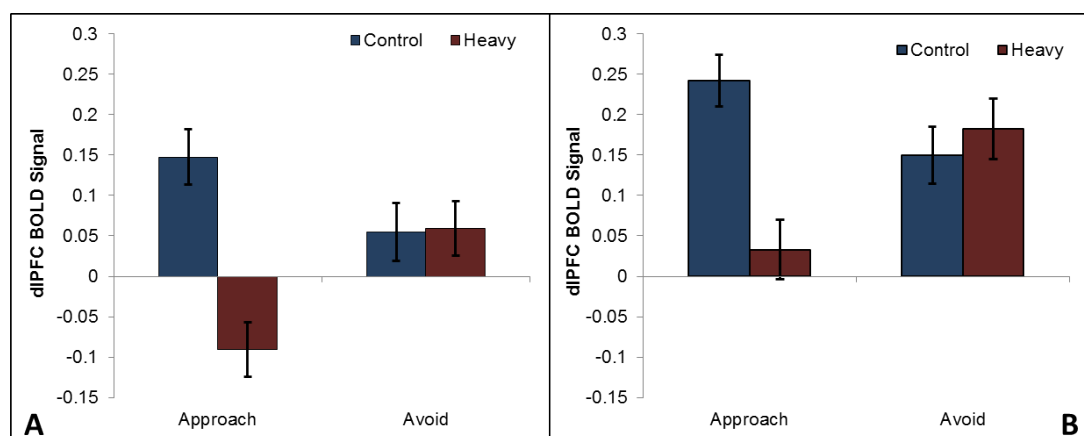
#### *Alcohol Stimulus-Response Compatibility (ASRC): Effect of Task*

Firstly, we performed a whole brain analysis across all participants on Approach-Bias (Approach-Alcohol > Avoid-Alcohol) and Avoid-Bias (Avoid-Alcohol > Approach-Alcohol). At the whole brain Family Wise Error (FWE) threshold of  $p<0.05$  no significant changes in BOLD activation were detected. Effects that survived the threshold of  $p<0.001$  (uncorrected) are included for descriptive purposes only (Table 4.3). A region of interest analysis using small volume corrections (SVC) centring on coordinates from previous

studies of substance approach bias (Cousijn et al. 2012; Wiers et al. 2014) detected no significant BOLD activation changes.

#### *ASRC: Group Differences*

The group x condition contrast revealed a significant interaction between heavy drinkers and controls in the dlPFC (15mm sphere with peaks at  $x=45$ ,  $y=32$ ,  $z=26$ ,  $Z=3.21$ , FWE  $p<0.05$ ; Figure 4.2A). We investigated this interaction by performing separate two-sample t-tests to assess group differences in each of the conditions (Approach-Alcohol and Avoid-Alcohol), using the same dlPFC SVC as for the interaction. This found that heavy drinkers showed greater deactivation compared to controls in the right dlPFC during Approach-Alcohol contrast ( $x=45$ ,  $y=32$ ,  $z=26$ ,  $Z=3.02$ , FWE  $p<0.05$ ; Figure 4.2A) but no group differences were detected for the Avoid-Alcohol contrast. To assess whether this was a genuine deactivation of this region, we repeated the same analysis compared to the Rest condition for which there was also a significant group x condition interaction at the same peak ( $x=45$ ,  $y=32$ ,  $z=26$ ,  $Z=3.21$ , FWE  $p<0.05$ ). As can be seen in Figure 4.2B, heavy drinkers showed significantly reduced activation compared to controls during Approach-Alcohol.



**Figure 4.2:** **A)** The group x condition interaction showing differences in Approach-Alcohol activation within the right dlPFC compared to a background of baseline performance; and **B)** the same interaction as compared to the contrast of rest.

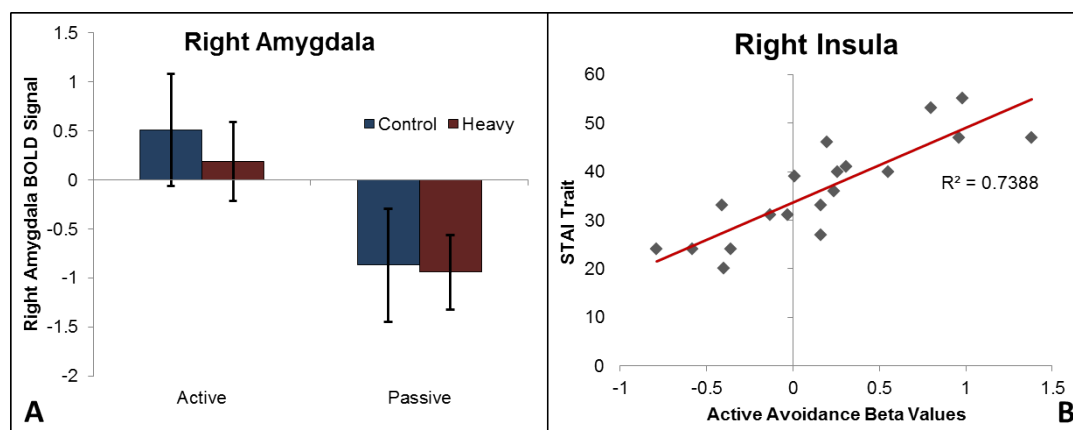
Correlation analyses were performed on Approach-Alcohol and Avoid-Alcohol activations to assess their relation to the wide variation in weekly alcohol consumption in the heavy drinking group. Whole brain analyses at the FWE threshold of  $p<0.05$ , or in ROIs after SVC, detected no significant correlations.

### Active-Passive Avoidance (APA) Task

Whole brain analysis of the Avoidance>Control-Go and Passive-Avoidance>Control-NoGo contrasts to assess the overall main effect of task detected no significant BOLD activation changes at FWE threshold of  $p < 0.05$ . For descriptive purposes only, we have also include effects that survived the threshold of  $p < 0.001$  uncorrected (Table 4.3). We then used SVC with a 5mm radius sphere, centred on previously identified coordinates (Levita et al. 2009; 2012). This revealed a significant increase in activation for Active Avoidance compared to Passive Avoidance with a peak in the right amygdala ( $x=18, y=8, z=-10, Z=2.41, FWE p < 0.05$ ; Figure 4.3A).

### APA Group Analyses

We then performed a between-groups analysis using a two-sample t-test. We detected no significant difference in BOLD changes between groups at the whole-brain FWE threshold of  $p < 0.05$ , an exploratory threshold of  $p < 0.001$  (uncorrected), or in ROIs after SVC.



**Figure 4.3: A)** The significant increase in activation for active avoidance>passive avoidance with a peak in the right amygdala ( $x=18, y=8, z=-10, Z=2.41$ ). **B)** The correlation between STAI trait anxiety with active avoidance activation in the right insula ( $x=32, y=11, z=6, Z=4.71$ ).

Correlation analyses were performed on Active Avoidance and Passive Avoidance activations to assess their relation to the wide variation in weekly alcohol consumption in the heavy drinking group. Whole brain analyses at the FWE threshold of  $p < 0.05$ , or in ROIs after SVC, detected no significant correlations. Additional correlation analyses were performed on Active Avoidance and Passive Avoidance activations to assess their relation to trait anxiety (STAI-T) scores in the heavy drinking group. Whole brain analyses at the FWE threshold of  $p < 0.05$  detected a significant positive correlation ( $r=0.859, p < 0.001$ ) with

Active Avoidance activation in the right insula ( $x=32$ ,  $y=11$ ,  $z=6$ ,  $Z=4.71$ , FWE  $p<0.05$ ; Figure 4.3B). There were no significant correlations detected for Passive Avoidance and trait anxiety.

**Table 4.3:** Uncorrected whole brain effects of both the Alcohol Stimulus-Response Compatibility (ASRC) and Active-Passive Avoidance (APA) tasks.

Alcohol Stimulus-Response Compatibility Task					
Cluster size (voxels)	Z	x	y	z	Region
<b>Main Effect of Approach&gt;Avoid <math>p&lt;0.001</math></b>					
113	3.471	-36	17	-26	Left temporal pole
41	3.317	-21	2	-22	Amygdala
<b>Main Effect of Avoid&gt;Approach <math>p&lt;0.001</math></b>					
35	3.289	-51	29	22	Left dorsolateral prefrontal cortex
Active-Passive Avoidance Task					
Cluster size (voxels)	Z	x	y	z	Region
<b>Main Effect of Active&gt;Passive Avoidance <math>p&lt;0.001</math></b>					
150	3.599	-6	-97	14	Left occipital pole
152	3.275	3	-49	2	Right posterior cingulate gyrus
59	3.142	30	-31	2	Right hippocampus
<b>Main Effect of Passive&gt;Active Avoidance <math>p&lt;0.001</math></b>					
108	4.339	-30	-91	2	Left inferior occipital gyrus

## Discussion

### *Summary of Findings*

Despite similar behavioural performance, heavy drinkers compared to controls showed deactivation of the right dlPFC during alcohol-approach compared to baseline discriminations, and reduced activation compared to rest. All participants showed a significant increase in right amygdala activation during Active-Avoidance compared to Passive-Avoidance. However, contrary to our predictions, there were no group differences on imaging or behavioural measures of this task. However, trait anxiety was positively correlated with Active-Avoidance activation in the right insula of heavy drinking participants.

### *Alcohol Stimulus-Response Compatibility (ASRC) Task*

The lack of behavioural differences is unexpected given our hypotheses and the findings of other studies using this behavioural task in heavy drinkers (Field et al. 2008; 2011). However, this reflects findings from Taylor et al. (**Study 3**), suggesting that the heavy drinkers in the present sample may be showing behavioural automatic alcohol-approach tendencies that are more similar to that of the alcohol dependent participants of Barkby et al. (2012), and thus are further along a trajectory of alcohol use towards dependence than predominantly heavy drinking students of previous studies.

In spite of comparable behaviour, functional imaging analysis identified a differential effect of automatic alcohol-approach in heavy drinking participants, specifically right dlPFC deactivation during alcohol-approach. The dlPFC is associated with executive control, and is particularly implicated in impulsivity (Volkow et al. 2011). For example, reduced activation in this region is associated with poor decision-making in cannabis users (Bolla et al. 2005) as well as poorer inhibitory control in cocaine (Bolla et al. 2004), cannabis (Eldreth et al. 2004), and methamphetamine using individuals (Salo et al. 2009). Increased activation of this region is also seen in response to drug-related cues in alcohol dependent individuals compared to controls (Heinz et al. 2007; Grüsser et al. 2004). In addition, Cousijn et al. (2012) found that increased dlPFC and ACC activation during Cannabis-Approach was related to better outcomes at follow up, suggesting that the cannabis users with greater activation in these regions had more control over their usage. When combined with our findings, one interpretation is that our heavy drinking individuals display reduced inhibitory control compared to the control group when approaching alcohol-related cues. This reduced activation compared to controls in light of no performance differences would indicate that heavy drinkers approach alcohol-related cues as quickly, but with significantly less self-control. As a result, we predict that these heavy drinkers would show behavioural differences in situations when this reduced control is detrimental, such as when experiencing negative affective states, such as those following stress induction.

### *Active-Passive Avoidance*

Across groups, we observed right amygdala activation during Active- compared to Passive-Avoidance, consistent with the findings of Levita et al (2012). The amygdala is associated



with anxiety (for a meta-analysis, see Etkin & Wager 2007) and neuroticism (Cremers et al. 2010). It also responds to aversive images (Harenski et al. 2009), and has been implicated in fear learning in adults (Hooker et al. 2008) as well as adolescents (Tzschoppe et al. 2014). The amygdala also has connections with the insula, mPFC and hippocampus, which when disrupted are thought to be responsible for neuroticism and the associated emotional responses to aversive stimuli (Ormel et al. 2013).

We did not find activation of the right NAcc for Active Avoidance or deactivation of the left NAcc during Passive Avoidance that is reported in previous versions of this task using aversive images (Levita et al. 2012). This may be a reflection of the subtly different task design as in our study participants avoided one aversive auditory stimulus rather than a selection of aversive images as in Levita et al. (2012). There was also no evidence of the hypothesised differential response to avoidance in controls and heavy drinkers. However, our sample inclusion criteria were based on weekly alcohol consumption, whereas we might find that it is more useful to consider subgroups of non-dependent drinkers that are based on their different motivations for drinking. Future studies could investigate these different profiles in heavy drinkers and assess whether they relate to differential responses on measures of automatic approach and avoidance behaviour. These profiles may also display different longitudinal patterns of alcohol use, which may indicate which are more prone to developing into dependence.

The lack of group differences in this task suggests this measure was unable to detect differential avoidance behaviour to a non-alcohol-related stimulus. However, the heavy drinking group showed an increase in trait anxiety that was robustly correlated with increased activation in the right insula. The insula is related to interoception and emotion (Gasquoin 2014), specifically in a number of anxiety-related disorders such as Post-Traumatic Stress Disorder (PTSD; Etkin & Wager 2007), while grey matter reductions within this region are reported in a number of mental health disorders including schizophrenia, depression, anxiety, obsessive compulsive disorder (OCD) and addiction (Goodkind et al. 2015). As a result, although there were no group differences in neural correlates of avoidance of aversive stimuli, anxiety was related to a greater avoidance response in heavy drinkers but not in controls.

### *Conclusion and Implications*

Heavy drinking participants showed reduced frontal responses during alcohol-approach, which may be interpreted as reflecting reduced executive control over approaching alcohol cues. This is in spite of no behavioural differences from controls on an alcohol-specific task. There were no behavioural or functional differences between heavy drinkers and controls in the avoidance of non-alcohol-specific aversive stimuli, indicating that there is not a dysfunctional generalised avoidance mechanism in heavy drinking. However, there was an association with greater right insula activation and trait anxiety scores within heavy drinkers, suggesting that these heavy drinkers with high anxiety scores may be prone to more avoidant responses to aversive stimuli.

Our study indicates that there are differences between heavy drinkers and control participants that are not detectable from behavioural tasks alone. With the use of functional brain imaging we have been able to detect that these heavy drinking individuals are processing alcohol-related cues differently to controls at a neuronal level and that their avoidance response to non-alcohol-related aversive stimuli is dependent on individual differences in anxiety.

## Chapter 3: General Discussion

This thesis has presented four papers investigating some of the neurocognitive characteristics of substance dependence, influential in vulnerability, maintenance and relapse. By understanding these mechanisms better we can improve treatment and prevention of addiction and, thus reduce its impact on society. Based on the literature reviewed in the General Introduction of Chapter 1, two specific areas of neurocognition have been identified as important in this advancement of addiction knowledge: affective impulsivity and the role of negative reinforcement. Additionally, the introductory chapter highlights the value of devoting more consideration to the individual differences within substance dependent populations. In an attempt to avoid some of the common pitfalls of addiction research this chapter also draws attention to a number of methodological issues including sample selection and levels of measurement, as well as the need to incorporate emotion and substance-related aspects into behavioural measures to make them more relevant to substance dependence.

In addressing these issues, this thesis investigated four hypotheses:

1. Not all the current methods for measuring impulsivity in substance dependent individuals are appropriate at every stage of dependence or for each participant group.
2. The current classifications of dependent individuals based on primary substance do not best reflect the different profiles within addiction.
3. Stress is influential in the progression of heavy drinking to alcohol dependence through the process of negative reinforcement.
4. Differential neural processing of automatic approach and avoidance behaviour is involved in the early stages of substance dependence.

These were investigated by conducting the four studies detailed below.

### 3.1. Summary of Findings

#### *Study 1: Impulsivity in alcohol and polydrug dependence: a multi-dimensional approach*

The first study in this thesis investigated a number of different aspects of impulsivity within a varied sample of abstinent substance dependent (AbD) individuals, using three levels of measurement: self-report, behavioural, and neural measures. AbDs were divided into polydrug and alcohol dependent groups and compared to controls on all measures. This study found that self-report measures better detected differences between controls and AbD participants than did behavioural and neural measures, but no differences were found between polydrug and alcohol dependent participants. Polydrug users also showed greater compensatory left IFG activation in response to successful inhibitions on the GNG task in spite of no behavioural differences. In addition, exploratory analyses that regrouped AbD participants by their drug dependence history found that only stimulant dependence had a significant impact on impulsivity scores: those without a history of stimulant dependence were no different from controls on self-report measures of impulsivity, while those with a history of stimulant dependence showed significantly higher scores. I proposed that these self-report measures are more sensitive to detecting impulsivity in long-term abstinent individuals than the behavioural or neuronal measures used, and suggested the need for development of a wider range of behavioural measures to assess more aspects of impulsivity.

#### *Study 2: Reclassification of preconceived diagnostic categories for substance dependence*

In the second study AbDs were reclassified based on their personality risk factors as opposed to grouping by primary dependence, a method that is used inconsistently throughout the field of addiction. Using a data-driven approach (Latent Profile Analysis), participants were grouped based on their scores on a number of self-report measures of impulsivity and affect with the hypothesis that the analysis would identify two groups: sensation seeking and self-medicating. The analysis in fact identified a group that scored high across all the measures (High AbDs) and another that scored low across these measures (Low AbDs). The latter group were not significantly different from controls on these measures but the High group scored significantly higher than both controls and Low

AbDs. Although there were no behavioural or neural group differences, fMRI found that High AbDs showed greater left IFG activation in response to GNG inhibition with increased length of abstinence. This study highlights the utility of grouping participants on their personality risk factors rather than on primary dependence as it uncovered important differences within a previously undifferentiated group of substance dependent individuals. Such differences are potentially important for improving treatment as well as further research investigations.

### *Study 3: Stress, Alcohol-Approach Bias and Avoidance Behaviour in Heavy Drinkers*

The third study assessed the effect of stress induction on automatic alcohol-approach behaviours and avoidance of aversive stimuli in heavy drinking individuals. Contrary to the hypotheses, there was no differential effect of stress on heavy drinkers compared to controls on either alcohol approach-bias or avoidance of an aversive non-alcohol related stimulus. However, one interpretation of the findings is that older heavy drinkers are comparable to alcohol dependent participants who also show no alcohol-approach bias, in contrast to younger heavy drinkers recruited in previous studies who do show Alcohol-Approach Biases. This study highlights the importance of investigating behaviours and mechanisms related to addiction across the whole spectrum of substance use and dependence, from early use through to long-term abstinence as their importance may vary at each stage.

### *Study 4: Neural Correlates of Automatic Approach and Avoidance Behaviours in Heavy Drinkers*

This study investigated the neural mechanisms of automatic alcohol-approach behaviours and avoidance of aversive stimuli in heavy drinking individuals. While there were no behavioural differences in Alcohol-Approach Bias, heavy drinking participants showed greater deactivation of the right dlPFC during alcohol-approach compared to controls. There were also no differences between controls and heavy drinkers in behaviour or brain activation to avoidance of an aversive stimulus, although there was a positive correlation between trait anxiety and right insula activation during active avoidance within heavy drinkers only. These findings can be interpreted to suggest that heavy drinkers approach

alcohol in a less controlled manner than light drinkers and there is a link between avoidance of aversive stimuli and anxiety in heavy drinkers. This study highlights the importance of using different levels of measurement, as the behavioural versions of these tasks (**Study 3**) did not detect any differences between controls and heavy drinkers.

### *Integration and Implications of Current Findings*

Overall, these findings provide mixed support for the hypotheses stated earlier. However, a number of conclusions can be drawn. Firstly, self-report measures appear to be more sensitive to impulsivity than behavioural and neural measures in AbDs, which highlight the importance of choosing appropriate levels of measurement to use at the different stages of drug use and dependence. Both **Studies 1** and **4** indicate the value of different levels of measurement at two different stages: **Study 1** provided support for the utility of self-report measures, while **Study 4** for the utility of neural measures.

Secondly, more consideration should be given to the individual differences within substance dependent populations as there is potential for identifying profiles of substance dependence that are based on personality risk factors and may prove to be more informative than traditional classifications based on primary substance. **Study 2** demonstrated regrouping AbDs based on personality risk factors and identified a subset of AbDs who were very similar to controls on all measures, and would otherwise have been indistinguishable from the remaining AbDs. Similarly, **Study 4** also hinted at the instance of individual differences in a sample of heavy drinking participants who showed a correlation between trait anxiety and insula activation in response to active avoidance of an aversive stimulus. While the significance of individual differences and the profiles of substance dependent individuals are only implied in the results of these four studies, we need to pursue this idea within the whole spectrum of substance use and dependence, from social use, through harmful heavy use to dependence and abstinence. The findings from **Study 3** draw attention to a difference between early social use and more established harmful use of alcohol, which may be of great consequence in the understanding of how such heavy use develops into dependent use.

Although the support for the hypotheses is limited, these investigations have brought together the role of impulsivity and emotion in substance dependence while considering the different levels of measurement and individual differences of substance dependent individuals. Through this process my thesis has also raised many more questions. The next sections of this final chapter will discuss some of these important questions, which include the different stages of the addiction development trajectory and the profiles within them, the populations from which participant samples are recruited, and the levels of measurement that are used to assess them. The final section of this concluding chapter will then discuss the limitations of the thesis along with possible directions for future investigations.

### **3.2.1: Developmental Trajectories of Addiction**

While neurocognitive addiction research investigates the role of certain mechanisms relating to the vulnerability, maintenance and relapse of addiction, conclusions drawn from this thesis suggest that this approach is too restrictive on our understanding of the disorder and that we should consider the possibility of a greater number of stages along a trajectory of substance use and dependence. Evidence of cognitive recovery during abstinence (Schulte et al., 2014; Stavro et al. 2013; Sullivan et al. 2000), including the findings of **Study 1**, suggests that the length of abstinence is important in the risk of relapse and highlights the possibility that those who maintain abstinence long-term are fundamentally different to those who relapse early. Using the example of alcohol use and dependence, **Study 3** drew attention to a possible difference between heavy social drinking during late adolescence and early adulthood, and more established heavy drinking into middle age.

This thesis proposes the idea that there are five distinct stages of substance use. The first stage is social use, in the case of alcohol this typically includes light social drinking within Government guidelines. However, during this early stage of alcohol use, many people experience a period of heavy social drinking that is nonetheless in line with social norms, such as often seen in (and almost expected of) university students, who frequently feature in studies of “heavy drinkers”. Arguably, these individuals are fundamentally different to the more established and older heavy drinkers as many of these young adults “grow out” of their heavy social drinking within a few years before it becomes established. However, the

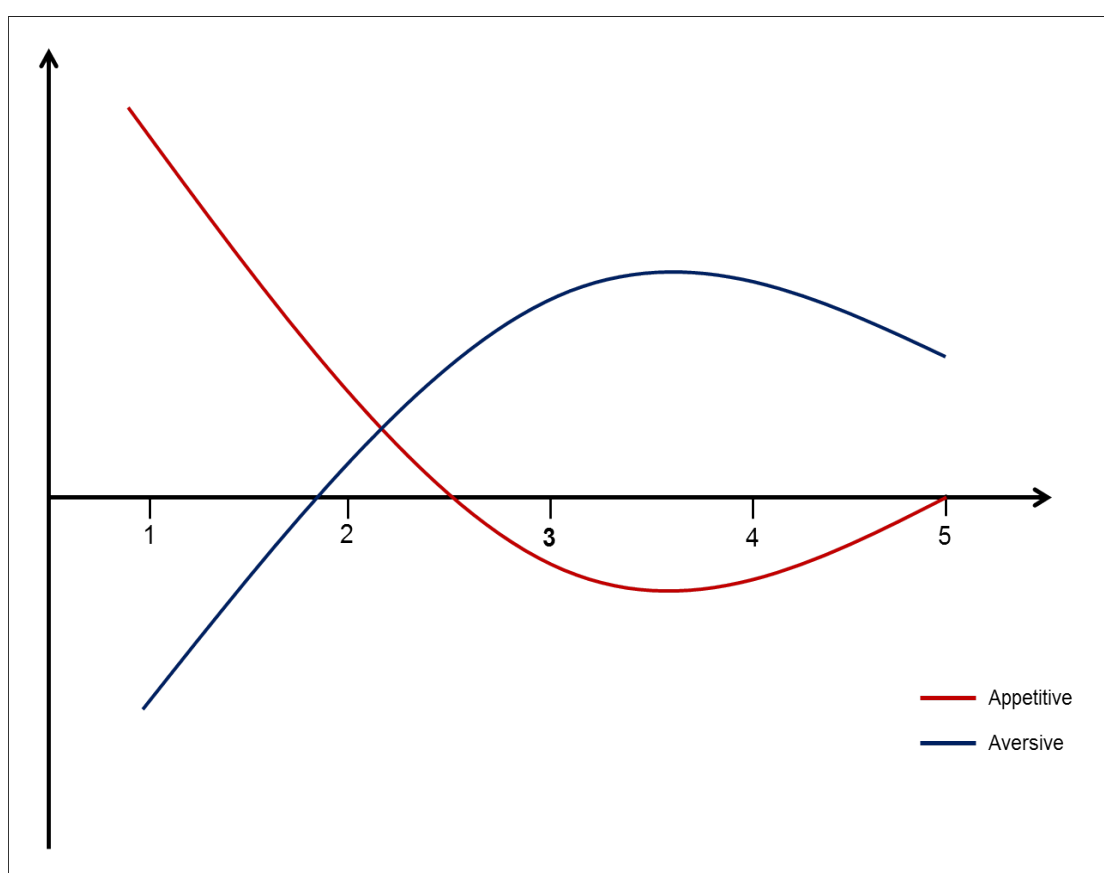
alcohol consumption of some of these social drinkers does not reduce as they mature, and thus they progress to the next stage. Substance use in stage 2 is established heavy use, which is excessive and harmful. Although use has not yet reached dependent levels, individuals are at greater risk of developing dependence. Admittedly, there is a blurred line between the two stages, and as yet there is little investigation of the distinction between the two. Again using the example of alcohol use, these more established heavy users are analogous to those in Studies 3 and 4; they are slightly older than the heavy social drinkers of other studies (e.g. Field et al. 2008; 2011), and have established patterns of regular harmful alcohol consumption.

Stage 3 is current dependence; often a very difficult group from which to draw firm conclusions as these individuals are usually in a cycle of current intoxication and withdrawal. This often means that recruitment is very difficult and instead forces research to recruit participants from stage 4, recent abstinence, which is no longer confounded by current intoxication or withdrawal. The fifth and final stage is long-term stable abstinence, in which individuals have remained abstinent for a sustained period of time. The path through the stages is generally progressive, but many will move backwards and forwards along it. For example, 65-75% of individuals who reach stage 4 (recent abstinence) will relapse back to stage 3 (current dependence) within the first 12 months (Sinha 2011), often repeating this cycle many times before reaching stage 5 (long-term abstinence), if at all. While long-term abstinent individuals are still at risk of relapse, this risk decreases dramatically the longer they remain abstinent (Dennis et al. 2007).

The mistake made by many investigations in addiction research is to regard stages 3–5 as one category. Individuals in stage 4 are not the same as someone in the throes of current dependence (stage 3) because the former will already have a different mind-set regarding substance use, not least because they are no longer intoxicated. There are a number of different processes that alter with each of these stages, using a speculative schematic example of just appetitive and aversive mechanisms these vary quite substantially at each stage along the trajectory (Figure 5.1). Appetitive mechanisms are generally high at the beginning of social use, where substance use is driven by reward, either from removing negative affective states, or increasing positive states. Many people never leave stage 1,



but those who move onto heavy use may have a reduced appetitive drive as prolonged substance use gradually creates anhedonia that reduces the rewarding effects of the substances (Koob 2008). In addition, aversive processes increase as drug use continues and begins to be driven by the desire to remove the negative effects of withdrawal. Once in the next stage, current dependence, appetitive mechanisms are seriously reduced and substance use is almost completely driven by aversive mechanisms through the process of negative reinforcement. Once individuals move into recent abstinence, however, their appetitive and aversive mechanisms plateau initially and then begin to normalise the longer they remain abstinent in stage 5.



**Figure 5.1:** A proposed description of the changing appetitive (red) and aversive (blue) processes along the trajectory of substance use and dependence. Stage 1: social use; stage 2: heavy use; stage 3: current dependence; stage 4: recent abstinence; stage 5: long-term abstinence. At the beginning of stage 1 substance use is driven by reward (either from removing negative affective states, or increasing positive states). This appetitive drive decreases in those who move onto stage 2, as prolonged substance use gradually creates anhedonia and reduces the rewarding effects while aversive processes increase and begin to drive substance use. Appetitive mechanisms are seriously reduced in stage 3 so that substance use is almost completely driven by negative reinforcement. These appetitive and aversive mechanisms plateau initially once in stage 4 and then begin to normalise with maintained abstinence in stage five.

Using the example of alcohol use, the findings from **Study 3** can be interpreted to support this argument. The finding that heavy drinking participants did not show a greater Alcohol-Approach Bias than controls is somewhat surprising given the previous literature, although this too is inconsistent (for a review, see Kersbergen, Woud, & Field, 2015). However, one interpretation of the findings is that the heavy drinkers in **Study 3** are further along the substance use trajectory than those of previous studies (e.g. Field et al. 2008; 2011). That is, the current heavy drinkers are in stage 2, whereas participants (often students) in previous studies are still in stage 1, although arguably at the higher end. The mean age and weekly alcohol consumption of **Study 3**'s heavy drinkers supports this (mean age 34.3 years, mean use = 58.3 units/week) as it is much higher than of those in previous samples (e.g. Field et al. 2008, mean age = 23.3 years; mean use = 30.4 units/week). Although lifetime exposure was not recorded, we can make the assumption that older heavy drinkers in their mid-thirties (as in **Study 3**) have had greater alcohol exposure than those in their early twenties. This would suggest that the heavy drinkers in this thesis are in stage 2 and, thus, are different to the stage 1 social drinkers (albeit heavy social drinkers) in other studies.

As discussed in **Study 3**, the lack of Alcohol-Approach Bias differences in the current sample of heavy drinkers compared to controls is a similar pattern to that seen in recently abstinent alcohol dependent participants (Barkby et al. 2012). This perhaps implies that alcohol-approach behaviour is prevalent at stage 1 of the trajectory (in social drinkers) when drinking motives are driven by appetitive mechanisms. As alcohol use continues into more established heavy drinking (stage 2), these appetitive mechanisms reduce and aversive mechanisms come into play so that alcohol use is driven by the need to avoid withdrawal symptoms (either physiological, psychological or both). These more established heavy drinkers, like recently abstinent alcohol dependent individuals (stage 4), are conflicted, with cognitive processes to approach as well as to avoid alcohol. This is seen in other motivational models of alcohol use (Cox et al., 2006) and would explain why the older heavy drinkers in **Study 3** appear not to show abnormal Alcohol-Approach Bias, as their avoidance bias is equally strong and thus balances it out; something that the Alcohol Stimulus Response Compatibility (ASRC) task is not able to distinguish.

Interestingly, Spruyt et al. (2013) found that alcohol dependent participants showed an Alcohol-Avoidance Bias. These alcohol dependent participants were tested 18-21 days after their last drink, compared to the four-five days after admission for Barkby et al.'s (2012) participants who showed no difference from controls. This extra few weeks may have allowed patients time to develop an “active avoiding strategy” (Townshend & Duka, 2007) during early stages of treatment and thus move themselves along the trajectory towards stage 5 (long-term abstinence). More recently abstinent patients, such as those recruited by Barkby et al. (2012), as well as the established heavy drinkers in **Study 3**, would not yet developed this alcohol-avoidance. This would suggest the existence of a continuum from enhanced alcohol-approach in social drinkers, through normalised alcohol-approach in established and dependent drinkers, to enhanced avoidance in recently abstinent dependent users, which normalises again with extended abstinence (stage 5).

However, Spruyt et al. (2013) also found that alcohol dependent participants who showed greater avoidance bias were more likely to relapse within three months of treatment, which appears to contradict this assumption. Nevertheless, the authors argue that maintaining this alcohol-avoidance pattern is harmful because it prevents abstinent individuals from engaging with alcohol. This precludes repeated experience of the emotional processes required to maintain abstinence, preventing the development of suitable coping skills and response strategies for when they are exposed to alcohol and, thus are more susceptible to relapse. This is different from a balance of approach and avoidance where they are equally strong, which, arguably could be suggested as a sign of recovery.

The findings of **Study 1** from long-term abstinent substance dependent individuals also lend support for this argument of a trajectory of substance use. There was very little difference in AbDs compared to controls on behavioural and neural measures of impulsivity, which in more recently abstinent (Naim-Feil et al. 2014) and current users (Ersche et al. 2011) are highly associated with substance dependence. As discussed in **Study 1**, one potential explanation for this is that these long-term abstinent participants have undergone a certain amount of recovery during an average of 12 months since last substance use. Such improvements in inhibitory control (Hopwood et al. 2011; Morie et al.

2014; Bell et al. 2014) as well as in executive functioning (Schulte et al., 2014; Stavro et al. 2013; Sullivan et al. 2000) have been reported in extended abstinence. **Study 1** also considers that high impulsivity is associated with poor treatment retention and early relapse (Moeller et al. 2001; Patkar et al. 2004; Evren et al. 2012), which may mean that substance dependent individuals with higher levels of impulsivity had already relapsed before being recruited into the study, thus biasing the sample with only relatively low impulsive individuals.

### **3.2.2 Individual Differences and Profiles of Substance Use and Dependence**

While the evidence from **Studies 1** and **3** provide support for the presence of a trajectory of substance use and dependence, there are also individual differences within substance using populations. These individual differences may explain why, for example, some manage to sustain abstinence while others relapse very soon after detox. Therefore, it is important to consider whether, and how much, these individual differences have an influence at other stages along the trajectory, with different profiles of substance use reflecting different pathways through the trajectory. **Study 2** identified two such profiles of AbDs: one that appears to be very similar to controls on measures of impulsivity and affect, and another with significantly higher scores on these measures.

There is a suggestion that some profiles may be particularly associated with specific substances. For example, **Study 2** found that High AbDs were more likely to have had a history of stimulant dependence than Low AbDs. While the findings did not support Becker et al.'s (2012) two-route theory into addiction in which they suggest the presence of a sensation seeking and a self-medicating route into addiction, the idea that different profiles may have preferences for certain substances is also referred to by Becker and colleagues. For example, they suggest that sensation seeking types are more likely to use stimulant substances, such as cocaine and amphetamines, while self-medicating types are more likely to prefer sedative drugs, such as opioids and benzodiazepines. Further support for this theory is seen in a study that used real-time electronic diaries to track drug use, mood and craving (Epstein et al. 2009), in which they found that individuals more often reported themselves to be in a good mood prior to cocaine use and experienced negative feelings

prior to heroin craving. Similarly, anxiety sensitivity and hopelessness are more linked to anxiolytic and opioid dependence, sensation seeking with risk for alcohol dependence, and impulsivity with risk for cocaine dependence (Conrod et al. 2000; and see Mitchell and Potenza 2014, for a review of how different aspects of impulsivity relate differentially to each type of substance).

However, other studies do not support this view (Chakroun et al. 2004; Gillespie et al. 2012), as they found that heroin dependent individuals with and without a history of cocaine dependence did not show any difference in sensation seeking scores to healthy controls (Nielsen et al. 2012). In addition, Shaffer and colleagues (2004) proposed the existence of an “addiction syndrome” in which the individual becomes dependent on a particular substance (or behaviour, such as gambling) as a result of other external events and influences. These might include early stressful life events, genetics, but also the availability of certain drugs. In line with this, Swendsen and Le Moal (2011) suggest that levels of vulnerability to addiction fall into three categories that are unrelated to substance choice: sociodemographic factors; psychiatric and psychological factors; biological and genetic factors. Thus, these studies suggest that the addiction outcome is largely arbitrary and there are more important factors that should be addressed during treatment.

Such factors that may be more useful in addiction treatment include the impulsive and affective personality risk factors used in **Study 2**. Consequently, we should focus less on the “what” and more on the “why” of addiction. In order to do this, however, we should also consider each of the different stages along the substance use trajectory to assess and then predict individual progression. While the two-route model is intuitively appealing and Becker et al. (2012) provide substantial support for it in terms of the sex differences in substance use patterns, the above discussion of the different trajectories of drug use suggest these personalities may only be influential at certain stages. Since this theory regards routes *into* addiction and **Study 2** did not find support for these two distinct patterns in long-term abstinence, it is possible that Becker et al.’s two profiles are only reflected at these early stages and develop differently over the course of substance dependence. Therefore, this adds further incentive to investigate the different stages along the substance use trajectory in order to detect where and how these profiles differ.

### 3.2.3: Sample Selection

The next issue raised by this thesis is that of sample selection and participant recruitment. The current understanding of impulsivity in substance dependence is based on the participant samples that have been recruited so far. However, studies often differ on their definitions and quantification of variables such as length of abstinence, length of use, and exposure. For example, a meta-analysis by Smith et al. (2014) noted that there was little consistency in the recording of the amount or length of drug use, suggesting that their findings need to be considered with caution. It is highly probable that this also applies to a number of other investigations in the addiction field.

Using the example of **Study 1**, AbD participants were divided into alcohol dependent (participants with a history of dependence on alcohol only) and polydrug dependent (participants with a history of dependence on two or more substances). This grouping did not take into account the use of any other substances that did not reach dependent levels, although many were used at very high and harmful levels. In addition, polydrug participants were grouped as such due to their history of dependence on two or more substances, regardless of which substances these were. Although the combinations always included either alcohol, cocaine or opioids, the additional substances varied enormously, producing extensive different combinations of substances and potentially a number of quite different drug user profiles. Grouping all of these people into one category may not be appropriate and could hide the subtle differences between these profiles. In fact, **Study 2** identified two AbD groups that were largely independent of substance and highlighted two important profiles that may be more valuable in the successful treatment and prevention of addiction.

The current method of grouping substance dependent individuals for treatment is usually based on their primary substance of dependence. While this is a vital approach for safe and successful detoxification, it is not a necessary requirement for research and thus may be more appropriate to categorise participants another way. The study of poly-substance dependence would particularly benefit from an alternative approach as there is little (if any) consensus on how such participants should be classified. Further complications arise with the question of where the preference for a particular drug comes from. Using individuals with dual-dependence on heroin and cocaine as an example, there are at least

two distinct types: one type who primarily favour heroin, but also use cocaine to keep them functioning; the other type who primarily favour cocaine, also use heroin to help ease the “come down”. Within just this one example there are two very different reasons for use of the same substances, which perhaps will require similarly distinct treatments. Consequently, as attempted by **Study 2**, it may be more appropriate to pay less attention to the actual substance(s) used and focus instead on the reasons for use, particularly on personality risk factors. **Study 2** was able to show that this approach is useful because we identified a subset of AbDs who were no different from controls on self-report or neurocognitive measures of impulsivity and affect. This approach also identified a second group of AbDs who scored significantly higher than both controls and Low AbDs on these self-report measures.

Such an approach may also be of value in the classification of heavy drinking individuals. For example, in Studies 3 and 4 the heavy drinking participants displayed a variety of drinking patterns that could be roughly divided into two. One group displayed a drinking pattern of daily or almost daily alcohol consumption at moderate levels (approximately five UK units) adding up to a weekly count that exceeded Government guidelines. However, the second pattern involved approximately the same weekly consumption, but this was consumed over just one or two, often consecutive, days (usually Friday and Saturday). While the sample size was not sufficiently large to split the heavy drinking group according to these distinct patterns, future investigations that attempt to classify heavy drinking individuals based on personality risk factors may find these divisions in drinking patterns are reflected, with the potential for detecting differences in alcohol motivations between them.

In addition to the possibility of profiles of substance dependence, care should be taken to give due consideration to other areas of variation in our sample populations, such as the extent of substance use. Other studies using Latent Profile Analysis have used these factors to identify drug user profiles. For example, Agrawal (2007) identified four profiles of substance users that were based on the types of substances they used: cannabis only; stimulants and hallucinogens; prescription drugs; and poly-substance use. They found that anxiety related to the prescription group, depression and nicotine to the poly-substance

group, and then alcohol dependence and antisocial personality disorder to all groups. Harrell et al. (2014) also used Latent Profile Analysis to find five classes: older nasal heroin/crack smokers; older, less-educated poly-substance users; younger multi-injectors; less-educated heroin injectors; and more-educated nasal heroin. In addition, Dias et al. (2015) used factor analysis to identify three factors that predicted greater severity of cocaine use. Factor one related to age, education and gender (the lowest use seen in younger, less-educated female participants); factor two related to the extent of psychological difficulties (e.g. impulsivity and depression); and factor three was related to the use of other substances. While these findings are important and thought-provoking, such investigations are in the early stages and we need to see the same techniques repeated at all stages of addiction in order to identify the consistent themes that run through the trajectory of substance use and dependence.

### *Stimulant Dependence*

Much of the research into impulsivity in substance dependence has been conducted in stimulant users. While a considerable proportion is also conducted in alcohol dependence, there is comparatively little in opioid dependent individuals (for a review of inhibitory control, see Smith et al. 2014). Stimulant use is strongly associated with impulsivity, and it may be that other substances are not so robustly connected. The dopamine system is closely linked with increased impulsivity, and stimulants create a dopamine “rush” when taken (Volkow et al. 2011). Alone, however, the mesolimbic dopaminergic system it is not sufficient to explain the reward processes of addiction. The opioid system is related to feelings of satiation, sedation and “bliss” (Comings & Blum 2000), as well as for creating the sense of euphoria associated with heroin or alcohol (Mitchell et al. 2012), as well as amphetamine (Colasanti et al. 2012; Jayaram-Lindstrom et al. 2007). The “high” produced by a brief intense dopamine increase that is associated with stimulant intake often is not reported in nicotine and alcohol use, and, according to Daglish et al. (2008), never with opioids. As a result, substances that have less direct influence on the dopaminergic system, such as opioids and alcohol may find there is less of a role for impulsivity in their dependence.



Accordingly, **Study 1** conducted exploratory analyses that regrouped polydrug dependent participants based on their substance use history and found that only when the groups were divided on the presence or absence of stimulant dependence, but not of alcohol or opioid dependence, was there a difference in the scores of impulsivity self-report measures. Similarly, **Study 2** found a greater incidence of stimulant dependence history in AbD participants who scored higher on self-report measures of impulsivity (High AbDs). Some also argue that stimulant dependent individuals are fundamentally different to those dependent on opioids (Baldacchino et al. 2015) as they show differences on behavioural tasks (Badiani et al. 2011; Vassileva et al. 2014), in particular that cocaine dependent individuals show greater risk taking than heroin dependent individuals (Bornovalova et al. 2005). Future research should investigate this link further so as not to assume that all drug users are the same as highly impulsive stimulant dependent individuals.

### *Control Participant Recruitment*

As with any investigation of mental health disorders, unaffected control participants are recruited as a comparison group. Consequently, it is necessary to match control participants to the experimental group as much as possible on factors such as age, IQ and education to ensure that any group differences found are really due to addiction. However, mental health disorders are often comorbid with addiction (Conway et al. 2006), meaning that many substance dependent participants also have complex mental health histories. Arguably, control participants should also be matched (where possible) on mental health histories to ensure we are measuring differences relating to addiction and not, for example, to the propensity for depression.

The same issue arises when recruiting control participants with little or no history of drug use. Only 16-17% of people who use substances develop dependence (Wagner 2002), with many never experiencing any problems at all. If we recruit control participants with no experience of substance use, how do we know that they are different from those that become dependent? Karen Ersche and colleagues (e.g. Morein-Zamir et al. 2015; Smith & Ersche 2014) have begun to investigate the difference between those who can use stimulants regularly without problem and those who succumb to dependence, which is arguably of fundamental importance to the understanding of addiction. However, such

research into drug (but not alcohol) use is at a very early stage, while the study of alcohol use and dependence is particularly valuable in this instance as the prevalence and social acceptability of its use enables researchers to study the early pre-dependence stages without the legal connotations surrounding other substances.

### **3.2.4: Levels of Measurement and Methodological Considerations**

Another important point that has been raised by this thesis regards the levels of measurement used for the study of addiction: self-report, behavioural and neural measures. Both **Study 1** and **Study 4** demonstrated how each level plays an important role at the different stages of addiction. For example, these studies detected neural differences that were not seen behaviourally, as is also reported in cannabis dependent individuals who show neural responses during inhibitory control that are functionally distinct from controls in spite of no behavioural differences (Tapert et al. 2007). Furthermore, **Study 1** indicated that self-report measures were generally more sensitive in AbDs than behavioural measures of impulsivity. This too is also reported by others, for example Vonmoos et al. (2013) found increased self-report, but not behavioural, impulsivity in recreational cocaine users. On the other hand, a study of recently abstinent participants found that behavioural measures better predicted risk of relapse than self-report measures (Stevens et al. 2015). This evidence suggests that each level of measurement has its own utility at the various stages of addiction. As a result, we should take advantage of these differences and apply them appropriately in order to improve our understanding of each stage of addiction.

For example, a potential explanation for the sensitivity of self-report compared to behavioural measures in **Study 1** is that the former assesses aspects of impulsivity that are more influential at this later stage (long-term abstinence). This suggests that not all measures of impulsivity are necessarily appropriate at all stages of substance use and dependence, and perhaps should be treated separately in order to understand the role played by each facet of impulsivity at every stage. The greater sensitivity of self-report measures in **Study 1** suggests not that self-report measures are better (in fact, there are many arguments for why they are worse, see Verdejo-Garcia et al. 2008 for a discussion on the advantages and disadvantages of self-report compared to behavioural measures), but that these are the only measures that are currently able to detect differences between

long-term AbDs and control participants. Currently there are few aspects of impulsivity that can be measured at all three levels of measurement. As a result, researchers should use a battery of measures when testing impulsivity in order to incorporate a variety of different aspects and thus produce multi-task behavioural indices of addiction (Sharma et al. 2014).

Meanwhile, we also need to consider what distinguishes self-report from behavioural and neural measures. One explanation may be that the self-report measures are assessing “hot” cognition, involving reasoning and motivation that are influenced by emotion. For example, in conjunction with the non-emotional subscales of Premeditation and Perseverance, the UPPS Impulsive Behaviour Scale (Whiteside & Lynam 2003) also measures Positive and Negative Urgency. These latter two constructs specifically assess the regulation of behaviour in the context of extreme positive or negative affect respectively, and are likely responsible for some of the differences detected between controls and AbDs in **Study 1**. In contrast, many behavioural measures of impulsivity, such as with the GNG task, assess logical and rational “cold” cognition that has little relation to emotion. Involvement of hot cognitive measurements, including those incorporating substance-related cues (as seen in Studies 3 and 4 with approach and avoidance of alcohol-related images), particularly relate to vulnerability for dependence as well as craving- and stress-induced relapse.

This is where the difference between non-specific and cue-specific tasks comes into play. By introducing drug-relevant elements into these tasks, they become more applicable to the processes involved in addiction. All the behavioural tasks used in Studies 1 and 2 were non-specific to substance dependence, only detecting very subtle differences at the neural level. The SST, GNG and IED are cold measures. Although the Kirby involves the salient cue of money, this is a hypothetical cue and framed in such a way as to encourage a calculation strategy rather than an emotional response. However, Studies 3 and 4 did include alcohol cues, but still detected no group differences, which rather undermines this argument. Nevertheless, the discussion in **Study 3** as well as earlier sections of this final chapter have provided potential reasons for the lack of differences found that relate to the different stages within a trajectory of substance use and dependence.

### 3.3. Limitations and Future Directions

Inevitably, this thesis has a number of limitations. The first of which was that, while I have proposed a longitudinal theory of substance use and dependence with different neurocognitive profiles at each stage, the four studies that make up this thesis only sampled individuals from two of the five stages. Consequently, I have been unable to confirm this theory or to account for which specific aspects of impulsivity correspond to each stage. While future efforts should be made to substantiate this theory, researchers should also be encouraged not to treat impulsivity as one construct or to assume that one measure alone is sufficient when investigating the role of this multifaceted construct in addiction. Furthermore, neurocognitive investigation of addiction in general would benefit from the creation of behavioural measures that account for the emotion-relevant constructs often seen in self-report measures of impulsivity, such as positive and negative urgency.

Secondly, while **Study 1** attempted to use a number of different measurements of impulsivity, it was not completely comprehensive. Realistically, the time constraints of research limit the number of measures that can be used. Consequently, the ICCAM Platform Study (of which Studies 1 and 2 were a subset) restrained the number measures of impulsivity to those that were deemed most appropriate for the questions of the overall study. The restrictions of the ICCAM Platform Study protocol also meant that recruitment of substance dependent participants for Studies 1 and 2 was limited to long-term abstinent individuals.

Similar limitations were also encountered in the recruitment of only heavy drinkers into Studies 3 and 4. The addition of a current dependent group may have been more informative as it would have provided an additional stage along the trajectory of substance use and dependence. Unfortunately, the difficulties in recruitment of currently dependent participants who are not intoxicated or in serious withdrawal meant that this was not possible within the time frame. An alternative approach would be to recruit recently abstinent individuals, although this would be less informative for the understanding of the process of development into addiction as these individuals will arguably have a different relationship with alcohol. Nevertheless, investigation of current dependent participants

using neurocognitive paradigms would be very beneficial to our understanding of addiction, if the confounds of intoxication and withdrawal could be addressed adequately. Thirdly, it is likely that the recruitment of the heavy drinking individuals introduced a bias as a large proportion of eligible individuals were unable to participate because their working hours (usually 9am-5pm) coincided with the opening hours of the MR scanner. This perhaps explains why so many studies into “heavy drinking” are conducted in students. Less time-consuming investigations or surveys that can be conducted over the internet are better able to recruit a more representative sample of established heavy drinkers, although it is possible that these would make up yet another profile of substance use.

And finally, due to the limiting factor of time, there was no neural assessment of stress induction in **Study 4**. While this is pure speculation, we might have found that the increased dlPFC activation in the heavy drinkers increased following stress induction and that the insula activation for active avoidance following stress was even greater in those with higher anxiety scores.

### *Outstanding Issues*

The main question that this thesis was not able to answer concerned the role of stress. **Study 3** did not find a differential effect of stress induction on appetitive and aversive behaviour in heavy drinkers. This is perhaps because the sample was relatively small, in which only a minor proportion were susceptible to stress induction. In fact, as Becker et al. (2012) suggest, there may be two separate types of individuals, one whose substance use (in this case alcohol use) is driven by a sensation seeking personality, and another that is more susceptible to stress (self-medicating). While **Study 2**’s reclassified AbDs did not reflect these two routes into dependence, these may be more apparent in established heavy drinking individuals who are at a less advanced stage of the substance use trajectory.

Further questions also arose during the completion of this research. Although this could not be quantified within the restraints of the protocols of these studies, it became apparent that affective disorders were prevalent in both AbD and heavy drinking participants. In particular, the AbDs recruited for **Study 1** (and **2**) often reported either self-medicating or sensation seeking reasons behind their initial drive for substance use,

reflecting the two-route model of addiction proposed by Becker and colleagues (2012) and initiated the attempt to regroup participants in **Study 2**. Consequently, future research should be directed at systematic investigations of anxiety and depression within substance dependent populations.

It also became apparent while conducting **Studies 3** and **4** that heavy drinking participants often reported not insignificant drug use in addition to their substantial alcohol consumption. In fact, a number of potential heavy drinking participants were excluded due to current or past excessive substance use. Furthermore, many of these heavy drinking individuals had complex mental health histories. While this complicated recruitment of suitable participants, it highlights an important area for future research as, generally speaking, the individuals with the most complex mental health histories also used the most substances.

### *Future Studies*

There are many directions for further investigations to continue the research presented in this thesis, of which the theory of a trajectory of substance use is an obvious choice. Future investigations could begin with a broad study sampling individuals from the five proposed stages along the trajectory: social use, heavy use, dependence, recent abstinence and long-term abstinence. This could be achieved using online surveys to facilitate recruitment of large sample sizes, making use of self-report measures, particularly in studies focused on alcohol use, which is extremely prevalent. A data-driven approach could then be used to identify profiles at each of these stages. This would also enable comparison of profiles at each stage. Additional demographic information as well as data on substance use, including the length and extent of use should also be collected in order to provide useful markers that may relate to these profiles.

The information collected from this first project would inform later investigations using much smaller samples from each of the different stages along the trajectory. These investigations would assess the specific neurocognitive mechanisms relating to the profiles identified in the previous project and evaluate their validity. A particular focus of these

secondary studies should be to assess the aversive and appetitive motivations as they change at the different stages along the trajectory.

### **3.4. General Conclusions**

The aim of this thesis was to investigate the role of affective impulsivity in substance dependence. This was a two-stage process: firstly through the investigation a number of different aspects of impulsivity in a large group of abstinent substance dependent individuals; and secondly by focussing on pre-dependent alcohol use to investigate the role of appetitive and aversive processes in the development of addiction.

These investigations examined four hypotheses. Firstly, that not all the current methods for measuring impulsivity in substance dependent individuals are appropriate at every stage of dependence, or for each participant group. This is apparent throughout this thesis, particularly in **Study 1**, where self-report measures were found to be more sensitive to differences between controls and AbDs than behavioural or neural measures. The second hypothesis was that current classifications of substance dependent individuals based on primary substance do not best reflect the different profiles with addiction. Using a data-driven approach, two groups were identified that were divided by high and low scores across both impulsivity and affective measures. Significant differences between these groups reflected experience of childhood adversity and a history of stimulant dependence. However, this was only at the level of AbDs and may not reflect the differences in drug users at all the stages of substance use and dependence. The third hypothesis was that stress plays an influential role in the development of alcohol dependence through the process of negative reinforcement. There was no differential effect of stress on automatic approach and avoidance mechanisms in heavy drinking individuals compared to controls. Nevertheless, a longitudinal theory of substance use and dependence is proposed as an explanation that highlights the presence of a number of different stages along a trajectory of drug use, on which these heavy drinkers are at a more advanced stage than those in many previous studies. Finally, the hypothesis that differential neural processing of automatic approach and avoidance behaviour is involved in the early stages of substance dependence was supported in appetitive but not aversive responses within heavy drinkers.

Although more questions are raised by this thesis than are answered, conclusions indicate that current impulsivity research into substance dependence is in need of clarification and is restricted by the limitations of the measures available. The introduction of more appropriate behavioural measures that reflect differences between the stages of dependence would not only improve knowledge of addiction, but also of the individual differences within the substance using and dependent population. This thesis should be used as a blueprint to guide future research, specifically on the trajectory of substance use and dependence and on the different neurocognitive profiles at each stage, which will have implications for the treatment and prevention of substance dependence.



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## Appendix

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