

**Psychotic-like symptomatology and reward responsivity in  
chronic ketamine and cannabis users**

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**UCL Doctorate in Clinical Psychology****Thesis declaration form**

I confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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## **Overview**

This thesis assesses psychotic-like symptomatology and reward responsivity in chronic users of two illicit drugs, cannabis and ketamine. As use of these drugs is steadily increasing, with cannabis being the most widely used drug worldwide (following alcohol, caffeine and tobacco) and the recent proliferation of ketamine misuse in parts of Asia, Europe and the United States, it is important to examine the effects of their habitual use. While research has linked cannabis use to sub-clinical psychotic-like symptoms, longitudinal studies examining the association between cannabis use, psychotic-like symptoms and transition to psychosis have revealed mixed findings. Additionally, although acute ketamine administration has been shown to produce psychotic-like symptoms in drug-naïve volunteers, there has been less research on the effects of chronic ketamine use.

Part 1 of the thesis is a literature review investigating the assessment of cannabis use in studies of individuals meeting clinical ‘high risk’ criteria for transition to psychosis. It examines measures of cannabis use, as well as findings regarding the association between cannabis and subsequent conversion to psychosis. It also examines whether such studies measured further significant outcome variables, such as social and role functioning. Finally, the literature review considers the limitations in how cannabis use has been assessed and the implications of this for future research on the extent to which cannabis influences the development of psychotic-like symptomatology and risk of conversion to frank psychosis.

Part 2 of the thesis comprises an investigation of symptoms of prodromal psychosis and reward responsiveness in three groups – chronic users of cannabis, ketamine, and

healthy controls. This investigation formed part of a joint project conducted with one other trainee clinical psychologist examining the chronic effects of cannabis and ketamine use on psychosis proneness and cognitive functioning.

The empirical paper reports a between subjects study, comparing 20 cannabis users, 20 ketamine users and 20 healthy controls on a number of self-report measures indexing depression (BDI-II), psychosis-like symptoms and schizotypy (PQ-B and O-LIFE), and trait anhedonia (TEPS), and on two laboratory-based tasks assessing reward sensitivity (the 'Probabilistic Reward Task') and effort-based decision making (the 'Effort-Expenditure for Rewards Task'). Both drug using groups were found to have higher levels of schizotypy (O-LIFE) and positive psychosis symptomatology (PQ-B) than controls, while group differences were found on the probabilistic reward task, with controls demonstrating greater response bias than cannabis users and greater discriminability than ketamine users. No group differences were found on the effort-based decision-making task.

A critical appraisal of the research forms Part 3 of the thesis. It describes the process of working collaboratively on the project rationale and design, reflections on recruiting and working with drug using participants, and thoughts on clinical implications of the project.

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## **Part 1: Literature Review**

**How has cannabis exposure been measured in studies investigating its role in risk of transition to psychosis?**

**Abstract**

**Background:** Cannabis use has been associated with the development of psychotic-like symptoms that characterise prodromal psychosis, the period marked by changes in functioning and sub-threshold psychotic-like symptoms that is thought to precede onset of frank psychosis. While studies have suggested an association between cannabis and the development of psychosis, the nature of the relationship remains unclear.

**Aims:** The aim of the current review was to examine how cannabis use is assessed in studies of ‘clinical high risk’ individuals at risk of transition to psychosis, and to ascertain the reported relationship between cannabis use and subsequent transition in these samples. It also reported on whether other significant outcome variables (e.g. functioning) were linked with cannabis use.

**Method:** A computerized literature search of PsycINFO and PUBMED databases was performed with the following keywords: cannabis, psychosis, positive symptoms and negative symptoms, prodrome, mania, bipolar disorder, schizoaffective disorder, schizophrenia, basic symptoms, and ultra-high risk. Studies were selected from those published between 2005 and June 2015, and the main exclusion criterion was non-human studies.

**Results:** There were few recent studies of individuals at high risk of transition to psychosis which assessed cannabis use and these were found to vary widely in measurements of cannabis exposure, making valid between-study comparisons difficult. The majority of studies did not find a relationship between cannabis use and

transition to psychosis. Most studies also did not include longitudinal assessment of other major outcome variables in their analyses.

**Conclusion:** Currently, the literature examining cannabis use in clinical high risk individuals is minimal and is hindered by a lack of detailed and consistent methods of assessing cannabis use. Many of these studies report no association between cannabis use and risk of conversion to psychosis, which may be a result of sample characteristics. Yet while the association may be weak, research among first-episode patients continues to suggest vulnerability for psychosis among cannabis-using individuals. Studies that undertake more comprehensive assessments of cannabis use and which map distinctive patterns of use are necessary. Such studies would benefit from incorporating objective, biological measures of cannabis use, controls for confounding variables such as use of other drugs and medications, and longitudinal assessments, including changes in use and functioning and other clinical outcomes over time.

## **How has cannabis exposure been measured in studies investigating its role in risk of transition to psychosis?**

### **1. Introduction**

#### *1.1 Overview*

Comorbid drug misuse and mental illness is common worldwide and presents serious obstacles for effective treatment, leading to poorer outcomes in the treatment of both primary psychiatric disorders and drug dependence (Carey et al, 1991; Hunt, Bergen & Bashir, 2002; Weaver et al, 2003). Individuals with psychotic illnesses have particularly high rates of comorbid substance misuse, with prevalence estimates suggesting that up to half of schizophrenic patients may also have substance use disorders, including higher rates of alcohol, tobacco, cannabis dependence, as well as use of other illicit drugs, and that the risk of substance use in schizophrenics is 4.6 times that of the general population (Dixon, 1999; Mueser et al, 1990; Regier et al, 1990; Volkow, 2001). Research suggests that the prevalence of comorbid substance use disorder in psychotic populations is moderated by clinical, demographic and socio-cultural variables (Lambert et al, 2005).

While prevalence studies suggest that drug use has decreased among children and adolescents in recent decades, alcohol and illicit drugs are widely available to these age groups and are viewed as a veritable rite of passage among adolescents, with the available opportunity to use illicit drugs reported by over 80% of US adolescents in the early 2000s (Currie, Small & Currie, 2005; NHS Information Centre, Lifestyle Statistics, 2011; Swendsen et al, 2012; Watson, Benson & Joy, 2000). Numerous studies have suggested that adolescence is a crucial developmental period implicated in the onset of mental illness and in risk of transition to psychosis (Kessler et al, 2007; McGorry, Purcell, Goldstone & Amminger, 2011).

Cannabis is the most widely used illicit drug worldwide, with psychosis patients frequently reporting using cannabis more than any other drug (Addington et al, 2013; Burns, 2013). Apart from its ability to induce transient psychotic-like symptoms from acute intoxication, long term use of cannabis has been linked to psychosis (D'Souza et al, 2004). Research suggests that earlier cannabis use among young people is associated with increased risk of conversion to frank psychosis and earlier onset of psychosis, although the mechanisms of these associations are as yet unclear (Arsenault et al, 2002; Casadio, Fernandes, Murray & di Forti, 2011; di Forti et al, 2014; Stefanis et al, 2013). Cannabis use has also been linked with earlier onset of sub-clinical psychosis-like symptoms, with studies suggesting that cannabis use prior to psychiatric symptoms may be linked to earlier age of onset and higher reported levels of prodromal symptoms in both first-episode psychosis patients and non-clinical populations (Compton et al, 2009; Fergusson, Horwood & Ridder, 2005).

Research on prodromal psychosis is important as it can improve knowledge of risk factors implicated in subsequent transition to psychosis and therefore inform treatment strategies for those at greater risk of transition. The prodromal period has been conceptualised as a period before the onset of frank psychosis, characterised by changes in functioning and sub-threshold, frequently self-experienced, symptoms, including changes in drive, motivation, cognition and emotion (Yung et al, 2005). As much research on the psychosis prodrome has been done retrospectively (i.e. in first-episode psychosis patients), it is difficult to reliably predict the duration and severity of symptoms that characterise this period (Yung et al, 1998; Yung et al, 2005). Nonetheless, researchers have developed the construct of the clinical 'high risk' state for psychosis, which encompasses the trajectory of symptomatology commonly present before psychosis; this 'high risk' state has also been referred to as the 'at-risk

mental state' (or 'ARMS'), the 'prodromal' period, and the 'ultra-high risk' (or 'UHR') state (Fusar-Poli et al, 2013; Schultze-Lutter, Schimmelmann & Ruhrmann, 2011; Yung, Phillips and McGorry, 1998).

This prodromal period or trajectory begins with an early pre-morbid phase during which initial changes may only be detectable to the individual himself, followed by what is considered to be the early prodromal phase, marked by 'basic symptoms' – subtle self-experienced deficits (e.g. in affect, such as increased anhedonia and depression) that may continue to be present throughout the course of the prodromal period (Yung et al, 2005). 'Attenuated positive symptoms' mark the late prodromal period, which include the presence of subthreshold overt or positive symptoms, such as ideas of reference, perceptual disturbances, etc. but at a frequency and intensity that would not meet diagnostic criteria for frank psychosis (Fusar-Poli et al, 2013; Yung et al, 2005). Brief limited intermittent psychotic episodes ('BLIPS' or 'BIPS') may also occur during this late prodromal period and are defined as transient psychotic episodes lasting less than one week (e.g. unusual thought content, disorganised speech, unusual perceptual experiences, etc.), occurring together with functional decline or sustained low functioning (Olsen & Rosenbaum, 2006). Finally, transition to frank psychosis is indicated by increased intensity and duration of these symptoms coupled with functional decline.

### *1.2 Rationale for the current review*

Given the concerning potential for sub-threshold psychotic symptomatology to lead to psychosis, and the possible influence of cannabis in exacerbating such symptoms or reducing the age of onset of psychosis, it is important for researchers to examine this relationship between cannabis, prodromal symptoms and risk of

transition (Minozzi et al, 2010). A recent review of such studies suggests that there are several key factors involved in the pathways from cannabis use to transition to psychosis, including early, recent and lifetime use of cannabis, and genetic vulnerability to psychosis (Burns et al, 2013). Hypotheses attempting to explain the association suggest that the relationship may be: (1) confounding (i.e. factors other than cannabis use are responsible for conversion), (2) that there is an interaction (i.e. cannabis use is in part a cause, with other vulnerability factors influencing conversion), (3) that people with psychosis or psychotic-like symptoms may be more likely to use cannabis as a form of self-medication, and (4) that cannabis alone may cause psychosis (Minozzi et al, 2010). Yet while there may be an increased risk of psychotic symptomatology in cannabis users, there remain significant limitations in the literature as to the precise relationship between cannabis and psychosis, and whether the relationship is in fact causal to some degree (Minozzi et al, 2010; Richardson, 2010). Among these limitations, which include differences in methodological quality, populations studied and outcomes analysed, differences in how cannabis use has been measured are significant.

Temple, Brown & Hine (2010) argue that significant limitations in the measurement of cannabis exposure impede researchers' ability to draw conclusions about harms and risk associated with cannabis use. Such limitations include variability in cannabis use measurement, such as lack of detail on rates of use, focus on self-report or retrospective reports, inclusion/exclusion of dependence measures, lack of objective measures which are also limited in measuring historical use; the classification of users, e.g. lifetime, frequent, 'regular', recreational users; and assumptions about consumption and dosage (i.e. more frequent use is often assumed to mean higher dose, irrespective of amount, type or potency of cannabis used)

(Temple et al, 2010). Studies such as those mapping the relationship between cannabis and psychosis may also be limited by confounds in recruitment methods. Control groups may differ in significant other ways from cannabis users which are not measured, particularly when cannabis use among peers is normative behaviour (Temple et al, 2010). Therefore, in the field of high risk treatment-seeking individuals, the risks associated with cannabis use generally might be inflated as the focus is on a constellation of specific symptoms for which users are seeking help; such studies may overlook the prevalence of cannabis users with schizotypal traits or psychotic-like symptoms that are not problematic and risk amplifying the alleged association between cannabis and psychosis.

### *1.3 Aims*

The purpose of the current review is to critically investigate how cannabis exposure has been measured in studies linking its use to the development of psychosis. Given the recent emergence of studies utilising the ‘high risk’ construct to examine pathways to conversion to psychosis, it was decided to limit the review to more recent studies which examined the role of cannabis in *transition* to psychosis rather than simply to the risk of developing psychotic symptomatology, traits or sub-threshold symptoms without conversion to frank psychosis. Thus the focus was on studies that prospectively followed individuals that initially presented as high-risk and addressed the issue of whether or what proportion subsequently transitioned to psychosis throughout the course of the study.

The main aims of this review were to examine the following areas:

- To assess how cannabis use is measured, including the reliability and validity of measures of cannabis use in longitudinal studies of at risk individuals

- Was cannabis found to be significantly associated with conversion to psychosis?
- Apart from conversion from an at-risk mental state to psychosis, what other significant outcome variables were assessed (e.g. functioning)?

An examination of these areas in the included studies will be followed by a discussion of the limitations in the methods used to assess cannabis use.

## **2. Review Methodology**

### *2.1 Search*

A search of the relevant literature was carried out using the following keywords: cannabis, psychosis, positive symptoms and negative symptoms, prodrome, mania, bipolar disorder, schizoaffective disorder, schizophrenia, basic symptoms, and ultra-high risk. The truncated keyword ‘prodrom\*’ was also included to include both ‘prodrome’ and ‘prodromal’. These words were entered into the thesaurus function in PsycInfo to ensure similar relevant terms were searched. The AND/OR functions were used to combine search terms and results were limited to human studies published in English peer-reviewed journals between 2004 and the current date (2015). The date limitation was employed as the concepts of prodromal psychosis and ‘at risk’ mental states for conversion to psychosis are recent constructs which have only begun to be formally investigated following the development of several measures since the early 2000s. Therefore the focus of the current review is on more recently published studies.

PubMed was also searched using the same criteria to ensure inclusion of further relevant studies; the majority of results from this search were duplicates, which were

excluded. No other relevant articles were found using PubMed. (See Appendix 1 for details of searches.) A hand-search of articles and relevant authors appearing in reviews was also carried out.

## 2.2. *Exclusion criteria*

While studies that examined onset of high risk symptoms (or criteria that would classify cannabis users as ‘ultra-high risk’) were interesting and clinically relevant, those that did not go on to examine subsequent transition to psychosis were excluded. Further exclusion criteria were as follows: qualitative studies, studies with no reference to cannabis, studies focusing largely or exclusively on genetic mapping, psychiatric case studies, studies which focused on anti-psychotic medications, fMRI and other brain-scanning studies, studies not focusing specifically on cannabis and transition to psychosis (e.g. prevalence rates of cannabis use and/or clinical course of psychotic symptoms among patients with enduring psychoses; therapies for cannabis use disorder), studies of synthetic cannabis use, studies focusing exclusively on cannabis-induced psychosis, and studies on acute cannabis administration.

## 2.3 *Inclusion criteria*

Inclusion criteria were: *i*) studies of individuals considered ‘at risk’ (e.g. ‘ultra-high risk’ or ‘clinical high-risk’) based on clinical assessment, *ii*) those which assessed participants’ cannabis use, and *iii*) studies which included a longitudinal design to assess rates of transition of these high-risk samples to frank psychosis.

Studies were included if they used established diagnostic measures to assess ‘at-risk’ mental states. These included the Structured Interview for Prodromal Syndromes (SIPS, which contains the Scale of Prodromal Symptoms, SOPS; Miller et

al, 1999; 2002), the Comprehensive Assessment of the At-Risk Mental State (CAARMS; Yung et al, 2005), and the Schizophrenia Proneness Instrument – Adult Version (SPI-A; Schultze-Lutter, Addington, Ruhrmann, & Klosterkötter, 2007) or the Bonn Scale for the Assessment of Basic Symptoms – Prediction List (BSABS-P, Schultze-Lutter, & Klosterkötter, 2002), an abbreviated version of the SPI-A. These instruments are internationally recognised and validated measures for the diagnosis of ‘at-risk’ mental states, profiles of prodromal symptomatology which incorporate risk factors implicated in possible conversion to psychosis (Yung et al, 2004).

#### *2.4 Diagnosing high risk states*

Despite individual variation, measures which diagnose ‘high risk’ mental states, and thus increased vulnerability for the development of psychosis, require inclusion in at least one of several categories, including ‘attenuated positive symptoms’ (APS), ‘brief intermittent psychotic symptoms’, ‘genetic risk and deterioration’, and ‘Basic Symptoms’ (Addington & Heinssen, 2012). The ‘attenuated positive symptoms’ category includes individuals who experience a minimum of one positive psychotic symptom (e.g. grandiose ideas, perceptual abnormalities, etc.) for at least one week in the past three months, but at a sub-threshold level for frank psychosis (Miller et al, 2002). ‘Brief intermittent psychotic symptoms’ involves the presence of at least one positive psychotic symptom experienced in the past three months ostensibly meeting threshold for psychosis but at a lesser frequency, i.e. lasting less than one week, and spontaneously remitting (Yung & McGorry, 1996a). ‘Genetic risk and deterioration’ requires both functional decline (defined as a  $\geq 30\%$  reduction in functioning as assessed by the Global Assessment of Functioning scale, GAF-M) for at least one month in the previous year together with having either a close relative with a

psychotic disorder or having schizotypal personality disorder, as diagnosed by DSM-IV (Ruhrmann et al, 2010). The ‘basic symptoms’ approach defines individuals at risk based on subtle self-experienced disturbances in cognition, perception and speech which do not meet threshold for psychosis symptomatology and are thought to be present from the earliest prodromal phase (Klosterkötter, Hellmich, Steinmeyer & Schultze-Lutter, 2001; Ruhrmann, Schultze-Lutter & Klosterkötter, 2003).

### **3. Results**

The initial search produced 1244 potentially relevant articles. Studies that were initially considered from this pool fell largely into two categories: those that examined the association between cannabis use and factors relating to expression of psychotic illness (e.g. age at onset in presentations of first-episode psychosis patients) and those that examined cannabis use in relation to psychotic symptoms (e.g. during prodromal period, prior to illness onset), sometimes including consideration of eventual transition to psychosis. These studies were grouped according to population and design and assessed for inclusion if they in some way assessed the relationship between cannabis use and subsequent transition to psychosis. Potential studies largely fell into several categories: those that assessed first-episode psychosis patients (tending to collect information on substance use at intake and retrospectively), general population-based studies (e.g. assessing incidence of psychotic-like symptoms and substance use in samples from the general population, or longitudinally), and studies of individuals considered ‘high-risk’ (i.e. fulfilling clinical criteria to be considered higher risk for the development of psychosis, e.g. ‘ultra-high risk’), often assessing cannabis and other substance use cross-sectionally, but also followed over time to track rates of transition to psychosis.

Based on the inclusion and exclusion criteria, 11 studies were selected which reported on cannabis use in individuals defined as ‘at risk’ for the development of psychosis, and which referred to transition to psychosis (see Table 1). One article from 2013 was found which reviewed 10 studies assessing substance use in clinical high risk for psychosis populations (Addington et al, 2014). These studies were assessed and seven which included assessment of cannabis were included in the present review; one was excluded because it pre-dated inclusion criteria (i.e. published within past ten years), one because it did not report on substance abuse or dependence, and one because it did not report on cannabis use (Phillips et al, 2002; Ruhrmann et al, 2010; Thompson, Nelson & Yung, 2011). In addition to these seven studies, four more recent studies were identified as meeting inclusion criteria (see Table 1).

**Table 1.** Research studies assessing cannabis use and transition to psychosis in clinical high risk samples, 2005-2015

Study	High risk population studied	High-risk sample size (n)	Comparison Group?	Mean age per group	Duration of follow-up (months)	Frequency of follow-up	High-risk criteria	Number of high-risk conversions to psychosis (n and % of high-risk sample)
Auther et al, 2012	Recognition and Prevention (RAP), New York, USA	101 (66 M, 35 F)	59 controls (30 M, 29 F)	CHR = 16.09 controls = 16.15	35.64 (mean)	6 month intervals, or when conversion thought to have occurred	SOPS	15* (14.9%)
Buchy et al, 2014	Enhancing the Prospective Prediction of Psychosis' (PREDICT), Canada and USA	170 (96 M, 74 F)	none	non-converters = 19.8 converters = 19.7	48	not reported	SIPS (COPS)	29 (17.1%)
Buchy et al, 2015	North American Prodrome Longitudinal Study 2 (NAPLS-2), Canada and USA	735 (423M, 312 F)	278 controls (140 M, 138 F)	CHR = 18.5 controls = 19.6	24	6 month intervals	SIPS (COPS)	90 out of 362 UHRs assessed at 24 month completion (24.9% completers)
Cannon et al, 2008	North American Prodrome Longitudinal Study 2 (NAPLS-2), Canada and USA	291 (170 M, 121 F)***	134 matched controls	18.10	up to 30	6 month intervals	SIPS	82 (out of 291, or 28.2%)

<b>Study</b>	<b>High risk population studied</b>	<b>High-risk sample size (n)</b>	<b>Comparison Group?</b>	<b>Mean age per group</b>	<b>Duration of follow-up (months)</b>	<b>Frequency of follow-up</b>	<b>High-risk criteria</b>	<b>Number of high-risk conversions to psychosis (n and % of high-risk sample)</b>
Corcoran et al, 2008	Centre of Prevention and Evaluation (COPE), New York, USA	32	none	drug users = 20.9 non-users = 17.4	up to 24	3 month intervals; total varied per participant	SIPS	n not reported; no differences in conversion rates between drug users vs. non-users
Dragt et al, 2010	Dutch Prediction of Psychosis Study, Amsterdam, Netherlands	68 UHRs (47 M, 21 F)	none	19.00	range: 2.5-37	not reported	SIPS and/or BSABS-P	17 (25%)
Dragt et al, 2012	European Prediction of Psychosis Study, Germany, Finland, Netherlands and England	242 CHRs	none	cannabis users = 22.9 non-users = 22.3	18	9 month intervals	SIPS and/or BSABS-P	37 (15.3%)
Korver et al 2010	Dutch Prediction of Psychosis Study, Amsterdam, Netherlands	63 UHRs (42 M, 21 F)	58 controls (28 cannabis users, 30 non-cannabis)	cannabis UHRs = 20.4, non-cannabis UHRs = 18.8 cannabis controls = 21.6 non-cannabis controls = 19.8	36	in-person at 9, 18, and 24 months, by telephone at 36 months; total varied per participant	SIPS and/or BSABS-P	17 (27%)
Kristensen & Cadenhead, 2007	Cognitive Assessment and Risk Evaluation (CARE), San Diego, USA	48 'at risk' patients (26 M, 22 F)	none	18.60	24	1 month intervals	SIPS	6 (12.5%)**

<b>Study</b>	<b>High risk population studied</b>	<b>High-risk sample size (n)</b>	<b>Comparison Group?</b>	<b>Mean age per group</b>	<b>Duration of follow-up (months)</b>	<b>Frequency of follow-up</b>	<b>High-risk criteria</b>	<b>Number of high-risk conversions to psychosis (n and % of high-risk sample)</b>
Russo et al, 2014	CAMEO, Cambridgeshire, England	60 HRs (31 M, 29 F)	60 controls (26 M, 34 F); address-matched	high-risk = 19.89 controls = 22.60	24	3 month intervals	CAARMS	3 (5%)
Valmaggia et al, 2014	Outreach and Support in South London (OASIS), London, England	182 UHRs (104 M, 78 F)	none	22.90	24	at 24 months	'UHR' criteria (as in SIPS and CAARMS)	26 (14.3%)

\* Auther et al (2012) did not report number of conversions to psychosis in main paper, only in abstract.

\*\* Analyses performed on transitions within one year, not 2 year study duration.

**Table 2.** Details of cannabis use assessment in studies assessing cannabis use and transition to psychosis in clinical high risk samples, 2005-2015.

Study	Cannabis use measures at baseline	Details on cannabis use assessment	Primary cannabis measure used in analyses of transition	Cannabis use re-assessed at follow-up?	Objective cannabis measure details	Reported on cannabis dependence?	Cannabis-psychosis analyses controlled for use of other drugs?	Reports on anti-psychotics?
Auther et al, 2012	KSADS-E	Lifetime cannabis use and use in past 6 months	Lifetime cannabis use/abuse	Yes	None reported	Yes - dependence was exclusion criterion	Yes	No
Buchy et al, 2014	DUS	Severity of use	Severity of cannabis use in past month (DUS)	No	Not assessed	Yes	Unclear	Yes - use of anti-psychotics was exclusion criterion
Buchy et al, 2015	SCID, DUS and cannabis use questionnaire	Severity of use and detailed assessment of rates and patterns of use over lifetime	Severity of cannabis use in past month (DUS)	Yes (DUS only)	Not assessed	Yes - dependence was exclusion criterion	Yes	Somewhat - use of anti-psychotics was exclusion criteria for controls only
Cannon et al, 2008	SCID or KSADS-PL	N/A - assessed 'substance abuse'	History of substance abuse (DSM-IV diagnoses)	No	None reported	No ('substance abuse')	N/A	Somewhat - proportion were enrolled in studies of anti-psychotics and other treatments, but no further information on medication provided
Corcoran et al, 2008	K-SADS-PL (ages 12-15), DIGS (16+) & cannabis use in past 30 days	Lifetime use at baseline and use in past 30 days at follow-up	N/A (cannabis use assessment was not analysed in relation to transition)	Yes	None reported	Yes	Yes	Somewhat - mentions anti-psychotics but no detail provided; controlled analyses for use of medication

<b>Study</b>	<b>Cannabis use measures at baseline</b>	<b>Details on cannabis use assessment</b>	<b>Primary cannabis measure used in analyses of transition</b>	<b>Cannabis use re-assessed at follow-up?</b>	<b>Objective cannabis measure details</b>	<b>Reported on cannabis dependence?</b>	<b>Cannabis-psychosis analyses controlled for use of other drugs?</b>	<b>Reports on anti-psychotics?</b>
Dragt et al, 2010	CIDI and DSM-IV	Lifetime use, age at onset of frequent use	Lifetime cannabis use/abuse	No	None reported	Yes	Somewhat - use of 'hard' drugs was exclusion criteria; no discussion of nicotine or alcohol use	No
Dragt et al, 2012	CIDI and DSM-IV	Lifetime cannabis use and cannabis use disorder	Lifetime cannabis use and cannabis use disorder	No	None reported	Yes	Somewhat - use of 'hard' drugs was exclusion criteria; no discussion of nicotine; controlled for 'alcohol use disorder' in analyses (on which groups differed significantly)	Yes
Korver et al 2010	CIDI	CHR group assessed on use, amount, onset, frequency and duration of cannabis use	Lifetime or current cannabis use at baseline	No	None reported	No	No - use of 'hard' drugs was exclusion criteria (but no objective tests reported); no discussion of alcohol or nicotine	No - some received treatment from referring mental health institutions, but no details
Kristensen & Cadenhead, 2007	SCID or KSADS-PL	Division of sample into no/minimal use w/o impairment and abuse or dependence in remission	Lifetime or current cannabis use, dependence/abuse (in remission) at baseline	Yes	Urine toxicology screen at baseline and 6-month intervals	Yes - dependence was exclusion criterion	Yes - nicotine also found to be predictive of transition and 4 of 6 conversions smoked both cigarettes and cannabis; excluded use of other drugs in past 30 days	Yes, - varied by participant (referrals made if deterioration observed and subjects were allowed to use meds)

<b>Study</b>	<b>Cannabis use measures at baseline</b>	<b>Details on cannabis use assessment</b>	<b>Primary cannabis measure used in analyses of transition</b>	<b>Cannabis use re-assessed at follow-up?</b>	<b>Objective cannabis measure details</b>	<b>Reported on cannabis dependence?</b>	<b>Cannabis-psychosis analyses controlled for use of other drugs?</b>	<b>Reports on anti-psychotics?</b>
Russo et al, 2014	Novel substance use tool	Abuse/dependence, influence on psychotic-like experiences, age of lifetime first substance use, prevalence and frequency of current and past use.	N/A (cannabis use assessment was not analysed in relation to transition as only 3% transitioned)	No	Not assessed	Yes	Yes - current alcohol use also found to be significantly higher for high-risk group	Yes ( $\geq 1$ week prior treatment with anti-psychotics was exclusion criterion)
Valmaggia 2014	Modified Cannabis Experience Questionnaire (Barkus)	Current use, age of first and last use, frequency and duration of use, and unpleasant experiences related to use	Lifetime use, frequency of use, use starting before age 15, continued use during follow-up period	Yes	None reported	No	Unclear; analyses were done separately per drug and no significant differences in transition rates between users/non-users of other drugs were found; however tobacco and alcohol were not assessed (potential confounders)	No

### *3.1 General characteristics of studies*

All of the studies reviewed were naturalistic studies of treatment-seeking at-risk individuals and all formed part of clinical programmes designed to identify and monitor those meeting criteria for ‘high risk’ status for conversion to psychosis. Six studies were based at several locations in North America, three in continental Europe and one in the UK. One study’s programme (Kristensen & Cadenhead, 2007) formed part of a larger consortium of research centres, participants from which were included in Cannon et al’s (2008) study. It was included here as more detailed analysis of the 48 participants was provided. It is assumed that the sample in one study (Dragt, 2010) formed part of a larger study (Dragt, 2012), but this could not be confirmed at the time of completing the review.

A broad assessment of each study’s design suggests that there were three main types: (1) those that compared high risk individuals to healthy controls on substance (including cannabis) use patterns, (2) those that compared substance (including cannabis) using high-risk individuals to non-substance using high risk individuals, and (3) one study that followed high risk individuals over time (retrospectively comparing those who converted to psychosis against non-converters) (see Table 1).

The number of ‘at risk’ participants included in each study ranged between 32 and 735 and there were significantly more males than females included in most samples (with the exception of Russo et al, 2014), while one study (Corcoran et al; 2008) did not report on gender. Five of the 11 studies included a comparison group of healthy controls; in some cases these were non-substance using controls, and in others, details of their substance use was also reported and assessed in a similar way as the high risk sample.

Across all studies, the mean age ranged from 16.09 to 22.90 years for high-risk samples and 16.15 to 22.60 years for controls, which underscores researchers' consensus regarding the significance of late adolescence and early adulthood as a critical period of risk of the onset of psychosis (Van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009).

A primary difference between the studies was how they assessed the relationship between cannabis use and subsequent transition to psychosis. While all of the studies included were longitudinal in design, reporting on follow-up of the high-risk cohort over time to establish which ones transitioned to a state of frank psychosis, the majority of studies assessed current and/or past cannabis use at baseline only. Some studies which reported collecting data on cannabis use during follow-up assessments (Auther et al, 2012; Buchy et al, 2015; Corcoran et al, 2008; Kristensen & Cadenhead, 2007; and Valmaggia et al, 2014), but few of these actually reported follow-up cannabis use data.

Five of the 11 studies divided their high-risk samples into groups based on drug use for the purpose of analysis – four of these (Dragt et al, 2010; Dragt et al, 2012; Korver et al, 2010; Kristensen & Cadenhead, 2007) did so based on lifetime use of cannabis (i.e. 'ultra-high risk' lifetime cannabis users versus 'ultra-high risk' non-cannabis users) and one (Corcoran et al, 2008) did this for lifetime drug use in general (i.e. 'drug users' and 'non-drug users'). One of these five studies (Korver et al, 2010) had a control group comparison and also divided controls into cannabis users and non-cannabis users.

### 3.1.1 Exclusion criteria re: substance and medication use

Only some of the studies incorporated use of illicit drugs and medicines in their exclusion criteria. Exclusion of drug use differed between studies, with some focusing on substance dependence disorder, others on recent use of illicit drugs, and others on current or recent use of ‘hard drugs’. While not all studies reported on use of other medications, several studies excluded participants based on use of anti-psychotics.

Three of the 11 studies (Auther et al, 2012; Buchy et al, 2015; Kristensen & Cadenhead, 2007) excluded high-risk participants if they met criteria for diagnosable DSM-IV substance dependence disorder; Buchy et al (2015) also excluded controls who met these criteria. Kristensen & Cadenhead (2007) further excluded participants who had used illicit drugs within 30 days of initial assessment. Three studies listed use of “hard drugs” (e.g. cocaine, heroin, ecstasy, amphetamines) as exclusion criteria (Dragt et al, 2010; Dragt et al, 2012; Korver et al, 2010). Three studies excluded participants if they experienced ‘attenuated positive symptoms’ attributable to current substance use (Corcoran et al, 2008; Dragt et al, 2010; Korver, et al 2010). Three studies included varied exclusion criteria related to the use of anti-psychotic medication: Russo et al (2014) excluded participants who had previously used anti-psychotics for more than one week, Buchy et al (2014) excluded all prior and baseline anti-psychotic treatment, and Buchy et al (2015) reported on only excluding controls currently using psychotropic medication. As will be discussed, objective verification of these exclusionary criteria was only reported in one study (Kristensen & Cadenhead, 2007).

### *3.2 Clinical Diagnoses of High Risk Status*

All 11 of the studies used internationally established criteria to ascertain ‘high-risk’ status based on the four main domains of clinical high-risk symptomatology: attenuated positive symptoms, brief intermittent psychotic symptoms, genetic risk and deterioration, and basic symptoms. The majority of studies used the SIPS – five employed this measure exclusively (Buchy et al, 2014; Buchy et al, 2015; Cannon et al, 2008; Corcoran et al, 2008; Kristensen & Cadenhead, 2007) and three used the SIPS and/or the BSABS-P (Dragt et al, 2010; Dragt et al, 2012; Korver et al, 2010). One study reported having only used the SOPS (a measure contained within the SIPS; Auther et al, 2012), while one used the CAARMS (Russo et al, 2014) and another reported using ‘ultra-high risk’ criteria as assessed in both the SIPS and CAARMS (Valmaggia et al, 2014). One study lacked clarity in reporting whether all ‘high-risk’ individuals in its sample met SIPS criteria (reporting that “at each site, from 30-50% of the referred case patients met [SIPS] criteria for study entry”), suggesting that a proportion of included participants did not meet ‘clinical high risk’ threshold (Cannon et al, 2008). (See Table 1 for tabulation of screening tools used in each study.)

### *3.3 Measurement of cannabis use*

All studies assessed cannabis use at baseline and reported this, with the exception of Cannon et al (2008) who did not report specific details of cannabis use. In general, studies differed in terms of the extent of their cannabis use assessments, with some reporting detailed information on current and past use. Others grouped cannabis use together with use of other substances under the umbrella category of

‘substance use’ and did not provide detailed information on patterns of cannabis use, both past and present (i.e. at baseline).

### 3.3.1 Self-report Measures

Cannabis use in the studies was assessed using a number of clinical measures which examine substance use, including abuse or dependence. Eight studies included one or a combination of the following reliable and validated instruments: Structured Clinical Interview for DSM-IV Disorders (SCID; First, Spitzer & Gibbon, 1995), the Composite International Diagnostic Interview (CIDI; Andrews & Peters, 1998), two versions of the Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime version (K-SADS-PL; Kaufman, Birmaher, Brent, et al 1997) and Epidemiological version (K-SADS-E; Orvaschel, 1994), and the Diagnostic Interview for Genetic Studies (DIGS; Nurnberger et al, 1994).

The SCID was used in three studies to assess for a range of comorbid DSM-IV psychiatric disorders, which included diagnoses of current and lifetime substance (including cannabis) abuse and dependence (Buchy et al, 2015; Cannon et al, 2008; Kristensen & Cadenhead, 2007). Three studies used the CIDI (rather than the SCID) to assess mental disorders according to DSM-IV and ICD-10 diagnostic criteria, including assessment of cannabis use, abuse and dependence (Dragt et al, 2010; Dragt et al, 2012; Korver et al, 2010). The CIDI assesses a wide range of cannabis use behaviours including current use, amount, onset of use, frequency and duration of use (Korver et al, 2010) Cannabis abuse and dependence in these studies was specifically assessed according to DSM-IV criteria (Dragt et al, 2010; Dragt et al, 2012; Korver et al, 2010).

To account for the inclusion of adolescent participants, four studies employed the K-SADS-PL or K-SADS-E for assessment of DSM-IV disorders in school-age children, including substance use disorders (Auther et al, 2012; Cannon et al, 2008; Corcoran et al, 2008; Kristensen & Cadenhead, 2007). Cannon et al (2008) and Kristensen & Cadenhead (2007) used this measure in cases where the SCID was not age-appropriate. Corcoran et al (2008) specified use of the K-SADS-PL for 12-15 year olds and employed the DIGS for participants aged 16 and older, which similarly assesses for DSM-IV disorders. Auther et al's study used the K-SADS-E as their sole clinical measure, not only to assess cannabis and other substance use, but also to screen for psychotic disorders at baseline and to confirm later transition to psychosis (Auther et al, 2012). Both versions of the K-SADS employed in these studies assess lifetime substance use; for cannabis use specifically, this included lifetime use, use in the six months prior to baseline, and frequency of lifetime use (Auther et al, 2012).

Two studies (Buchy et al, 2014; Buchy et al, 2015) assessed cannabis use with the Drug Use Scale (DUS, Drake, Mueser & McHugo, 1996). Buchy et al (2014) relied solely on this scale in assessing cannabis use, while Buchy et al (2015) employed this measure in addition to the SCID (assessing for dependence or abuse) and a further cannabis use questionnaire developed from previous literature. The DUS assesses the severity and frequency of substance use in the past month, recording separate severity and frequency ratings for each of a number of different drugs (e.g. tobacco, cannabis, cocaine, etc.) (Drake et al, 1996). The severity ratings range from 1-4 (1 = abstinent, 2 = use without impairment, 3 = abuse, 4 = dependence) and the '3' and '4' ratings are in line with DSM-IV diagnoses of abuse and dependence respectively (Buchy et al, 2014). DUS frequency ratings consist of a five point scale

covering substance use in the past month (i.e., 0 = no use, 1 = once or twice per month, 2 = 3-4 times per month, 3 = 1-2 times per week, 4 = 3-4 times per week, 5 = almost daily; Drake et al, 1996). Buchy et al (2015) collected DUS severity and frequency data for both CHRs and controls.

Three studies used cannabis use measures which captured a wider range of data regarding patterns of past and current use than the aforementioned standardised instruments which largely focus on abuse, dependence and very recent use. Buchy et al (2015) devised a cannabis use questionnaire based on questions endorsed in previous literature, which elicited information on incidence of prior use, number of times used throughout lifetime, current and historical use, frequency, pattern, and social and temporal environment of use (Buchy et al, 2015). This was used in addition to their inclusion of the SCID and DUS (Buchy et al, 2015). Valmaggia et al (2014) similarly employed a more thorough assessment of cannabis use, using a modified version of the Cannabis Experience Questionnaire (Barkus, Stirling, Hopkins & Lewis, 2006) to assess lifetime use of cannabis and other substances. The Cannabis Experience Questionnaire also contains questions concerning subjective experiences of cannabis use, including subscales centred on pleasurable experiences, psychotic-like experiences and after-effects associated with cannabis use (Barkus et al, 2006). They followed-up lifetime-endorsed substances with detailed questions regarding current use, age of onset and last use, and frequency and duration of use (Valmaggia et al, 2014). Valmaggia et al (2014) also asked lifetime cannabis users about unpleasant experiences linked to their cannabis use and past users were asked further questions about decisions to quit (Valmaggia et al, 2014). One study (Russo et al, 2014) gathered a similar range of information as Valmaggia et al (2014), using what they termed a 'novel substance use assessment tool' which

assessed frequency, age of first use, the experience of unusual symptoms whilst intoxicated, whether substances were used to relieve any unusual or disturbing symptoms, current use/ use over the past three months, and period of greatest past use (Russo et al, 2014).

All of the cannabis use assessment tools discussed above are notably self-report measures, and are retrospective in their assessment of past cannabis use and associated experiences. The main disadvantage of self-report measures is their reliance on the subjective motivation of participants to be truthful in reporting past experiences and behaviour, relying on memory for accurate reporting, aspects of which have been found to be impaired in chronic cannabis users (Solowij & Battisti, 2008). While previous research suggests that retrospective reports of drug use, and particularly cannabis use, are indeed reliable, various factors implicated in ‘at-risk’ mental states may have affected the reliability of such reports (Johnson & Mott, 2001, in Dragt et al, 2010). For example, Valmaggia et al (2014) suggest that help-seeking individuals being interviewed in clinical settings may be incentivised to minimise current or recent use, impacting on self-reported cannabis use.

### 3.3.2 Objective measures of cannabis use

Only one of the 11 studies reported on having objectively measured cannabis use. Kirstensen and Cadenhead (2007) carried out urine toxicology screens for cannabis use at baseline and at six-month follow-up intervals and reported that six participants tested positively for cannabis during the study (all of whom were included in their ‘cannabis-using’ group, defined by cannabis abuse or dependence in remission). Interestingly, the authors only mention the urine screening once in their paper, and

do not elaborate on how positive test results for cannabis relate either to changes in cannabis use in these subjects or to eventual transition to psychosis. However, they recommend more frequent drug-testing for future studies to gain a fuller picture of the relationship between cannabis use and transition to psychosis (Kristensen & Cadenhead, 2007). None of the other studies reported on urine or other objective measures of cannabis use, with several having overtly acknowledged this (see Table 2).

### 3.3.3 Prevalence, ‘lifetime’ and frequency of cannabis use

As previously noted, despite all of the studies being longitudinal, most studies focused their analyses of cannabis use on data collected regarding current and historical use at baseline and, despite reporting that cannabis use was assessed at follow-up, did not report extensively on changes in use at follow-up assessment, with several exceptions (Buchy et al, 2015; Corcoran et al, 2008; Valmaggia et al, 2014).

There was wide variation in how the studies defined cannabis users according to past and current use. Five studies divided their high-risk samples into either ‘drug-users’/‘non-users’, or ‘lifetime cannabis users’/‘non-users’ for the purpose of comparing variables such as prevalence of psychotic-like symptoms, functioning, transition to psychosis, etc. The one study that employed a ‘drug user’/ ‘non-drug user’ paradigm based ‘drug use’ categorisation on dependence diagnoses for tobacco or alcohol *or* “prior exposure to any other drug of abuse” (Corcoran, 2008). Two of these studies (Dragt et al, 2010, Dragt et al, 2012) defined ‘lifetime’ cannabis use as having used cannabis at least five times in the past, and for both, their category of ‘high-risk’ lifetime cannabis user also included individuals who had used cannabis

much more frequently; e.g. in Dragt et al, 2010, 42.8% of ‘lifetime cannabis users’ currently used cannabis ranging from ‘almost daily’ to ‘1-3 days per month’ at baseline. Korver et al (2010) similarly divided their ‘high-risk’ sample into ‘cannabis users’/‘non-users’, with the cannabis using group varying widely in frequency of use – 42% of this group were reported to use cannabis frequently at intake (varying between daily use and 1-3 times per month). There was similarly wide variation between the 58% of ‘high-risk’ cannabis users in Korver et al’s (2010 study) who reported only past, not current, use of cannabis, ranging from two weeks to one year prior, and at varying frequencies during these past periods of use. One study divided the ‘high-risk’ group into two based on lifetime cannabis use, but as current diagnoses of substance dependence were exclusion criteria, division was based on those with either (1) no use or (2) minimal use without impairment, versus those who met criteria for abuse or dependence in remission (Kristensen & Cadenhead, 2007). While other studies also assessed lifetime cannabis use (defined either as use at least once in the past), no other studies used this criterion to divide their ‘high-risk’ samples into users versus non-users.

The three studies that undertook more detailed assessments of current and past cannabis use, beyond the standardised clinical measures assessing for abuse and dependence (e.g. the SCID), unsurprisingly provided richer data regarding patterns of cannabis use in their ‘high-risk’ samples, and in two of the studies also their control groups (Buchy et al, 2015; Russo et al, 2014; Valmaggia et al, 2014). These three studies collected data on lifetime use, but rather than simply using it as a category of comparison to those who had not used cannabis, they obtained a wider range of detail in a number of dimensions.

The majority of the studies included measures of frequency of cannabis use in their assessments; only four studies did *not* report on measures of frequency (Buchy et al, 2014; Cannon et al, 2008; Corcoran et al, 2008; Kristensen & Cadenhead, 2007). In many cases, reports of frequency centred on ‘lifetime frequency’ rather than current/recent frequency of use.

Among studies reporting on cannabis use frequency that compared high risk samples to controls, Auther et al (2012) found that high risk individuals in their sample reported significantly higher rates of lifetime cannabis use than healthy controls (35% of high risk sample vs. 11.9% of the healthy controls) and that the high risk participants were also likely to have used cannabis in the past six months. Along similar lines, Buchy et al (2015) found that the clinical high risk sample reported significantly greater lifetime cannabis use and greater mean number of occasions of past cannabis use than controls, although the two groups did not differ on current cannabis use frequency. Korver et al (2010) did not provide details on frequency between cannabis-using controls and ultra-high risk patients in their sample, but they did report a significant correlation between frequency of cannabis use and several prodromal symptoms when combining cannabis users from both groups. Finally, Russo et al (2014) reported that the median frequency of cannabis use in the past three months was significantly higher for high risk individuals than for the healthy volunteers in their study, while the groups did not differ in past frequency of cannabis use (with past use defined as the period of greatest past use prior to the previous three months). Russo et al (2014) concluded that current and past rates of cannabis use were similar in their high risk sample.

Focusing on frequency of use in studies comparing cannabis-using and non-cannabis using high risk groups, there was variation in the proportion of participants

reporting lifetime and recent use. Dragt et al (2010) reported that 35 (or 51.5% of the total UHR sample) had used cannabis more than five times in the past, with 15 of these individuals having used recently, at varying frequencies. In their larger sample of CHR individuals, Dragt et al (2012) found that a slightly smaller proportion of individuals reported more than five occasions of previous cannabis use (102, or 42% of the total sample), with 73.5% of these lifetime users having used in the past year and 25.5% having used in the month prior to intake. Lastly, Valmaggia et al (2014) reported lifetime cannabis use in 73.6% (103 individuals) of their total high risk sample, with 52.2% reporting using cannabis at least once per week. They found that 26.9% were using at baseline and 30.7% of the total sample had used cannabis for more than five years (Valmaggia et al, 2014).

#### 3.3.4 Cannabis use disorder or dependence

As previously reported, three studies excluded participants if they met criteria for any DSM-IV substance dependence disorder (Auther et al, 2012; Buchy et al, 2015; Kristensen & Cadehnhead, 2007), although in one of these (Buchy et al, 2015), several high risk participants reported dependence at follow-up and were included in subsequent transition to psychoses analyses. This was the only study that reported on cannabis dependence at follow up.

Five studies reported rates of cannabis dependence or cannabis use disorder at baseline, with a range of between 0 and 32.4% of high-risk participants meeting dependence criteria (Buchy et al, 2014; Corcoran et al, 2008; Dragt et al, 2010; Dragt et al, 2012; Russo et al, 2014); two of these studies reported that no high-risk users were dependent at baseline (Corcoran et al, 2008; Russo et al, 2014), although one noted six cases of cannabis dependence in remission (Corcoran et al, 2008). The

remaining three studies did not report on cannabis dependence or diagnosable cannabis use disorder.

### 3.3.5 Age at onset of cannabis use

Only four studies reported on age of first cannabis use, sometimes termed ‘age of onset’ of cannabis use. The only one of these studies with a control group, Buchy et al (2015), found a significant difference between their CHR and controls on mean age of first use of cannabis (15.7 for CHR group vs. 16.6 years in controls). For the other three studies, the mean age of onset of cannabis use was reported as 16.8 years (Dragt et al, 2010), 17.3 years (Dragt et al, 2012), and 15.5 years (Valmaggia et al, 2014). Interestingly, Dragt et al (2010) found a significant association between younger age of onset of cannabis use and younger age of onset of prodromal symptoms, although the sample studied was relatively small.

### 3.4 *Assessment of relationship between cannabis use and conversion to psychosis*

The majority of studies reported using established criteria to determine conversion to psychosis; in most cases this was the SIPS and in two cases this was the Interview for the Retrospective Assessment of the Onset of Schizophrenia (IRAOS; Häfner et al, 1992) which is reported to “sufficiently” document early onset of prodromal symptoms retrospectively (Dragt et al, 2010; Dragt et al, 2012).

Despite the fact that all of the studies included reference to cannabis use and subsequent conversion to psychosis in high risk samples, the studies varied widely in how they analysed the relationship between cannabis use and transition.

Excluding the study that did not disaggregate cannabis use from misuse of other substances generally (Cannon et al, 2008), the reported rates of transition in high-

risk samples ranged between 5% (or 3 individuals in this sample; Russo et al, 2014) and 27% (or 17 high risk individuals; Korver et al, 2010; see Table 1 for further transition rates). Corcoran et al (2008) did not report numbers of individuals who transitioned, but did report that there were no differences in conversion rates between drug users and non-users. Cannon et al (2008), who reported a 35% transition rate in their sample, suggested that a history of substance use disorder was a major predictor of subsequent conversion to psychosis; however they did not specifically report on cannabis use disorder and transition.

Four studies did not perform analyses on rates of cannabis use and transition to psychosis. One of these focused on ‘substance abuse’ and not cannabis use specifically (Cannon et al, 2008). Two reported that only three participants transitioned, which was too few to analyse statistically (Russo et al, 2014 and Korver et al, 2010). Finally the fourth, Corcoran et al (2008), did not analyse the relationship between cannabis use and transition, but rather focused on prodromal symptoms, finding that cannabis use was associated with increases in subthreshold psychotic (particularly perceptual disturbances) over time.

Seven out of the eleven studies performed statistical analyses on rates of cannabis use and transition to psychosis. Both of the studies that did analyse cannabis use in relation to transition *and* included a healthy control comparison group found that baseline reports of lifetime cannabis use did not significantly predict conversion to psychosis (Auther et al, 2012; Buchy et al, 2015). However, Buchy et al (2015) found however that of the proportion of individuals completing two years of follow-up, controls had significantly lower rates of cannabis use than CHR participants who were psychotic.

Among the other five studies that analysed cannabis and transition, three definitively found no significant relationship between cannabis use and transition (Buchy et al, 2014; Dragt et al, 2010; Dragt et al, 2012). Buchy et al (2014) concluded that cannabis use severity was not predictive of subsequent conversion in their sample, while Dragt et al, (2010) found no significant differences in the transition rate between the high risk cannabis using and non-using groups. Dragt et al, (2012) similarly found no relationship between cannabis use and transition or between cannabis use disorder and transition.

Only Kristensen and Cadenhead (2007) reported a significant association between cannabis abuse and dependence and conversion to psychosis, though four of the five high risk individuals in their study who transitioned also used nicotine (which was also found to be significantly associated with conversion).

Valmaggia et al's (2014) study provided an arguably more nuanced assessment of the relationship, reporting that while there was no significant difference in transition rates between high risk cannabis users versus high-risk non-users, among cannabis users, those with more frequent and earlier first use (i.e. before age 15) were more likely to transition.

### *3.5 Assessment of relationship between cannabis use and other major outcome variables (e.g. functioning)*

Apart from various reports of prodromal symptomatology (which are not addressed in this review), most of the studies included here did not report on other significant outcome variables related to cannabis use. Among the ones that did, as with cannabis use assessments, data was often reported at baseline but not tracked longitudinally and reported at follow-up.

Auther et al (2012) and Corcoran et al (2008) were the only two studies to report on the relationship between cannabis use and social and role functioning. The former utilised the Global Functioning: Role Scale (GF: Role; Niendam, Bearden, Johnson & Cannon, 2006) and Global Functioning: Social Scale (GF: Social; Auther, Smith & Cornblatt, 2006). Auther et al (2012) found that at baseline, clinical high risk lifetime cannabis users had higher global functioning than non-users, and this continued at follow-up, though there were no group differences in role functioning. Clinical high risk cannabis *abusers* in their CHR sample (n = 10, a subsample of CHR cannabis users) were found to have higher social functioning (GF: Social) scores at baseline than non-cannabis using high risk individuals; these cannabis abusers had better social functioning scores at follow-up, though there were no statistical group differences at follow-up (Auther et al, 2012). No group differences were found in role functioning (GF: Role) at baseline or follow-up.

Corcoran et al (2008) used the modified Global Assessment of Function (as in the SIPS; Miller et al, 2003) to assess global function. While drug-using and non-using high risk individuals were comparable on global functioning at baseline, periods of reported increased use of cannabis was associated with increased functional impairment in cannabis users (Corcoran et al, 2008). Their analyses controlled for use of other drugs and anti-psychotic medication, which suggests a distinct effect of cannabis use on functioning in this sample.

Dragt et al (2010) reported poor functioning (again using the mGAF) in their overall high risk sample at baseline, but did not report on the relationship between functioning and cannabis use, nor on functioning at follow-up. Similarly, Dragt et al (2012) reported similar levels of poor functioning in both high risk lifetime cannabis

users and high risk non-users, but did not report follow up or comment on the relationship with cannabis use.

Cannon et al (2008) reported on functioning, suggesting that poorer functioning and heightened severity of prodromal symptoms in high risk individuals brought forward the risk of transition; however, functioning was not analysed in relation to cannabis use.

Two studies reported on the association between cannabis use and significant outcome variables other than functioning. These were neuropsychological functioning (Korver et al, 2010) and the incidence of other psychiatric diagnoses such as anxiety and depression (Russo et al, 2014). In the former, no relationship was found between frequency of cannabis use and any of the neuropsychological tests administered in total sample of high risk individuals (Korver et al, 2010). Russo et al (2014) reported on comorbid psychiatric diagnoses using the MINI DSM-IV in their high risk sample, finding that 69.1% had more than one diagnosis, but they did not map the association between cannabis use and comorbid diagnosis, nor did they examine stability of diagnoses longitudinally.

#### **4. Discussion**

This review sought to examine how cannabis use was assessed in studies of clinical high risk individuals that address incidence of transition to psychosis. The aims of the review included an examination of cannabis measurements, whether cannabis use was significantly associated with conversion to psychosis and whether the relationship between cannabis use and other significant outcome variables was assessed.

#### *4.1 Strengths and limitations*

The current studies all used standardised instruments to define their high risk samples and most utilised standardised self-report measures to assess cannabis use at intake, which represent significant strengths. Similarly, most studies reported on established criteria used to determine conversion status (e.g. SIPS and IRAOS). Those studies that included a control group provided a useful means of comparing the high risk samples on cannabis use and transition, though in several cases the samples groups were relatively small. A relative strength in some studies was controlling for use of other drugs and alcohol in analyses of transition to psychosis, though others were less clear in reporting this.

The main findings from the review support the hypothesised variability of cannabis use assessment between the studies. While most of the studies used reliable and valid clinical instruments to assess dimensions such as lifetime use, cannabis dependence and severity of use in the past month, the majority of studies limited their assessment to these measures, focusing on retrospective assessments of lifetime use at baseline, and did not obtain broader assessments of patterns of use both historically and longitudinally, which may have impacted on their analyses of cannabis use and transition.

This is a significant shortcoming in these recent studies, as the high risk groups consisted of treatment-seeking individuals; accessing help and enrolling in such studies may have conferred benefits over time such as improved functioning and possible reductions in cannabis use. Neither of these variables were frequently reported on or included in analyses of transition rates. Most of the studies also relied on self-report, with only one of the eleven studies including an objective assessment (urine screening) of cannabis use. Several of the included studies excluded DSM-IV

diagnoses of cannabis dependence, which will likely have impacted on how representative their high risk samples were, given the high prevalence rates of comorbid cannabis dependence in individuals with first-episode psychosis (Wisdom, Manuel & Drake, 2015). There was also variability in the extent to which the studies reported on and controlled for use of medications such as anti-psychotics, with several studies listing anti-psychotic use as an exclusion criterion, and others allowing treatment with anti-psychotics but not reporting on rates of use or incorporating possible effects of medication in analyses of transition.

Several other limitations in cannabis measurement highlight methodological weaknesses in the current studies. None of the included studies asked about types or amounts of cannabis used. This is particularly worrying – not only is frequency of use not equivalent to amount of cannabis consumed, but given the saturation of Western markets with high-potency cannabis and the recent findings that high-potency cannabis is associated with increased risk of psychosis compared to lower-potency varieties (e.g. hashish), studies that overlook assessment of this dimension of cannabis use might only be able to make tentative speculations about the possible associations between heavier cannabis use and psychotic symptomatology (di Forti et al, 2009; Hardwick & King, 2008). Also, while several studies used ‘age of [cannabis use] onset’ as a measurement variable, to determine whether younger age was significantly associated with other use variables or transition (as it has been found to be associated with age of onset of psychosis and first hospitalization in retrospective assessments of individuals with psychosis; Galvez-Buccollini et al, 2012), the variable may be limited in its usefulness unless followed by reliable assessments of use frequency, as the age at which an individual first uses cannabis may be followed by broad variation in patterns of subsequent use. For instance,

Dragt et al (2010) commenting on their examination of age of onset of prodromal symptoms and age of first cannabis use, report that 20 out of 35 of the cannabis users in their study stopped using cannabis at the time of intake. They suggest that past cannabis use may have influenced early experiences of prodromal symptoms (Dragt et al, 2010). However, without further information about patterns of use following first use, it is difficult to ascertain the homogeneity of the group.

Overall, there was relatively weak evidence among the included studies to suggest that transition to psychosis was associated with cannabis use. This may accurately reflect the wider clinical picture. Conversely, this may in large part relate to weaknesses and variability between studies in cannabis use measurement or small sample sizes with lower incidence of cannabis use. The increasing emphasis on detection of risk factors and prodromal symptoms may be influencing reported declining rates of transition, either by providing earlier effective treatments, or via the identification of greater numbers of individuals who present as high risk but who do not transition (Yung et al, 2007; Addington et al, 2014).

#### *4.2 Theoretical and Clinical Implications*

The studies that went beyond assigning all lifetime users to the overarching category of ‘cannabis users’ (vs. ‘non-cannabis users’) and provided more thorough data on past and recent patterns of use provided richer clinical pictures of their cannabis-using high risk samples. Valmaggia et al (2014) reported that transition to psychosis was not associated with lifetime cannabis use *per se*, but that it *was* associated with higher frequency of use, earlier age of first use and continued use during follow up (during reported presence of prodromal symptoms) in high risk users. These associations would not have been possible had the authors not obtained

extensive information about cannabis use both historically and over the study's course. Russo et al (2014)'s was another such study which compiled detailed information on patterns of substance use. Although changes in cannabis use were not tracked throughout follow-up, the authors acknowledged that the substance use profiles of their high risk groups, including the relatively low frequency of cannabis use in their high risk sample (9%), low rates of weekly and absence of daily use relative to other studies (e.g. Dragt, 2010; Korver, 2010), and low transition rates might indicate that their high-risk sample was not broadly representative of other high risk individuals (Russo et al, 2014). However, they highlight the important question of how substance, particularly cannabis, use may influence the development of sub-threshold psychotic-like symptoms and the extent to which such symptoms are implicated in eventual transition to psychosis (Russo et al, 2014). Buchy et al (2015) noted that change in use severity may be an important factor in transition, as retrospective assessments of psychotic individuals showed that change in frequency of use to daily use prior to onset was associated with greater risk of prodromal symptoms. Examining whether distinct patterns of substance use, including mono- and poly-drug user profiles and changes in use, may be more predictive of the onset of prodromal symptoms and subsequent development of psychosis would be an interesting avenue for future research. Although there is already a body of literature assessing the association between substance use and psychotic-like symptomatology, it may be the case that existing studies suffer from similar limitations and confounds in drug assessment as in the present studies.

The inclusion of measures of functioning in several of the studies was helpful in linking cannabis use in high risk populations with broader clinical outcomes (Auther et al, 2012; Corcoran et al, 2008). However, most did not examine associations

between cannabis use and such outcomes, which is somewhat unusual in light of studies of first-episode patients which highlight long-term prognoses that include various measures of poorer functioning (e.g. poorer cognitive functioning and premorbid adjustment, etc.; Waddington, 2005). Given the relatively short duration of follow-up and rates of transition in the present studies, it is possible that longitudinal measures of functioning are not as yet standard practice in studies of clinical high risk populations.

#### *4.3 Limitations of current review*

The current review was limited by its very specific inclusion criteria – studies of clinically assessed high risk individuals which included measures of cannabis use and transition to psychosis. The small number of studies may reflect lack of research in this particular area, but was also a result of the date limitations at the outset of the search. As discussed, many other studies share similarities to those included here, such as investigations of the links between cannabis use and prodromal symptoms in other populations or retrospective assessments of cannabis use in individuals already diagnosed with psychosis. A widening of inclusion criteria (e.g. studies focusing on individuals with higher rates of psychotic-like symptoms, rather than those considered at high clinical risk) may therefore have allowed for a broader assessment of the relationships between cannabis use and psychosis.

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## Appendix 1

### Search strategy

#### *PsycINFO search terms*

	Terms
1	cannabis.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] or exp Cannabis/
2	exp Psychosis/
3	exp "Positive and Negative Symptoms"/
4	exp Prodrome/
5	mania.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] or exp Mania/
6	bipolar disorder.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
7	schizoaffective disorder.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] or exp Schizoaffective Disorder/
8	schizophren*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] or exp Schizophrenia/
9	basic symptoms.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
10	ultra-high risk.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
11	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12	1 and 11
13	limit 12 to (human and english language)
14	limit 13 to yr="2004 -Current"

*PubMed search terms*

	Terms
1	psychosis.af. [af = all fields]
2	(positive symptoms and negative symptoms).af. [af = all fields]
3	(prodrom* or prodrome).af. [af = all fields]
4	mania.af. [af = all fields]
5	bipolar disorder.af. [af = all fields]
6	schizoaffective.af. [af = all fields]
7	schizophrenia.af. [af = all fields]
8	basic symptoms.af. [af = all fields]
9	ultra-high.af. [af = all fields]
10	risk [Medical Subject Heading / MeSH Terms] or exp risk
11	9 and 10
12	cannabis/ or cannabis.mp. [Medical Subject Heading / MeSH Terms]
13	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 11
14	12 and 13
15	limit 14 to [humans [MeSH Terms] and English [language]]
16	limit 15 to [2004/06/06 [Publication Date] : 2015/06/06 [Publication Date]]

## **Part 2: Empirical Paper**

### **Psychotic-like symptomatology and reward responsivity in chronic ketamine and cannabis users**

**Abstract**

**Background:** Drug use has been linked to psychosis, but the relationship has not yet been fully understood. Further, chronic drug use has been hypothesised to increase sensitivity to drug rewards while decreasing sensitivity to non-drug rewards and has been found to model symptomatology of prodromal psychosis, which may aid our understanding of how psychosis develops.

**Aims:** Anhedonia, a key feature of depression and substance misuse, and a negative symptom of psychosis, has particularly been linked to deficits in reward responsiveness. The present study aimed to build on previous research by (1) assessing prodromal psychosis symptomatology in chronic cannabis and ketamine users, and (2) objectively assessing their reward responsiveness.

**Participants:** Sixty participants, 25 women and 35 men aged 18-43, completed the study.

**Design:** A between subjects design compared three groups – 20 dependent ketamine users, 20 dependent cannabis users, and 20 control participants (who occasionally used illicit drugs). Participants completed a drug use history interview, self-report questionnaires (Beck Depression Inventory, BDI; Temporal Experience of Pleasure Scale, TEPS; O-Life; Prodromal Questionnaire – Brief, PQB) and two cognitive tasks examining reward sensitivity (probabilistic reward task, PRT) and effort-based decision-making (Effort-Expenditure for Rewards Task, EEfRT).

**Results:** Both drug using groups had higher levels of schizotypy (O-LIFE) and positive psychosis symptomatology (PQ-B) than controls. The drug-using groups demonstrated differences on the probabilistic reward task: controls had greater response bias than the cannabis users and also greater discriminability than the ketamine users. The groups did not differ on the effort-based decision-making task.

**Conclusion:** These findings support previous research demonstrating high levels of positive and negative psychosis-like symptoms in chronic cannabis and ketamine users. The mixed results in the drug-using groups' reward responsiveness may be partly explained by group differences in depression and tobacco use. These findings have clinical implications for the assessment and treatment of individuals at higher risk of developing psychosis.

**Key words:** Addiction, chronic effects, cannabis, ketamine, psychosis, psychosis proneness, schizotypy, anhedonia, motivation

## **Psychotic-like symptomatology and reward responsivity in chronic ketamine and cannabis users**

### **Drug use and psychosis**

Rates of drug misuse, including alcohol, tobacco, cannabis and other illicit drugs, are higher in patients with psychotic disorders. Higher substance use rates in psychotic patients are seen both at onset (first episode of psychosis) and in those with chronic psychotic illness (Regier, Farmer, Rae et al, 1990; McCreadie, 2002; Barnett, Werners, Secher et al, 2007). Further, drug use has been found to be a key predictor of conversion from an ‘at risk’ or prodromal state to full-blown schizophrenia (Cannon et al, 2008).

Over 200 studies have focused on the potential associations between cannabis, the most widely used illicit drug in the world, and psychosis, noting the high prevalence of cannabis use among psychosis patients and exploring how cannabis potency, frequency, duration and age of first use may influence the risk of transition to psychosis (Arseneault, Cannon, Witton & Murray, 2004; Barnet et al, 2007; Green, Young & Kavanagh, 2005; di Forti et al, 2014; Moore et al, 2007). Cannabis use has particularly been linked to higher levels of prodromal symptoms and higher incidence of transition to psychosis in individuals considered to be ‘high risk’ in a number of studies (Kristensen et al, 2007; Miettunen et al, 2008; Rosen et al, 2006).

Higher potency cannabis strains (‘skunk’) have saturated the market in recent years and have been particularly linked with the development of psychosis (Di Forti et al, 2009; 2015; Moore et al, 2007; Wylie et al, 1995). Research also suggests that a less frequently used drug of abuse, ketamine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist with marked psychotomimetic properties, may be associated with psychosis (Anis, Berry, Burton & Lodge, 1983). Chronic

ketamine use has also been found to mimic some symptoms of psychosis and its more potent relative, phencyclidine (PCP), also an NMDA-receptor antagonist, has been associated with prolonged psychotic reactions in some users (Allen & Young, 1978; Krystal et al, 1994).

As yet, the nature of any relationship between using recreational drugs and psychosis has not been established. Recent research examines *i*) possible causal links (i.e. drug use causing psychosis), *ii*) common risk factors implicated in both addiction and psychosis, *iii*) whether presence of psychosis increases the risk of substance use, and *iv*) whether accessing treatment for one disorder (addiction or psychotic illness) might facilitate detection of the other and thus raise reported rates of comorbidity (Barkus & Murray, 2010).

### **Addiction and reward processing**

Animal and human studies of drug addiction have shown that increasing exposure to drugs leads to the development of compulsive drug-seeking and taking behaviours, which are characterised by intensive and rigid directedness towards drug use and neglect of other previously important and pleasurable activities (Wolffgramm & Heyne, 1995; Robinson & Berridge, 2000; Deroche-Gamonet, Belin & Piazza, 2004; Vanderschuren & Everitt, 2004, 2005; Anselme, 2009).

Drug addiction can be understood as a chronic brain disease involving motivation, memory and reward systems, and chronic drug use has been hypothesised to influence the development of neuroadaptations in the mesocorticolimbic dopamine system, stimulating pathological desire for drugs, so that ‘wanting’ the drug supersedes its pleasurable effects, which reduce over time as tolerance develops (Anselme, 2009; Robinson & Berridge, 1993). These changes in the neurobiological

reward system are hypothesised to contribute to an imbalance in the processing of drug and non-drug rewards, resulting in hypersensitivity to drug rewards and hyposensitivity to non-drug rewards (Anselme, 2009; Blum et al, 2000; Goldstein & Volkow, 2002; Kalivas & Volkow, 2005; Koob & Le Moal, 1997; Bühler et al, 2010). Craving and acute abstinence is thought to exacerbate this imbalance and thereby influence the vicious cycle of cessation of drug use and subsequent relapse characteristic of drug addiction (Goldstein & Volkow, 2011; Koob & Le Moal, 2008; Koob & Volkow, 2009). While laboratory and neuroimaging studies support this hypothesised hypersensitivity to drugs and drug-related stimuli in addicted individuals, evidence for hyposensitivity to non-drug rewards is more mixed, limiting our understanding of how non-drug rewards are processed (Lawn et al, 2015).

### **Anhedonia – a key feature of drug addiction, depression and psychosis**

Anhedonia, the inability to experience pleasure or react to pleasurable stimuli, is understood to be a fundamental symptom of depression (APA, 2000). It is also a core negative symptom of schizophrenia and a potentially significant symptom preceding its onset, with associated impacts on social functioning (Cohen et al, 2010; Yung & McGorry, 1996b).

It has been argued that hedonic capacity is a trait in that the capacity to experience pleasure differs between people, with some individuals having a lower capacity for pleasure (Meehl, 1975). According to this theory, the anhedonic individual is inherently less responsive to positive reinforcers and thus anhedonia has been considered a potential trait related to vulnerability to depression (Loas, 1996; Meehl, 1975). Recent findings however suggest that the construct of anhedonia is

more complex; for example, individuals with schizophrenia diagnoses exhibit high anhedonia when assessed using ‘trait’ measures but do not demonstrate anhedonia using controlled lab-based measures (Cohen et al, 2011). This example illustrates the difficulty in clinical assessment and treatment implications of anhedonia and has led researchers to call for a more refined conceptualisation of anhedonia which distinguishes between its different functional aspects, e.g. ‘consummatory anhedonia’ or hedonic responsivity to rewards and ‘anticipatory’ or ‘motivational anhedonia’(reward ‘wanting’) which relates to the drive to pursue rewards, as research has shown that depressed and schizophrenic patients can experience in-the-moment pleasure despite deficits in motivation to pursue such rewards (Treadway & Zald, 2010). More recently, the concept of ‘decisional anhedonia’ has been proposed as a means of capturing the role of anhedonic symptoms in decision-making, as anhedonia has been hypothesised to play a key role in reward responsivity and has been associated with dysfunction in the brain reward system, specifically related to motivation and effort-based decision-making (Pizzagalli et al, 2008; Treadway & Zald, 2010; Treadway & Zald, 2013).

Research has also examined the relationship between anhedonia and substance misuse. Anhedonia has been associated with the transition from recreational to excessive drug use and also in withdrawal symptomatology, abstinence and relapse to drug taking (Hatzigiakoumis, Martinotti, Giannantonio, Janiri, 2011; Martinotti et al, 2012; Volkow et al, 2002). Evidence suggests that acute cessation of drug taking in chronic users may result in diminished processing of non-drug rewards coupled with an increase in anhedonia, (Lawn et al, 2015; Goldstein & Volkow, 2011; Koob & Le Moal, 2008; Koob & Volkow, 2009; Pizzagalli et al, 2005). Heinz et al (1994) found anhedonia to be a common symptom shared by schizophrenic,

depressed and alcohol dependent patients during withdrawal and they theorised that this was related to hypoactivity of dopaminergic transmission in the brain's reward system, which was supported by neuroimaging evidence (Heinz, Schmidt & Reischies, 1994).

### **Prodromal psychosis: symptomatology**

Research on transition to psychosis postulates the existence of a prodromal period where changes in functioning and sub-threshold diagnostic symptoms (including changes in affect, perception, thought processes and drive) are frequently experienced before the onset of threshold psychosis symptoms (Yung et al, 2005). It has been characterised as the period of time between initial self-experienced or self-reported changes and the onset of the first observable psychotic symptoms. This time period lasts between months and years although identifying discrete time points in the onset and 'offset' of the prodrome is difficult as the boundary between 'pre-psychotic' and 'psychotic' is blurred (Yung & McGorry, 1996b, Yung et al, 2003). Studies of first-episode psychosis have identified common features of the prodromal period including reduced attention, reduced drive and motivation, depressed mood, sleep disturbance, anxiety, social withdrawal, suspiciousness, deterioration in role functioning and irritability (Yung & McGorry, 1996b).

By developing knowledge of the specific presentations and mechanisms underlying the onset and progression of psychosis, early assessment and interventions which aim to minimise or prevent the onset of full-blown psychosis may be possible (Yung & McGorry, 1996a; McGorry, 1998). Research has shown that lack of early intervention and an extended 'duration of untreated psychosis' leads to poorer prognosis and outcomes among adolescents (NICE Guidelines,

2013). For early intervention to be effective, clinicians need valid methods of diagnosis to reliably identify symptoms that put individuals at risk of developing full-blown psychosis (Yung et al, 2004). This is particularly true since the wide range of prodromal psychosis symptoms has very limited predictive power in determining whether presence of any cluster of these symptoms will in fact lead to psychosis (McGorry, 1998; Yung et al, 2003). The prodromal period cannot be defined by ‘necessary and sufficient’ symptoms as symptoms are non-specific (Olsen and Rosenbaum, 2005).

A number of measures have been used in an attempt to accurately define the initial prodromal period and its progressive stages (Klosterkotter et al, 2001; Yung et al, 2003). Two approaches to detecting and measuring prodromal symptoms have emerged – the ‘basic symptoms’ approach and ‘attenuated positive symptoms’ (Olsen & Rosenbaum, 2005). The basic symptoms approach assesses symptoms characterising the earliest prodromal phase, but also thought to be present during the entire progression of psychosis; basic symptoms are subtle self-experienced deficits in areas such as perception, cognition, language, motor function, initiative, energy, etc. (Olsen and Rosenbaum, 2005; Simon et al, 2007; Yung et al, 2005). Assessment instruments employing this approach include the Bonn Scale for the Assessment of Basic Symptoms (BSABS), the Schizophrenia Prediction Instrument – Adult Version (SPI-A), and the Early Recognition Inventory (ERIAS). The second approach operationalises ‘Attenuated Positive Symptoms’, focusing on symptoms in the late prodromal phase and includes the Comprehensive Assessment of At-Risk Mental States (CAARMS) and the Structured Interview of Prodromal Syndromes (SIPS) as the main assessment instruments (Olsen and Rosenbaum, 2005).

While a review of these instruments suggests that they are all able to detect individuals at increased risk of psychosis, they generally give more weight to positive symptoms and underestimate negative symptoms and other symptoms unrelated to full-blown psychosis (e.g. anomalous self-experience) (Olsen and Rosenbaum, 2005). Interestingly, in a study of ‘ultra-high risk’ young people, high levels of ‘negative’ type symptoms (including disturbances of affect and cognition, decreased energy and difficulty tolerating stress) were found to be more predictive of psychosis than sub-threshold ‘positive’ symptoms (Yung et al, 2005). This may suggest a greater role for negative symptoms in fuelling the transition from non-troublesome positive symptoms to actual psychosis (Van Os, 2002; Yung et al, 2005). The role of negative symptomatology in the prodrome period cannot be underestimated given the high incidence of drug use in individuals with psychosis and the significance of anhedonia in schizophrenia, depression and substance abusing populations.

### **Prodromal symptomatology and chronic drug use**

Chronic patterns of drug use may not only influence the risk of psychosis but also can offer useful models for understanding psychosis and the prodromal profile. Acutely, both ketamine and cannabis induce psychosis-like symptoms in healthy individuals (Morgan, Mofeez, Brandner et al, 2008; D’Souza et al, 2004). Using the ‘basic symptoms’ approach, Morgan et al (2012) assessed schizophrenia proneness and neurocognitive function in non-psychotic individuals dependent upon ketamine, cannabis and cocaine, and found that ketamine and skunk users demonstrated high levels of attentional and cognitive disturbances. This was the first study of its kind to assess schizophrenia proneness in users of these drugs and to identify distinct

profiles consistent with those of individuals who subsequently transitioned from prodrome to psychosis. Chronic ketamine users in particular exhibited the greatest levels of basic symptoms compared to the other two drug groups, demonstrating a high level of affective symptoms comparable to clinically assessed prodromal patients who transitioned to psychosis. This was consistent with increased depressive symptoms characteristic of chronic ketamine use (Morgan et al, 2012; Muetzelfeldt et al, 2008).

### **Aims**

The present study has two main aims. First, it seeks to build on Morgan et al's (2012) findings by assessing prodromal symptomatology using self-report measures (O-LIFE, PQ-B) in dependent cannabis and ketamine users, and to compare these to healthy controls. If the drug groups score highly on measures of schizotypy and positive psychosis symptomatology relative to controls, this may provide further support for the recommendation that future studies on the risk of transition to psychosis should dissociate symptoms associated with chronic drug use from those that are characteristic of prodromal psychosis.

The second aim focuses on reward processing aspects of anhedonia and will objectively measure differences in reward motivation and hedonic processing in the two groups of dependent drug users (cannabis and ketamine), comparing these to healthy controls. A self-report trait anhedonia measure, the Temporal Experience of Pleasure Scale (TEPS; Gard, Gard, Kring & John, 2006) will be administered alongside two laboratory-based tasks. The first will assess reward sensitivity using a probabilistic reward task based on signal detection theory (Pizzagalli et al, 2005), and will attempt to capture differences in participants' ability to modulate behaviour

as a function of prior reinforcements, which may aid our understanding of which aspects of hedonic processing might be dysfunctional in dependent drug users. The second task, the ‘Effort-Expenditure for Rewards Task’ (or ‘EEfRT’, Treadway et al, 2009) will assess reward motivation and effort-based decision-making by measuring willingness to expend effort for rewards (which would be expected to be low in individuals exhibiting anhedonia). Given the co-morbidity of psychiatric conditions in which anhedonia is a significant factor and our current limited understanding of motivational deficits for non-drug rewards in drug dependent populations, objectively examining motivated behaviour may inform treatment strategies for anhedonia (e.g. the development of behavioural therapies to reinforce behaviour motivated towards non-drug rewards).

### **Hypotheses**

On the basis of Morgan et al’s (2012) study of chronic ketamine and cannabis users and previous studies examining reward responsivity in depressed and schizophrenic patients, the following predictions were made:

- 1) It is predicted that the cannabis and ketamine using groups will score higher than controls on measures of psychosis-like symptomatology as indexed by the four subscales of the O-LIFE and PQ-B.
  
- 2) On the probabilistic reward task (‘PRT’), it is hypothesised that there will be differences between groups in response bias toward more frequently rewarded stimuli (the main outcome variable in this task), with the two drug-using groups showing weaker response bias relative to controls (Bogdan & Pizzagalli, 2006;

Heerey, Bell-Warren & Gold, 2008; Pizzagalli, Jahn & O'Shea, 2005; Pizzagalli, Iosifescu & Hallett, 2009). Due to potential cognitive effects of long-term drug use, we also predicted group differences in accuracy, reaction time and discriminability, with the drug using groups performing less accurately, more slowly and with less ability to discriminate between stimuli than controls.

3) On the effort-based decision making task ('EEfRT'), it was hypothesised that groups would differ on propensity to choose the task requiring greater effort ('hard' task), with the cannabis and ketamine groups making less 'hard' choice tasks as the probability of winning decreases.

4) Further exploratory within-group correlations between drug use, self-report measures and task outcomes will be carried out.

## **METHOD**

### **Power Calculation**

The power calculation was based on Morgan et al's (2012) study investigating psychosis-proneness and neurocognitive function in individuals dependent on ketamine, cannabis or cocaine. They found significant differences in SPI-A scores between controls, dependent cannabis and dependent ketamine users, with a large effect size across domains. Using the 'G\*Power 3' program (Faul, Erdfelder, Lang and Buchner, 2007), statistical power analysis estimated a total sample size of 42, or 14 participants per group to obtain statistically significant results with a power level of 0.80 and alpha level of 5% (based on the 'Pizzgalli' probabilistic reward task and likelihood of obtaining an interaction between three groups across two time points).

The number was slightly lower than that used in Morgan et al's study and, as our initial design incorporated a similar clinical interview to Morgan et al's (2012) study, we increased the sample to 60 in total (20 per group).

### **Participants and Design**

A between-subjects design was used to compare ketamine users, frequent cannabis users and controls who reported no regular illicit drug use. Participants were recruited through advertisement and via snowball sampling (Solowij, Hall & Lee, 1992). All participants provided written informed consent and were paid £20 for their participation upon completion of the study. Inclusion criteria were: men and women aged 18-50 years, native English speakers or fluent in English if a second language, no use of psychiatric medication or use of mental health services in the past six months, and no diagnosis of alcohol use disorder. Further, each group had to meet specific criteria for illicit drug use as rated by the Severity of Dependence Scale (SDS, Gossop et al, 1992), as follows:

- The ketamine using group scored at least 3 or more on the SDS for ketamine use.
- Cannabis users reported using high potency cannabis ('skunk') on more than 50% of the occasions they consumed cannabis and scored 3 or more on the SDS for cannabis use.
- Use of other illicit drugs in the cannabis and ketamine groups was 2 or less on the SDS for other drugs (e.g. benzodiazepines). One exception was use of cannabis in the ketamine group, which is common, and the SDS cut-off for cannabis in this group was raised to 3.

- Controls were recreational poly-drug users (i.e. infrequent use of illicit drugs in the past and/or present) and had to score 2 or less on the SDS for any illicit drug use.

### **Joint Thesis**

This thesis formed part of a joint research project and was completed together with one fellow trainee clinical psychologist, Lisa Harvey (UCL: Ultra high risk for psychosis? Chronic ketamine and cannabis users' performance in attribution assignment and auditory hallucination tasks). See Appendix 1 for further details of contributions made by each trainee.

### **Ethics**

The study was approved by the UCL Graduate School Ethics Committee (see Appendix 2).

### **Procedure**

Prior to taking part, participants were given either a hard or electronic copy of the study information sheet (see Appendix 3) outlining details of the testing procedure. Participants were invited to an individual testing session and were asked to abstain from using drugs and alcohol for 12 hours prior to the start. At the start of the session, they were asked to provide written, informed consent (see Appendix 4). They were asked for information on demographics, use of drugs and alcohol over the past two days, and their current and past drug use. They then completed the series of assessments given below. A urine sample was collected to give an objective index of recent drug use.

## **Assessments**

Tests were chosen to assess substance dependence, mood (including aspects of depression and anhedonia) and psychotomimetic symptoms. Computer-based cognitive tasks were used to assess motivated behavior and a structured interview explored subjective views of individual performance on and perceived aims of these tasks. Assessments were administered in the same order to all participants as follows: SDS (one each for cannabis, ketamine, and other frequently used-drugs), Spot the Word, EEfRT computer task, BDI, TEPS, O-LIFE, PQ-B, Probabilistic Reward Task, and brief interview about tasks following completion of testing. (Three other computer-based tasks relevant to the other researcher were included in the testing protocol but are not included here.)

## **Objective Measure of Recent Drug Use**

Urinalysis was carried out for all participants using DrugCheck® NxStep Onsite Urinalysis Test Cups, which indicated presence or absence of 12 drugs: amphetamine, barbiturate, buprenorphine, benzodiazepine, cocaine, MDMA/ecstasy, methamphetamine, methadone, oxycodone, phencyclidine, and cannabis.

## **Subjective Rating Scales**

*Severity of Dependence Scale (Gossop, Griffiths, Powis & Strang, 1992)*

The Severity of Dependence Scale (SDS) consists of five questions related to problems of recent drug dependence and asks respondents if they have experienced these at any time in the past year, e.g. ‘During the past year, did you think your use of cannabis was out of control?’ Respondents choose from the following answers:

‘never/almost never’, ‘sometimes’, ‘often’, or ‘always/nearly always’, scored on a four-point scale (0-3; 0 is ‘never/almost never’, 3 is ‘always/nearly always’). A total score is based on scores for the five items was derived to assess overall dependence per drug. All participants completed an SDS each for cannabis, ketamine and other illicit drugs if used more than once a month over the past year. The SDS was used both as a screening tool in determining eligibility for inclusion in the drug-using groups, and was also administered during the testing session.

*Spot-the-Word Test: Version B (Baddeley, Emslie & Nimmo-Smith, 1993)*

This lexical decision test was administered to provide an estimate of premorbid verbal intelligence (as it correlates with such estimates, e.g. NART). This measure was used both as a means of matching groups for premorbid intelligence and also for comparing scores on cognitive tasks to premorbid intelligence across groups. It was chosen as it is a non-anxiety inducing estimate.

The task instructs respondents to tick the item they believe to be the real word from each of 60 pairs of words and nonsense words (e.g. ‘wraith – sribble’, ‘palindrome – lentathic’, ‘drobble – infiltrate’). The sum of correctly identified words constitutes a score denoting pre-morbid IQ, with a maximum score of 60. This version of the task produces a measure of IQ that, when tested in a large sample of wide ranging age and ability, has produced a correlation of 0.859 with performance on the NART, widely regarded as a valid and reliable predictor of verbal intelligence (Baddeley et al, 1993).

*The Beck Depression Inventory (BDI-II: Beck, Steer, & Brown, 1996)*

This is a 21-item self-report questionnaire assessing the presence and severity of depression symptoms as outlined in the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV: APA, 1994). This measure was used to explore the relationship between low mood, drug use and performance on cognitive tasks. Previous studies have demonstrated that low mood impacts on cognitive task performance, with an association between greater severity of depression and reduced performance in the domains of episodic memory, executive function and processing speed (McDermott & Ebmeier, 2009). Thus it was necessary to include a measure of depressive symptomatology so as to examine the relationship between mood and performance on cognitive tasks across groups in this study. Also, as the theoretical construct of anhedonia, a key component of depressive symptomatology, is central to the research aims, it was important to have a subjective measure of mood which contains an anhedonia subscale, which the BDI-II does (Pizzagalli et al, 2005; Joiner et al, 2003).

The BDI-II requires subjects to rate themselves on measures of the following dimensions: sadness, pessimism, past failure, loss of pleasure, punishment feelings, self-dislike, self-criticalness, suicidal thoughts, crying, agitation, loss of interest, indecisiveness, worthlessness, loss of energy, changes in sleeping, irritability, changes in appetite, concentration difficulty, tiredness or fatigue, and loss of interest in sex (Beck et al, 1996). Each item asks participants to choose from 4 options of Likert-scale type responses which range from a score of 0 ('not applicable') to 3 ('severe 'rating for recent experience of the item in question).

A score for overall severity of depression is calculated by adding together totals for all BDI-II items, with 63 as a maximum possible total score. The BDI-II also contains two subscales, comprising ‘Cognitive’ and ‘Somatic’ symptoms, which have been found to be valid constructs within the more robust dimension of general depression (Steer, Ball, Ranieri & Beck, 1999; Wang & Gorenstien, 2013). The Cognitive subscale consists of eight items (pessimism, past failures, feelings of guilt, self-dislike, self-criticalness, suicidal thoughts, and worthlessness) and the Somatic subscale 13 items (sadness, loss of pleasure, crying, agitation, loss of interest, indecisiveness, loss of energy, changes in sleep pattern, irritability, change in appetite, concentration difficulty, tiredness/fatigue, and loss of interest in sex). Finally, other research has devised a separate construct of an anhedonic subscore for the BDI-II, comprised of four items which specifically tap features of anhedonia (loss of pleasure, loss of interest, loss of energy and loss of libido) (Joiner et al, 2003; Pizzagalli et al, 2005). Each subscale score results from totaling the relevant items.

*Short Oxford-Liverpool Inventory of Feelings and Experiences Questionnaire (O-LIFE) (Mason, Claridge & Jackson, 2005)*

The O-LIFE is a self-report measure comprised of 43 items, and has been developed as a questionnaire measuring ‘psychosis-proneness’, or schizotypy, in healthy populations. It was included in this study to index psychotic-like traits across groups.

The O-LIFE has been used widely in experimental and clinical studies and, at the time of its development, its contents were based on the most extensive study of schizotypal traits to date, involving factor analysis of 15 psychosis-proneness scales

in over 1000 subjects (Claridge, McCreery, Mason et al, 1996). This measure adopts a dimensional view of schizotypal characteristics and breaks down the construct of schizotypy into four factors: (i) unusual experiences, (ii) cognitive disorganisation, (iii) introvertive anhedonia, and (iv) impulsive nonconformity (Claridge et al, 1996). The O-LIFE has high internal consistency (Mason et al, 1995), high test-retest reliability (Burch, Steel & Hemsley, 1998), and high construct validity, having been used in studies across a wide range of research domains (Mason et al, 2006).

Sample items of questions included in the O-LIFE include:

- (12) Do you ever feel that your speech is difficult to understand because the words are all mixed up and don't make sense?
- (23) Can some people make you aware of them just by thinking about you?

Participants are asked to tick 'yes' or 'no' for each item. 1 point is given to yes responses and 0 to no responses for most items, with the exception of several items in which scores are reversed (items 4, 9, 17, 27, 30, 37, 39, 31). A total O-LIFE score is obtained by summing all items, and scores for each of the four subscales is obtained by summing scores for relevant items as follows:

1. *Unusual Experiences* – items relate to 'positive' psychotic-like symptomatology, propensity for unusual perceptual experiences (e.g. hallucinations), 'magical thinking' or beliefs and interpretations (e.g. delusions); includes 12 items (2, 5, 6, 8, 10, 13, 19, 23, 26, 29, 34, 35)
2. *Cognitive Disorganisation* – items relate for tendency for thoughts to be disordered or tangential, attention difficulties, etc.; includes 11 items (1, 7, 12, 16, 20, 24, 31, 33, 36, 38, 42).

3. *Introvertive Anhedonia* – items relate to negative psychotic-like symptomatology, or a tendency to introversion, anhedonia and asocial behavior; includes 10 items (4, 11, 15, 17, 22, 25, 27, 30, 32, 41)
4. *Impulsive Nonconformity* – items relate to tendency toward unstable mood and behavior (e.g. risk-taking or impulsive behavior that disregards social convention); includes 10 items (2, 9, 14, 18, 21, 28, 37, 39, 40, 43)

The first three subscales are in line with the three factor model of psychoses theorised by Liddle (1987) and consensus suggests that schizotypy reliably relates to these three components (both positive and negative psychosis symptomatology and cognitive disorganisation) (Mason & Claridge, 2006; Vollema & Hoijtink, 2000). The fourth subscale relating to ‘impulsive nonconformity’ reflects clinical evidence of the need for a broader concept of psychosis-proneness (e.g. the identification of common features between schizophrenia and bipolar disorder, which give weight to the theoretical view of psychosis as a unitary illness) (Mason & Claridge, 2006).

*Temporal Experience of Pleasure Scale (TEPS; Gard, Gard, Kring & John, 2006)*

The TEPS is a self-report scale designed to assess individual trait characteristics relating to two distinct aspects of the experience of pleasure (Gard et al, 2006). Based on neuroscience, social psychology and clinical psychology studies which give weight to conceptualising these aspects of pleasure as distinct processes, its authors developed the TEPS with two subscales distinguishing between anticipatory pleasure, which relates to pleasure experienced in anticipation of future pleasurable activities, and consummatory pleasure, which is pleasure experienced in the moment, upon reward attainment (Gard et al, 2006; Gard, Kring, Gard, Horan and Green,

2007). The authors hypothesise that anticipatory pleasure (the experience of wanting) activates motivational processes, which push the individual to go after a particular stimulus that will induce in-the-moment consummatory pleasure (Gard et al, 2006). The TEPS focuses on these two aspects of physical pleasure (as this type of hedonic experience is common across humans) and consists of 18 statements which participants are asked to rate in terms of how true or false the statements are for them. Sample items for each subscale include:

Anticipatory pleasure subscale:

- (1) When something exciting is coming up in my life, I really look forward to it.
- (2) When I think about eating my favorite food, I can almost taste how good it is.

Consummatory pleasure subscale:

- (6) I enjoy taking a deep breath of fresh air when I walk outside.
- (15) Looking forward to a pleasurable experience is in itself pleasurable.

Items are scored on a scale from one to six, where one is 'very false for me' and six is 'very true for me'. The 'anticipatory pleasure' subscale consists of 10 items (items 1, 3, 7, 11, 12, 14, 15, 16, 17, 18 – item 7 is reverse-scored) and the 'consummatory pleasure' subscale is 8 items (items 2, 4, 5, 6, 8, 9, 10, 13) (Gard et al, 2006). An overall score is obtained from summing all items, while subscale scores are obtained by totalling relevant items.

The TEPS is brief and has been found to be reliable, temporally stable and valid, as exploratory factor analysis in four independent samples of US students supports the theoretical differentiation of these two constructs of pleasure, though

confirmatory factor analysis has produced mixed results in terms of the measure's construct validity (Gard et al, 2006; Ho, Cooper, Hall, Smillie, 2014).

*Prodromal Questionnaire – Brief (PQ-B; Loewy, Pearson, Vinogradov, Bearden & Cannon, 2011)*

The PQ-B is a brief self-report screening measure for psychosis risk syndromes, developed in response to the need for more efficient and accurate methods of identifying psychosis risk in young people (Loewy et al, 2011; Loewy, Bearden, Johnson, Raine & Cannon, 2005). Evidence supports its effectiveness as a first-level screening instrument to identify at-risk individuals who would then undergo further clinical assessment (e.g. the CAARMS) to establish diagnosis (Loewy et al, 2011; Sandberg, Richards & Erford, 2013). It has been shown to be effective in differentiating between those with a prodromal or psychosis diagnosis and non-psychotic spectrum patients, as diagnosed by the SIPS (Structured Interview for Prodromal Syndromes), and has been recommended for use in screening help-seeking individuals for psychotic disorders (Loewy et al, 2011; Miller et al, 2003; Sandberg et al, 2013).

The PQ-B consists of 21 items pertaining to positive psychosis symptoms for which participants are asked to answer yes or no (scored 1 for 'yes' and 0 for 'no'). Totalling the items for these main questions results in a PQ-B total score. For items marked 'yes', participants are asked to indicate their agreement with the statement, "When this happens, I feel frightened, concerned, or it causes problems for me," on a 5 point Likert-style rating scale which ranges from 'strongly disagree' (scored as 1) to 'strongly agree' (scored as 5) (Loewy et al, 2011). A total PQ-B 'distress score' is obtained by adding together values for these secondary questions.

## Cognitive Tasks

The cognitive assessments used were chosen to objectively examine hedonic capacity, which was operationalised as reward sensitivity and responsiveness in each task.

### *1. Probabilistic Reward Task (Pizzagalli, Jahn & O'Shea, 2005; Pizzagalli, Iosifescu, Hallett, Ratner and Fava, 2009; Tripp & Alsop, 1999)*

The probabilistic reward task, or PRT, was developed by Pizzagalli et al (2005) and is rooted in signal detection theory. The PRT objectively assesses participants' tendency to respond to reinforcements by modulating their behaviour. Specifically, reward responsiveness is operationalised in this task by the degree of response bias participants display towards the more frequently reinforced of two different stimuli. Importantly, in signal-detection tasks such as the PRT, unequal frequency of reward between two types of correct responses to stimuli typically engenders a systematic preference for the response paired with the more frequent or greater reward (Macmillan and Creelman, 1991; McCarthy, 1991; Pizzagalli et al, 2005). Initial studies using the PRT hypothesised that reduced responsiveness to reinforced stimuli would serve as a behavioural expression of diminished hedonic capacity (Pizzagalli et al, 2005; Pizzagalli et al, 2009).

The PRT lasts approximately 20 minutes and was presented to participants on a 15.6 inch PC laptop monitor using Matlab 7.13 (R2011b). In each trial, participants focused on a fixation cross which appeared for 500ms, followed by a mouthless cartoon face for 500ms. Next, the stimulus appeared in the form of a straight line mouth on the previously mouthless face, which was shown for 97ms. After the

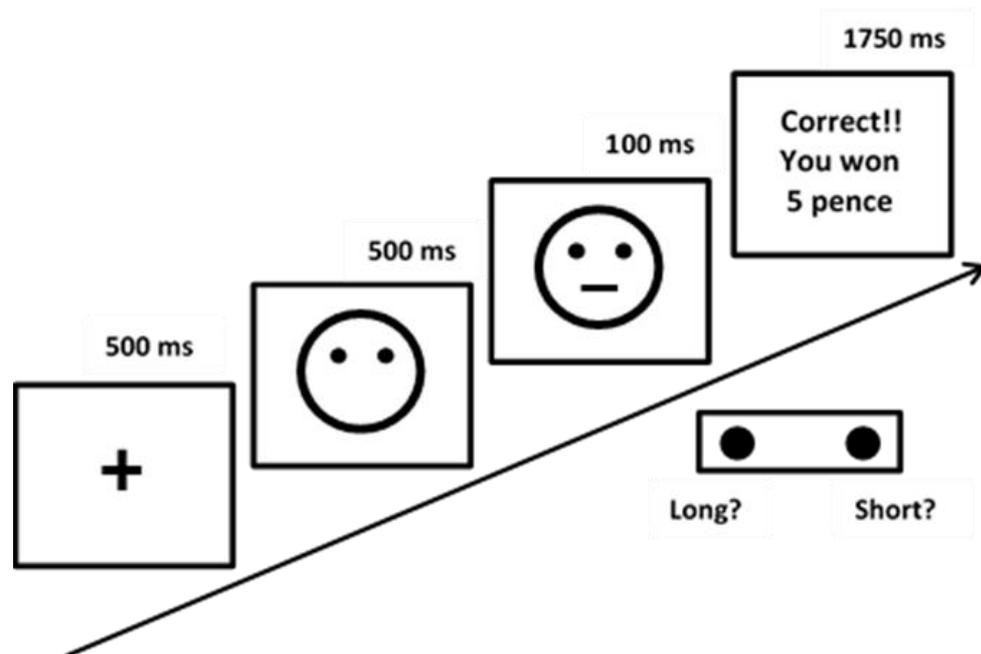
mouth disappeared, the mouthless face remained on the screen for 1500ms or until the participant made a response. Participants were instructed to make a choice as to whether the mouth displayed was short (8.2 mm) or long (9.1 mm) by pressing the appropriate button to indicate their choice – ‘v’ for a short mouth and ‘m’ for a long mouth.

The task was virtually identical to those used in prior studies that employed this paradigm (Pizzagalli et al, 2005; Pizzagalli et al, 2009; Tripp and Alsop, 1999), with several minor exceptions. The PC screen size was slightly smaller (1.4 cm smaller than the 17 inch screen used in Pizzagalli et al, 2009) and thus stimuli were proportionally reduced in size compared to the previously cited studies. Also, the task included two blocks comprised of 100 trials each rather than three blocks of trials as in previous studies, in an attempt to minimise cognitive fatigue, as the overall testing protocol was approximately two hours in duration.

As outlined in previous studies using this task, the duration of stimulus exposure and mouth sizes were selected after piloting so as to achieve overall hit rates of 75-85%. Differences between mouth sizes and length of stimulus exposure were small so as to provide a model environment for the development of response bias without unduly encouraging performance at chance level (Pizzagalli et al, 2009).

An asymmetric reinforcement ratio was used to generate a response bias using two versions of the task (McCarthy & Davison, 1979; Tripp & Alsop, 1999, as in Pizzagalli et al, 2009). In Version A, correct identification of the short mouth was rewarded three times more frequently than correct identification of the long mouth; thus, in this version, the short mouth was considered the ‘rich stimulus’ and the long mouth was the ‘lean stimulus’. The reward was indicated by a message appearing on the screen after participants pressed the button for the correct mouth, saying,

“Correct!! You won 5 pence.” Version B was reversed, so that the long mouth was the ‘rich stimulus’ and was reinforced three times more frequently than the ‘lean stimulus’ (the short mouth). Task versions, and therefore reinforcement allocation, were counterbalanced across participants.



**Figure 1. Schematic illustration of PRT design.** Each trial asked participants to decide whether the mouth shown was short (8.2 mm) or long (9.1 mm) by pressing ‘v’ (short) or ‘m’ (long). The reinforcement allocation was counterbalanced across subjects.

At the start of the task, participants were instructed to win as much money as possible by correctly identifying the mouth in each trial. They were informed that sometimes correct responses would be rewarded (“Correct!! You won 5 pence”), but that not all correct responses would be rewarded. Non-rewarded responses, which included both correct and incorrect responses, were followed by the message, “You did not win anything.” As in previous studies, a controlled reinforcer procedure was implemented, so that all participants would be rewarded for only 40 correct trials, 30

‘rich’ and 10 ‘lean’ (Johnstone & Alsop, 2000; McCarthy & Davison, 1979). This ensured that the reinforcement ratio remained constant irrespective of participants’ performance. Effectively, if participants responded incorrectly on a trial that was scheduled to be rewarded, the reward feedback would be delayed until the correct identification of the same stimulus type (‘rich’ or ‘lean’) in a later trial. Feedback (whether reward or non-reward) appeared on the screen for 1500ms immediately following a correct response and was followed by a blank screen for 2000ms. Importantly, participants were not told that one stimuli would be disproportionately rewarded.

2. *‘Effort-Expenditure for Rewards Task’ (EEfRT) (Treadway, Buckholz, Schwatzman, Lambert and Zald, 2009)*

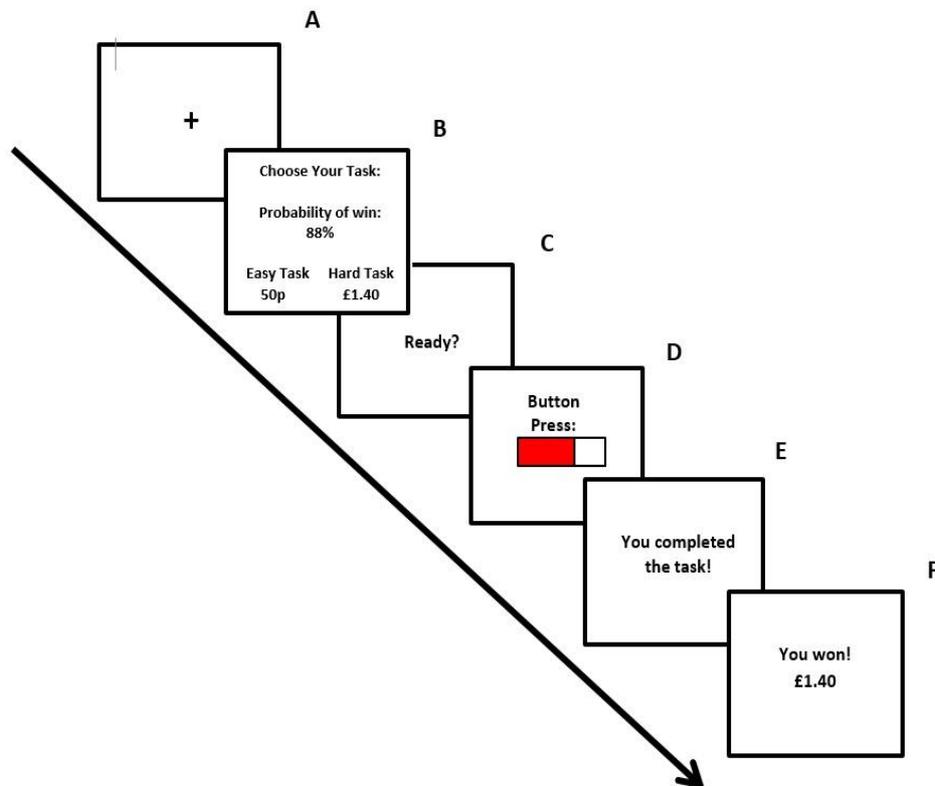
The Effort-Expenditure for Rewards Task (EEfRT) is an objective measure of effort-based decision-making that aims to examine the link between anhedonia and theorised reward ‘wanting’ (or anticipatory pleasure) in human participants (Treadway et al, 2009). It adapts a concurrent choice paradigm exploring effort-based decision-making in rodents (Salamone, Cousins, McCullough, Carriero & Berkowitz, 1994) in which participants are presented with a series of trials in which they are asked to choose between completing a ‘hard’ or ‘easy’ task, with the aim of earning changing amounts of money, with each trial differing in terms of probability that it will be rewarded (Treadway et al, 2009). The task therefore allows for an analysis of how reward magnitude, probability of being rewarded and expected reward (reward magnitude x probability) influence effort-based decision-making and anhedonia (Treadway et al, 2009). Performance on the EEfRT has been correlated

with trait anhedonia (as assessed by the Chapman Anhedonia scale), demonstrating construct validity (Treadway et al, 2009).

A modified version of the original EEfRT (Treadway et al, 2009) was used in this study; the main modification is that it was shortened and all participants completed 2 practice trials and 21 actual trials in total. Unlike Treadway et al's (2009) study, our task ended after 21 trials, rather than after an allotted period of time. This was done to shorten the overall testing protocol and simplify the task.

Each trial within the task began with a fixation cross appearing on the screen for 1000ms, followed by the presentation of details on the trial, including probability of winning and monetary values rewarded for easy versus hard task choice.

Participants were informed that they had 5 seconds to choose either the 'easy' or 'hard' task, otherwise the program would make a random choice. This was followed by a 1000ms 'Ready?' screen, and then the actual button-press task. Participants were required to make repeated and fast manual button presses within the allotted time, by pressing the spacebar quickly with the little finger on their non-dominant hand. Each button press increased the level of a bar on the screen and participants were informed that raising the bar to the 'top' would result in successful completion of the trial. Hard-task trials required participants to make 100 button presses within 21 seconds, while easy-task trials required 30 button presses within 7 seconds. A 2000ms feedback screen following completion of each trial informed participants whether they successfully completed the trial or not. If completed successfully, another feedback screen appeared for 2000ms with reward feedback (i.e. whether they had won money for that trial). (Treadway et al, 2009).



**Figure 2. Schematic diagram of a single trial of the ‘EEfRT’** A) Participants begin by seeing a 1000ms fixation cue. B) 5000ms choice period in which participants are presented with information regarding the reward magnitude of the hard task for that trial and the probability of receiving any reward for that trial. C) 1000ms ‘ready’ screen. D) Participants make rapid button presses to complete the chosen task for 7000ms (easy task) or 21000ms (hard task). A bar fills up with each button press until task is finished and bar is full. E). Participants are told whether they completed the task. F) Participants receive reward feedback as to whether they received any money for that trial.

For easy-task trials, participants could win 50 pence if the trial was rewarded.

Hard-task trials varied in potential win amounts; participants could win one of five amounts ranging between 70 and 200 pence. As only some completed trials were considered ‘win’ trials, participants were given probability cues at the start of each trial, with each trial being one of three probability levels: ‘high’ (88% probability of being a win trial), ‘medium’ (50% probability of win) and ‘low’ (12% probability of win). Probability levels applied to both hard and easy-task choice in each trial, and

each level was equally distributed across the task. Also, each probability level appeared once together with each level of monetary reward value for the hard task. The order of trials was randomised and participants were presented trials in the same (randomised) order (Treadway et al, 2009).

Before the start of the EEfRT, participants were informed that they would receive winnings for only two successfully completed and rewarded trials, which would be selected at random upon completion of the task. Participants were not given any further information about the distribution of hard vs. easy tasks. The variation in probability and reward values meant that participants had to make decisions within a brief amount of time, without the ability to calculate optimal response selection. The task was designed in this way so as to generate individual patterns of responses in participants' willingness to expend effort for differing expected rewards (Treadway et al, 2009).

### *Data Preparation for Cognitive Assessments*

#### *1. PRT*

Performance on the task was measured in terms of response bias, discriminability, reaction time (RT), and accuracy, based on previous studies (Pizzagalli et al, 2005, Pizzagalli et al, 2009, Bogdan & Pizzagalli, 2006). Response bias, the main outcome variable, reflects the participant's propensity to select the response paired with the more frequent reward, and thus the extent to which participants modulate their behavior by reinforcement history (Pizzagalli et al, 2009; Pizzagalli et al, 2005). Response bias was calculated as follows:

$$\text{Response Bias: } \log b = \frac{1}{2} \log \left( \frac{\text{Rich correct} \times \text{Lean incorrect}}{\text{Rich incorrect} \times \text{Lean correct}} \right)$$

High rates of correct response for the ‘rich’ stimulus (hits) and high miss rates for the ‘lean’ stimulus result in a high response bias.

Discriminability indexes participants’ ability to differentiate between the two stimuli and is therefore used as a measure of task difficulty. It was computed as follows:

$$\text{Discriminability: } \log d = \frac{1}{2} \log \left( \frac{\text{Rich correct} \times \text{Lean correct}}{\text{Rich incorrect} \times \text{Lean incorrect}} \right)$$

Other analyses were carried out on hit rate scores (percent correct responses) and RT to explore general task performance.

## 2. *EEfRT Task*

Data from the EEfRT was exported from Matlab into SPSS (version 22) for further analysis. Mean proportions of hard task choices were created for all subjects across each level of probability (12%, 50% and 88%), as in Treadway et al’s (2009) study.

## **Statistical Analyses**

Statistical Package for Social Sciences (SPSS Version 22) was used to perform all analyses. Group differences were analysed using one-way ANOVAs and, where data were non-parametric, Welch’s *t*-test. Where an effect of group was found, simple effects were explored using Bonferroni post hoc comparisons. Independent

samples t-tests were used to compare groups on drug use variables. Mann-Whitney U tests were used where data were non-parametric. Chi-squared tests were used to analyse categorical (e.g. dichotomous) data.

The PRT data were analysed using a number of 2 x 3 repeated measures analyses of variance (RMANOVA) with block (Block 1 and Block 2) as the within-subjects factor and group (control, cannabis, ketamine) as the between-subjects factor. Post hoc comparisons were Bonferroni corrected.

Data for the EEfRT were analysed using the same two methods as specified by Treadway et al (2009). The first method used repeated measures ANOVA with group as the between subjects factor and probability level (12%, 50% or 88%) as the within subjects factor.

EEfRT data was also analysed using generalized estimating equations (GEE), which allows for trial-by-trial modelling of time-varying parameters (in this case, changes in reward value of the hard choice task) and fixed effects (e.g. gender, group, anhedonia subscale scores, etc.) (see Treadway et al, 2009). GEE models were exploratory and were carried out using SPSS 22 using an unstructured correlation matrix, with the dependent variable as hard or easy task choice. A binary logistic distribution was used to model the probability of participants choosing the hard task. For all models, independent variables included probability, reward value, expected reward value, trial number, BDI-II total score, cigarettes smoked per day, and baseline button-pressing speed. Six models were tested in total. Each model included group and gender as factors. Covariates were probability level, hard-task reward value, expected value (probability x reward value), and baseline button pressing speed. Depression (BDI-II total scores) and cigarettes smoked per day were included as covariates as these were found to differ between groups.

Correlations were performed using Pearson correlations. Correlations were applied to three categories of data – drug use data, subjective ratings and task results (for PRT and EEfRT) and were conducted when significant group differences were found. The alpha-level was raised to  $p = 0.01$  for all correlations to reduce Type I errors.

## RESULTS

### 1. Demographics and Reported Drug Use (Tables 1-5)

There were 60 participants in total: 20 ketamine users (12 females), 21 cannabis users (7 females), and 20 controls (6 females). The ethnicities of participants in the ketamine, cannabis and control groups were respectively: Black/British (0/5/0), Indian (0/1/0), White British (17/9/13), White Other (4/3/3), Other – mixed race (0/2/3). There were no statistically significant differences between groups with respect to ethnicity ( $\chi^2(10, N = 60) = 17.462, p = 0.065$ ), nor were there group differences in gender ( $\chi^2(2, N = 60) = 4.251, p = 0.119$ ). There were no significant group differences in age or Spot-the-Word scores.

The highest level of educational attainment by ketamine, cannabis and control participants respectively were: GCSEs (4/5/2), College Diploma/NVQ/BTEC Levels 2-3 (8/3/2), A-Levels (5/1/5), Undergraduate degree (2/10/9), Post-graduate degree (1/1/2). There were no statistically significant group differences in highest educational attainment ( $\chi^2(8, N = 60) = 14.880, p = 0.062$ ). There were no significant group differences in employment status ( $\chi^2(4, N = 60) = 4.391, p = 0.356$ ); the current employment status for ketamine, cannabis and control participants respectively was: Unemployed (3/3/5), employed (17/15/12), student (0/2/3).

There were significant group differences in BDI total scores ( $F(2, 56) = 5.623, p = 0.006$ ), reflecting significantly lower scores in controls compared to both ketamine ( $p = 0.018$ ) and cannabis users ( $p = 0.013$ ) (Table 1). There were also group differences in BDI Cognitive-Affective subscale scores ( $F(2, 56) = 5.805, p = 0.005$ ), with ketamine users differing significantly from controls ( $p = 0.004$ ). Group differences in BDI Somatic subscale scores ( $F(2, 56) = 4.540, p = 0.015$ ) emerged with cannabis users differing significantly from controls ( $p = 0.018$ ). There were significant group differences on the BDI anhedonia sub-scale, which is comprised of 4 items from the BDI, including ‘loss of pleasure’ (item 4), ‘loss of interest’ (item 12), ‘loss of energy’ (item 15), and ‘loss of interest in sex’ (item 21):  $F(2, 56) = 3.992, p = 0.024$ . The cannabis group had higher scores on anhedonia than controls ( $p = 0.031$ ).

While only one control participant had clinically significant depression levels (BDI depression category ‘moderate’ or ‘severe’), the cannabis and ketamine groups had 7 and 8 participants respectively with clinically significant depression (BDI depression category: ‘mild’ – 5 cannabis / 6 ketamine; ‘moderate’ – 1 cannabis / 2 ketamine, ‘severe’ – 1 cannabis / 1 ketamine). There was a statistically significant association between group and clinical depression,  $\chi(2) = 6.9, p = 0.032$ , with the drug using groups more likely to meet the BDI cut-off for clinical depression.

**Table 1.** Group means (sd) for demographics (One-Way ANOVAs, Bonferroni corrected).

	<b>Controls</b>	<b>Cannabis Users</b>	<b>Ketamine Users</b>
<b>Age</b> (years)	27.25 (6.80)	27.75 (7.31)	26.85 (3.25)
<b>Spot the word score</b> (no. correct)	48.30 (3.36)	45.35 (3.84)	47.25 (5.20)
<b>BDI Total (n=59)</b>	5.32 (5.56)	<b>12.20 (9.00)<sup>a</sup></b>	<b>12.45 (7.47)<sup>b</sup></b>
BDI Cognitive- Affective	1.74 (1.69)	3.95 (3.59)	<b>5.15 (3.73)<sup>b</sup></b>
BDI Somatic	3.58 (4.32)	<b>8.25 (6.09)<sup>a</sup></b>	7.30 (4.66)
BDI Anhedonia	1.21 (1.40)	<b>2.65 (2.03)<sup>a</sup></b>	2.40 (1.57)

a = Can > Con, b = Ket > Con, (Bonferroni corrected *p* values)

As expected based on inclusion criteria, there were significant differences between groups in terms of days per month of current cannabis use (Welch's  $F(2, 30.427) = 252.76, p < 0.001$ ) and mean amount of cannabis used in a typical session (Welch's  $F(2, 31.487) = 37.564, p < 0.001$ ). The cannabis group used cannabis more frequently ( $p < 0.001$  compared to controls;  $p = 0.002$  compared to ketamine users) and used more cannabis in a typical session than the other groups (both  $p < 0.001$ ). There were also differences between groups on the Severity of Dependence Scale for cannabis ( $F(2, 26.536) = 44.313, p < 0.001$ ), with cannabis participants rating themselves as significantly more concerned than both controls and ketamine users about their cannabis use (both  $p < 0.001$ ) (see Table 2). The numbers of participants in the control, cannabis and ketamine groups who reported using cannabis at least once per month at the time of testing was 8, 20, and 13 respectively.

**Table 2.** Mean (sd) use of cannabis across groups (n = 20 per group).

	<b>Controls</b>	<b>Cannabis Users</b>	<b>Ketamine Users</b>	<b>p (group)</b>
<b>Number of days used in typical month</b>	1.62 (2.23)	<b>28.19 (4.74)***<sub>a, c</sub></b>	<b>10.10 (11.75)**<sub>b</sub></b>	p < 0.001
<b>Amount used in a typical session (mg)</b>	63.75 (147.48)	<b>1175.00 (553.34) ***<sub>c</sub></b>	223.75 (292.56)	p < 0.001
<b>Severity of cannabis dependence score</b>	0.10 (0.44)	<b>7.30 (3.39)***<sub>c</sub></b>	1.05 (2.50)	p < 0.001

*Difference significant at p < 0.05\*, p < 0.01 \*\* p < 0.001\*\*\**

a = Can > Con, b = Ket > Con, c = Can > Ket (Bonferroni corrected p values)

Similarly, there were group differences in ketamine use, again as expected. The mean (sd) days of current ketamine use per month for the control, cannabis, and ketamine groups were 0.02 (0.06), 0.00 (0.00) and 2.98 (6.60) respectively. A Mann-Whitney U test confirmed a significant difference between controls and the ketamine group in days per month of ketamine use (U = 367.00, p < 0.001) and also amount of ketamine (mg) currently used in a typical session (U = 365.00, p < 0.001)

Groups differed significantly in ketamine SDS scores (F (2, 57) = 266.391, p < 0.001) with ketamine users scoring significantly higher than controls (ketamine mean = 9.55 (2.56); controls mean = 0.10 (0.45)). Also, despite less frequent current use in ketamine users compared with their previous (pre-draught) heavy use, ketamine users rated themselves as more concerned than the other groups about their

ketamine use on the Severity of Dependence Scale, and their high mean rating is indicative of a higher level of self-reported dependence (Table 3).

The ketamine group used ketamine much more heavily in the past compared to currently, due mainly to widespread availability of the drug prior to the ‘ketamine drought’ at the time of data collection (Table 3).

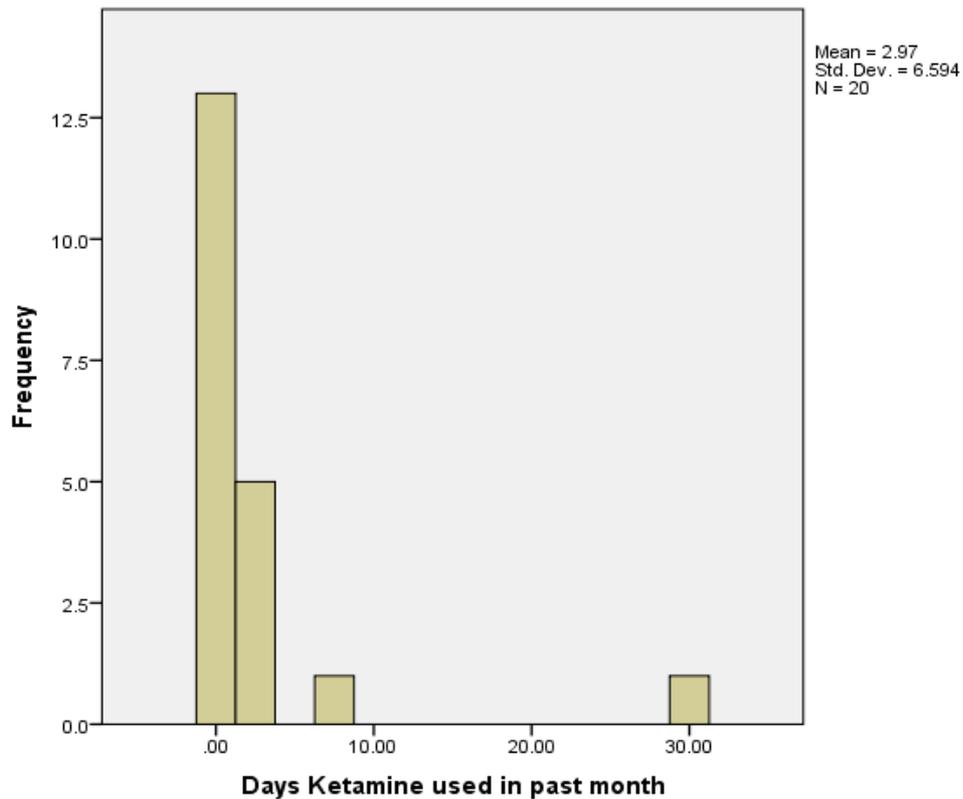
**Table 3.** Mean (sd) and median use of ketamine in ketamine group (n = 20), comparing past heavy use with current reported use.

	<b>Current reported use</b>	<b>Past reported use</b>
<b>Number of years of heavier use</b>	n/a	(n = 17)*
		5.647 (2.29)
<b>Number of days used in typical month</b>	2.98 (6.60)	29.29 (2.20)
<b>Amount currently used in typical session (mg)</b>	1355 (1055.42)	6075 (4104.48)
<b>Median amount used in typical session (mg)</b>	1250	4750
<b>Mean severity of ketamine dependence score</b>	9.55 (2.56)	N/A

\* *data missing for 3 participants*

Current use of ketamine in the past month in the ketamine group was therefore relatively low across participants (Figure 3).

**Figure 3.** Histogram depicting days of ketamine use in past month in ketamine group (n = 20).



Groups did not differ significantly in their current use of most other drugs, with the exception of tobacco (Welch's  $F(2, 34.893) = 18.085, p < 0.001$ ) and amphetamine (Welch's  $F(2, 25.495) = 4.912, p = 0.016$ ). The cannabis group used tobacco significantly more days per month than the control group ( $p < 0.001$ ); the ketamine group used amphetamine significantly more than both the control group ( $p < 0.001$ ) and the cannabis group ( $p < 0.01$ ) (See Table 4).

**Table 4.** Use of other drugs across groups (n = 20 per group).

	% regular drug use			Mean (sd) no. of days used per month		
	Controls	Cannabis	Ketamine	Controls	Cannabis	Ketamine
	(current use $\geq$ 1 day per month)					
<b>Alcohol</b>	100%	90%	95%	14.11 (7.49)	10.99 (8.61)	11.60 (8.59)
<b>Tobacco</b>	45%	95%	75%	8.71 (12.59)	<b>27.80*** (7.25)a</b>	20.05 (13.32)
<b>MDMA</b>	35%	30%	35%	0.58 (0.82)	0.38 (0.67)	0.58 (1.04)
<b>Amphetamine</b>	0%	5%	40%	0	1.00 (0.00)	<b>4.22 (2.73)**bc</b>
<b>LSD/Hallucin.</b>	10%	5%	10%	0.5 (0.7)	1.00 (0.00)	2.00 (0.00)
<b>Cocaine</b>	45%	20%	55%	1.14 (1.08)	1.50 (1.85)	1.81 (1.95)
<b>Benzodiazepine</b>	5%	15%	50%	0.27 (0.64)	1.21 (1.63)	3.03 (5.26)

*Difference significant at  $p < 0.05^*$ ,  $p < 0.01^{**}$   $p < 0.001^{***}$*

a = Can > Con, b = Ket > Con, c = Ket > Can (Bonferroni corrected  $p$  values)

Urinalysis results for all 60 participants across the 3 groups are given in Table 5.

**Table 5.** Urine screening results – % of urine sample analyses detecting each drug (n = 20 per group).

	<b>Control</b>	<b>Cannabis</b>	<b>Ketamine</b>
Missing data	15%	0%	10%
No drug	55%	5%	5%
THC	15%	95%	40%
PCP/Ketamine	5%	0%	5%
MDMA	0%	0%	0%
Amphetamines	0%	0%	10%
Benzodiazepines	5%	0%	65%
Cocaine	5%	10%	15%
LSD	0%	0%	0%
Buprenorphine	10%	0%	15%
Opioids	5%	10%	10%

## 2. Subjective Ratings – TEPS, O-LIFE, PQ-B

*Table 6. Mean (sd) scores on O-LIFE total and subscale scores in the control, cannabis and ketamine groups (n = 20 per group).*

	Controls	Cannabis	Ketamine
<b>O-LIFE Total Score</b>	11.85 (1.49)	<b>19.50 (7.25)**a</b>	<b>20.25 (6.61)**b</b>
Unusual Experiences	2.10 (1.55)	<b>6.10 (3.71)***a</b>	<b>5.15 (2.70)**b</b>
Cognitive Disorganisation	5.45 (3.97)	6.40 (2.64)	7.45 (2.95)
Introvertive Anhedonia	1.35 (1.23)	2.40 (2.01)	1.90 (1.62)
Impulsive Nonconformity	2.95 (1.73)	<b>4.60 (2.04)*a</b>	<b>5.70 (1.78)***b</b>

*Difference significant at  $p < 0.05^*$ ,  $p < 0.01^{**}$   $p < 0.001^{***}$*

a = Can > Con, b =Ket > Con, (Bonferroni corrected  $p$  values)

There was a main effect of group for O-LIFE total score,  $F(2, 57) = 9.221$ ,  $p < 0.001$ , reflecting higher O-LIFE total scores in both cannabis ( $p = 0.002$ ) and ketamine ( $p = 0.001$ ) users compared to controls; there were no significant differences between cannabis and ketamine users. There were main effects of group on two of the four O-LIFE subscales: Unusual Experiences ( $F(2, 57) = 16.014$ ,  $p < 0.001$ ) and Impulsive Nonconformity ( $F(2, 57) = 11.146$ ,  $p < 0.001$ ). Bonferroni corrected post hoc tests on these subscales revealed higher scores for both the cannabis and ketamine users compared with controls (Unusual Experiences:  $p < 0.001$  &  $p = 0.003$  respectively; Impulsive Nonconformity:  $p = 0.020$  &  $p < 0.001$

respectively). The cannabis and ketamine groups did not differ significantly from each other on these subscales.

*Table 7. Mean (sd) scores on TEPS total and subscale scores in control, cannabis and ketamine groups (n = 20 per group).*

	Controls	Cannabis Users	Ketamine Users
<b>TEPS Total score</b>	86.10 (11.74)	81.90 (12.64)	81.95 (13.61)
Anticipatory pleasure	46.45 (6.69)	46.10 (7.45)	43.75 (7.57)
Consummatory pleasure	39.25 (6.21)	35.80 (6.74)	40.15 (4.90)

*Difference significant at  $p < 0.05^*$ ,  $p < 0.01^{**}$   $p < 0.001^{***}$*

There were no significant differences between groups on TEPS total scores or the ‘Anticipatory Pleasure’ subscale. However, there was a trend toward significant group differences on the ‘Consummatory Pleasure’ TEPS subscale ( $F(2, 57) = 2.927$ ,  $p = 0.062$ ), driven by a trend difference between the cannabis and ketamine groups (ketamine scoring higher than the cannabis group:  $p = 0.077$ ).

*Table 8. Mean (sd) scores on PQ-B total and distress scores in control, cannabis and ketamine groups (n = 20 per group; n = 19 for distress score in ketamine group only).*

	Controls	Cannabis Users	Ketamine Users
<b>PQ-B Total score</b>	3.30 (3.48)	<b>9.15 (4.66)***a</b>	<b>8.55 (3.87)***b</b>
<b>Distress score</b>	9.10 (11.43)	<b>28.16 (19.83)*a</b>	<b>25.25 (12.25)*b</b>

*Difference significant at  $p < 0.05^*$ ,  $p < 0.01^{**}$   $p < 0.001^{***}$*

a = Can > Con, b = Ket > Con, (Bonferroni corrected  $p$  values)

There were significant differences between groups on PQ-B Total scores ( $F(2, 57) = 12.728, p < 0.001$ ) and on PQ-B Distress scores (Welch's  $F(2, 35.451) = 11.813, p < 0.001$ ). Both the cannabis and ketamine groups scored higher than controls on PQ-B total score (both  $p < 0.001$ ), and both drug groups scored higher on distress than controls (both  $p < 0.05$ ). There were no differences between the cannabis and ketamine groups.

### 3. Cognitive Assessments

#### I. PRT (Probabilistic Reward Task)

##### *i. Response bias*

Data for one participant was removed from analysis of response bias, as the bias score was more than 3 standard deviations above the mean. Figure 3 shows response bias data across task blocks. There was a trend towards an interaction of group x block ( $F(2, 56) = 3.015, p = 0.057$ ). For Block 1, there were no significant group differences. Controls differed significantly from the cannabis group in Block 2:  $t(39) = 2.8, p = 0.022$  (control vs. cannabis). There was only a trend level difference between controls and ketamine users in Block 2:  $t(38) = 2.23, p = 0.090$  and no difference between the cannabis and ketamine groups,  $t(38) = 0.52, p = 1.00$ . Within-group Bonferroni post hoc comparisons revealed that only the control group differed significantly in response bias between blocks ( $p < 0.001$ ), reflecting an increase in response bias from Block 1 to Block 2.

There was a significant main effect of block on response bias,  $F(2, 56) = 9.480$ ,  $p = 0.003$ , with response bias being significantly higher in block 2 than block 1 across all groups (which is in keeping with findings from previous studies that response bias generally increases across blocks; Bogdan et al, 2006; Pizzagalli et al, 2009).

There was a trend towards a main effect of group ( $F(2, 56) = 2.998$ ,  $p = 0.058$ ), reflecting a tendency for the cannabis group to have lower scores than controls ( $p = 0.059$ ) when Bonferroni corrected.

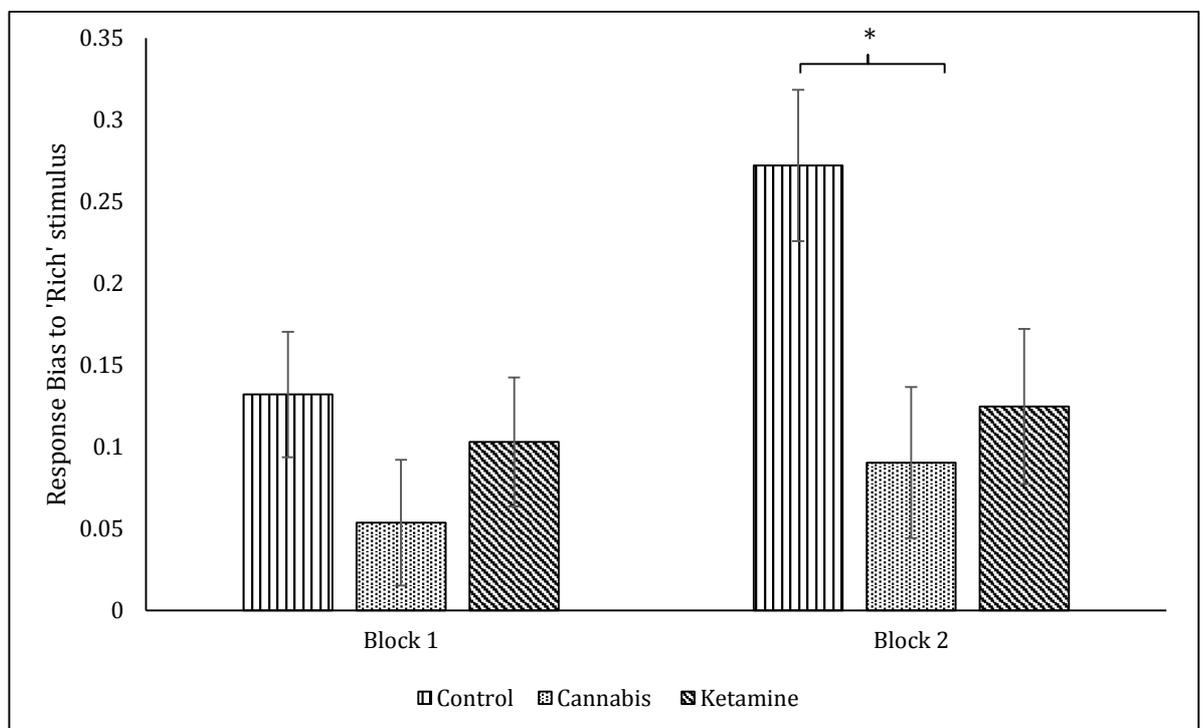
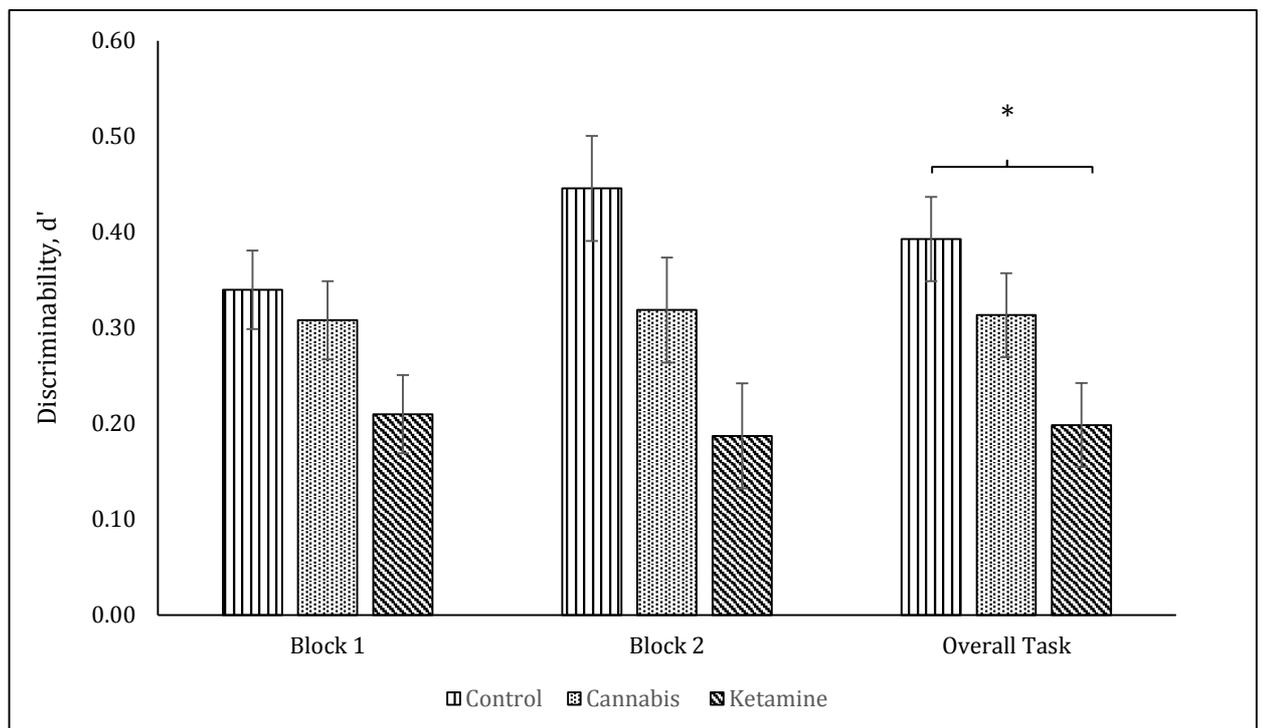


Figure 4. PRT response bias for the more frequently rewarded ('rich') and the less frequently rewarded ('lean') stimulus for control ( $n = 20$ ), cannabis ( $n = 20$ ) and ketamine participants ( $n = 19$ )

#### ii. Discriminability

Figure 4 shows data for discriminability ( $d'$ ) across task blocks. There was a trend for a group x block interaction,  $F(2, 57) = 2.740$ ,  $p = 0.073$ . There was a

significant main effect of group,  $F(2, 57) = 4.942$ ,  $p = 0.010$ , with mean  $d'$  significantly lower in the ketamine group than in the control group ( $t(39) = 3.126$ ,  $p = 0.008$ ). There were no differences between cannabis versus control or cannabis versus ketamine group. There was no significant main effect of block on  $d'$ ,  $F(2, 57) = 1.802$ ,  $p = 0.185$ .



**Figure 5.** PRT discriminability ( $d'$ ) for the 'rich' and 'lean' stimulus for control ( $n = 20$ ), cannabis ( $n = 20$ ) and ketamine participants ( $n = 20$ ).

### iii. Reaction Time

There was a significant main effect of group,  $F(2, 57) = 3.185$ ,  $p = 0.049$ , with mean reaction times fastest in the ketamine group. However, Bonferroni post-hoc comparisons revealed no significant differences between groups.

There was a significant block x stimulus interaction,  $F(2, 57) = 8.301, p = 0.006$ , with reaction times to the rich stimulus being faster than to the lean stimulus in Block 2 ( $t(59) = 4, p < 0.001$ ), but not in Block 1 (see Table 9).

There was a significant main effect of stimulus,  $F(2, 57) = 10.730, p = 0.002$ ; reaction times to the rich stimulus were faster than to the lean stimulus over the entire task.

**Table 9.** Mean (sd) PRT reaction times (seconds) per block and stimulus in control, cannabis and ketamine groups (n =20 per group).

	<b>Controls</b>	<b>Cannabis</b>	<b>Ketamine</b>	<b>Total</b>
<b>Block 1, Rich</b>	0.369 (0.125)	0.403 (0.163)	0.307 (0.091)	0.360 (0.133)
<b>Block 1, Lean</b>	0.381 (0.133)	0.400 (0.156)	0.306 (0.093)	0.362 (0.134)
<b>Block 2, Rich</b>	0.393 (0.137)	0.385 (0.154)	0.294 (0.107)	<b>0.358 (0.139)***</b>
<b>Block 2, Lean</b>	0.408 (0.138)	0.412 (0.168)	0.313 (0.149)	0.377 (0.149)
<b>Total</b>	0.388 (0.029)	0.400 (0.029)	0.305 (0.029)	0.364 (0.017)

*Difference significant at  $p < 0.05^*$ ,  $p < 0.01^{**}$   $p < 0.001^{***}$*

*iv. Hit Rates/Accuracy (percentage of correct responses) for each stimulus (rich or lean) type*

With respect to accuracy (proportion of correct responses, i.e. ‘hit rates’), there was a significant main effect of group,  $F(2, 57) = 3.830, p = 0.027$ , with the control group achieving significantly greater hit rates than the ketamine group for both types of stimuli ( $p = 0.028$ ).

There was a significant block by stimulus interaction,  $F(2, 57) = 6.641, p = 0.013$ , which was driven by higher hit rates (i.e. greater accuracy) for the ‘rich’ stimulus in Block 2,  $t(59) = 2.154, p = 0.034$ . There was no significant difference in hit rates for the lean stimulus between blocks (see Table 10).

**Table 10.** Mean (sd) PRT hit rates per block for rich and lean stimuli (n = 20 per group)

	Control	Cannabis	Ketamine	Total
<b>Block 1, Rich</b>	0.732 (0.127)	0.685 (0.129)	0.651 (0.122)	0.689 (0.122)
<b>Block 1, Lean</b>	0.608 (0.152)	0.636 (0.139)	0.571 (0.124)	0.605 (0.139)
<b>Block 2, Rich</b>	0.806 (0.124)	0.702 (0.137)	0.644 (0.151)	<b>0.717 (0.149)*</b>
<b>Block 2, Lean</b>	0.594 (0.124)	0.619 (0.185)	0.545 (0.153)	0.586 (0.157)
<b>Total</b>	<b>0.685 (0.022)*a</b>	0.661 (0.022)	0.603 (0.022)	

*Difference significant at  $p < 0.05^*$ ,  $p < 0.01^{**}$ ,  $p < 0.001^{***}$*

a = Con > Ket (Bonferroni corrected  $p$  values)

Replicating prior studies, there was a main effect of stimulus,  $F(2, 57) = 25.130, p < 0.001$ , with greater accuracy for the ‘rich’ than for the lean stimuli. Mean (sd) hit rates were 0.703 (0.015) for the rich stimulus and 0.596 (0.018) for the lean stimulus.

## II. ‘EEfRT’ (Effort-Expenditure for Rewards Task)

A 3 x 3 repeated measures ANOVA (hard-task choices at 12%, 50% and 88% probability level x group) revealed no significant group by probability level

interaction (Table 11). There was a significant main effect of probability level,  $F(2, 56) = 55.176$ ,  $p < 0.001$  (Greenhouse-Geisser corrected) which reflected increasing number of hard choice tasks as the probability of winning increased.

**Table 11.** Mean (sd) hard choices made for 12%, 50% and 88% probability of winning levels for control, cannabis and ketamine groups (n = 20 per group)

No. of hard choices	Control	Cannabis	Ketamine	Total
<b>12% probability</b>	3.05 (2.61)	2.35 (2.16)	2.40 (2.31)	2.60 (2.31)
<b>50% probability</b>	4.95 (1.57)	4.90 (1.37)	4.30 (2.20)	4.72 (1.75)
<b>88% probability</b>	5.95 (1.73)	6.00 (1.41)	5.55 (1.64)	5.83 (1.59)

### *Generalised Estimating Equations*

Six models using generalised estimating equations (GEE) were tested. For all models, the dependent variable was the dichotomous outcome of hard or easy task choice. A binary logistic distribution was used to model the probability of choosing the hard task. (See Appendix 3 for GEE results tables.)

Model 1 tested for main effects of trial number, probability, value (reward magnitude), baseline button pressing speed, expected value (EV), BDI-II Total Score and cigarettes smoked per day. Increases in probability of reward receipt, reward magnitude, and expected reward value were significant predictors of making hard-

task choices. There was a trend effect of cigarettes smoked per day on reducing the likelihood of making a hard task choice ( $b = -0.010$ ,  $p = 0.052$ ). Also as trial number increased, this reduced the likelihood of making a hard task choice ( $b = -0.008$ ,  $p < 0.001$ ).

Model 2 tested for an interaction between group and probability level. The model revealed no significant group by probability interaction for controls versus cannabis ( $b = 0.090$ ,  $p = 1.095$ ) nor ketamine users ( $b = -0.079$ ,  $p = 0.924$ )

Model 3 tested for an interaction between group and reward magnitude (or trial value). No significant interaction between group and reward magnitude was found for controls versus cannabis users ( $b = 0.062$ ,  $p = 0.620$ ) or for controls versus ketamine users ( $b = -0.052$ ,  $p = 0.603$ ) which suggests that group did not significantly predict hard choice trials of differing reward magnitudes.

Model 4 tested for an interaction between group and expected value (i.e. probability x reward magnitude). There was no significant interaction between group and expected value for controls versus cannabis users ( $b = 0.216$ ,  $p = 0.334$ ) or for controls versus ketamine users ( $b = -0.139$ ,  $p = 0.491$ ).

Model 5 tested for an interaction between group, reward magnitude and probability. No significant interaction was found between these variables for the control versus cannabis group ( $b = 0.083$ ,  $p = 0.344$ ) nor for controls versus ketamine users ( $b = -0.054$ ,  $p = 0.504$ ).

Model 6 tested for a main effect of BDI Anhedonia subscale scores. The model revealed no main effect of anhedonic scores on whether participants made hard choices ( $b = -0.049$ ,  $p = 0.178$ ).

In summary, none of models 2-5 revealed significant effects for the interactions tested, nor did model 6 reveal significant main effects for the main variable (anhedonia) tested.

#### **4. Correlations**

##### **I. Drug use and self-report measures**

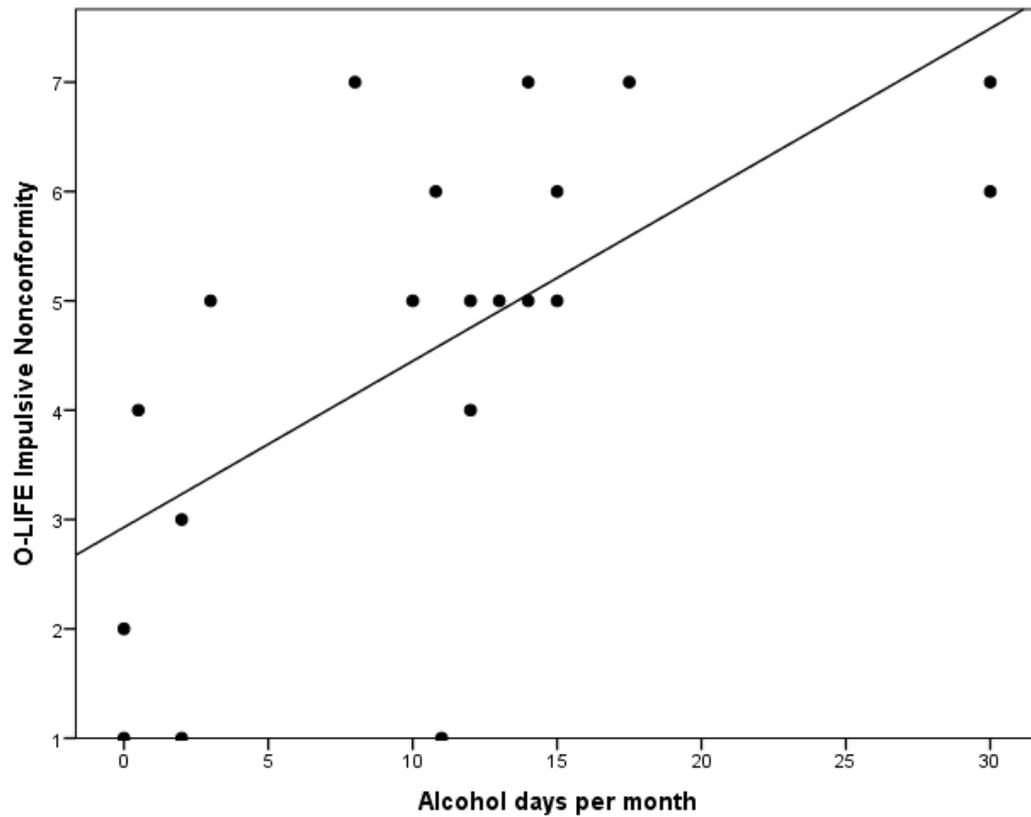
###### *i. Controls*

There was a trend towards a significant correlation between days per month of cannabis use and TEPS total ( $r = 0.543, p = 0.013$ ). There was also a significant correlation between mg of cannabis used in typical session and days per month use of MDMA ( $r = 0.649, p = 0.003$ ).

###### *ii. Cannabis group*

Significant correlations were found between alcohol use (number of days per month) and the O-LIFE Impulsive Nonconformity subscale ( $r = 0.643, p = 0.002$ ) (See Figure 3). There were also trends towards significant correlations between SDS cannabis scores and BDI total scores ( $r = 0.469, p = 0.037$ ) and between SDS cannabis scores and BDI Somatic subscale scores ( $r = 0.501, p = 0.025$ ).

**Figure 6.** Correlation between alcohol use and O-LIFE Impulsive Nonconformity subscale in cannabis users (n = 20)



*iii. Ketamine group*

Significant correlations were found between days per month of cannabis use and amount (mg) used in a typical session ( $r = 0.606$ ,  $p = 0.005$ ), and a nearly significant correlation between days per month of cannabis use and number of days per month of alcohol use ( $r = .558$ ,  $p = 0.011$ ). Amount of tobacco consumed per day was correlated with amount of alcohol used in a typical session ( $r = 0.663$ ,  $p = 0.002$ ).

## II. Task Correlations

### *i. EEfRT*

Within-group correlations revealed no significant correlations between EEfRT outcome variables any of the self-report measures (BDI, TEPS, O-LIFE and PQ-B).

### *ii. PRT*

No significant correlations were found between PRT outcomes and any of the three groups' self-report measures.

## **DISCUSSION**

To the best of our knowledge, this is the first study of chronic cannabis and ketamine users to investigate reward processing. The three groups studied were remarkably similar in age, gender, pre-morbid IQ, education, employment and use of other drugs. The cannabis users were highly dependent on cannabis and the ketamine users were highly dependent on ketamine. In line with hypotheses, the two drug using groups had significantly higher schizotypy (O-LIFE and PQ-B) scores than controls. On the probabilistic reward task, the control group showed a greater response bias than the cannabis group, and controls had greater discriminability scores than the ketamine group. There were no group differences on the 'Effort Expenditure for Rewards Task'.

### **Task Performance: PRT**

We used the probabilistic reward task (PRT; Pizzagalli et al, 2005) to compare groups in terms of their response bias towards the more frequently rewarded

stimulus, their ability to discriminate between stimuli, their accuracy, and reaction times. There were two main findings. Firstly, partly in line with hypotheses, the control group showed a significantly greater response bias in Block 2 towards the more frequently rewarded stimuli than the cannabis group. However, the predicted difference between controls and ketamine users did not reach significance in Block 2 (though there was a trend towards a difference). Secondly, the ketamine group was less able to discriminate between stimuli and less accurate overall than the control group. The cannabis group did not differ from the control group on discrimination or overall accuracy. The ketamine group was generally faster (smaller mean reaction times) than the other two groups, although no significant differences were found in post-hoc comparisons of groups.

There are several ways of interpreting these PRT findings. The first relates to differences in learning between the three groups. Only the control group demonstrated learning across blocks, showing a significant increase in response bias in Block 2 relative to Block 1. This learning suggests that the control group participants were able to modulate their behaviour increasingly over the two task blocks. Neither the cannabis group nor the ketamine group showed response bias changes across blocks, which indicates no evidence of any learning taking place. In Block 2, controls showed greater response bias than the drug using groups but only significantly so compared with cannabis users. Because positive reinforcers are, by definition, stimuli that increase the likelihood of behaviour and reinforcers play a crucial role in the formation of associations between salient cues and internal rewarding events, one can argue that diminished responsiveness to reinforcers may be a behavioural demonstration of hedonic hypofunctioning, or anhedonia (Rescorla & Wager, 1972; Spangel & Weiss, 1999; Pizzagalli et al, 2005). These findings may

therefore suggest that the cannabis users' (and to a lesser extent, the ketamine users') performance on the task reflected diminished reward responsiveness, or anhedonia, relative to controls.

On the PRT, the ketamine group discriminated less between stimuli than the control group, generally performed less accurately (i.e. had lower hit rates) than controls, and had faster response times than the other two groups. The cannabis group did not differ significantly from either controls or ketamine users on discriminability. The ketamine group's lower discriminability scores than controls may indicate that ketamine participants found the task more difficult, which might be explained by a number of factors. Visual discrimination between 'rich' and 'lean' stimuli may have been difficult, given the very small difference between mouth sizes (0.9mm). Performance on the task may have reflected more global cognitive impairments in the ketamine group, such as in working memory and aspects of executive functioning, which have previously found to be associated with frequent ketamine use (Morgan et al, 2009; Morgan et al, 2012). However, it should be noted that chronic cannabis use has also been found to be associated with deficits in attention, working memory and other aspects of executive function (Solowij, Stephens, Roffman et al, 2002; Crean, Crane & Mason, 2011).

Mean reaction times for the ketamine group were faster than for the other two groups' responses across both blocks. In light of their less accurate performance, this might indicate that the ketamine group sacrificed accuracy for speed on the task. This speed-accuracy trade-off may have influenced the ketamine group's diminished ability to discriminate between task stimuli relative to controls. Previous research has revealed mixed findings with respect to reaction time on the PRT. Pizzagalli et al (2005) did not find group differences in reaction time when comparing high versus

low BDI participants on PRT performance. However, a later study found significantly longer reaction times in subjects meeting clinical criteria for Major Depressive Disorder compared to controls (Pizzagalli et al, 2009). These findings highlight the importance of considering how group differences in depression in the present study may have influenced task performance, and will be discussed below.

### **Task Performance: EEfRT**

The EEfRT was used in previous studies as an objective measure of effort-based decision making to test the relationship between anhedonia and reward ‘wanting’. It was used here to determine the extent to which drug using groups might be less likely to make hard-task choices as the probability of winning decreased. Our hypothesis was not confirmed as neither the cannabis nor ketamine group demonstrated differences relative to controls in effort-based decision-making as operationalised in the EEfRT. We found that increases in the probability of reward receipt, reward magnitude and expected reward value were all predictors of participants making hard-task choices. These findings show that the task itself appears to have worked (Treadway et al, 2009). Further, hard-task choices decreased across groups as the task proceeded, which is also in line with previous findings (Treadway et al, 2009) and suggests the possibility of fatigue effects. In light of similar findings across groups, it is possible that the groups did not differ in effort-based decision making. Alternatively, the EEfRT may not have been sensitive to differences in performance between the three groups. Order effects may also have influenced EEfRT performance, as it was the first computer task in the two-hour testing protocol, which meant participants may have been particularly motivated to perform well. Treadway et al’s (2009) initial study found that participants with

higher trait and state anhedonia demonstrated a reduced willingness to make choices requiring greater effort in exchange for greater reward, which supports the notion that the EEfRT is a valid measure of putative reward ‘wanting’ (Treadway et al, 2009). However it may have been the case in the present study that the groups’ performance on this task of effort-based decision-making differed for reasons unrelated to substance use, comorbid depression or anhedonic traits.

### **Psychological well-being**

Both drug groups had high self-report scores on depression (BDI-II total scores) relative to controls, with 35% and 40% of the cannabis and ketamine samples respectively meeting criteria for clinical depression. Also interesting is the finding of higher BDI Cognitive-Affective subscale scores in the ketamine group relative to controls, suggesting greater incidence of depressive symptoms relating to cognitions and affect. Cannabis users had higher BDI somatic and BDI anhedonia subscale scores than controls, suggesting more physical symptoms of depression as well as higher clusters of anhedonic symptoms in this group. These findings suggest an association between chronic use of the respective drugs and depression, replicating previous studies (Morgan et al, 2010; Lev-Ran et al, 2013).

One longitudinal study of frequent and ex-ketamine users revealed increased BDI scores in both groups over one year of follow-up (Morgan et al, 2010). The authors hypothesised that depression in frequent users may be associated with increasing patterns of dependence on the drug, as depression is often comorbid in opiate and alcohol-dependent individuals (Morgan et al, 2010). The elevated depression scores in the ketamine group relative to controls in this study were therefore consistent with increased depressive symptoms characteristic of chronic ketamine use (Morgan et al,

2012; Muetzelfeldt et al, 2008), although other factors apart from ketamine use per se may have affected depression levels. Without measures of depression prior to and during heavier periods of ketamine use, it is difficult to delineate the relationship between the high levels of ketamine dependence and clinical depression in those who previously used the drug heavily but were experiencing a lack of ketamine as a result of the drought in supply which occurred during the present study.

Significantly higher depression relative to controls in the cannabis group may similarly suggest an association between frequent use of skunk and depressive symptomatology. Within the cannabis group, cannabis SDS scores and BDI-II total scores tended to moderately ( $r = 0.469$ ,  $p = 0.037$ ) correlate, as did cannabis SDS and BDI Somatic subscale scores ( $r = 0.501$ ,  $p = 0.025$ ), which further suggest a possible association between cannabis dependence and depressive symptomatology. As mentioned, significantly higher scores on both the BDI cognitive and anhedonic subscales in cannabis users (but not ketamine users) relative to controls suggests that different facets of depressive symptomatology may be implicated in frequent use of high-potency cannabis. A systematic review which controlled for baseline depression found that heavy cannabis use may be associated with an increased, though modest, risk for developing depression (Lev-Ran et al, 2013). A separate analysis found a dose-response relationship between cannabis use and depressive symptoms, with a highly significant effect across four separate Australian cohorts in the association between frequency of cannabis use and mean scores on depression measures (Horwood et al, 2012). However, again, without assessment of wider contextual factors, including baseline depression prior to the development of chronic skunk use, it would be difficult to draw any conclusions about causal relationships between cannabis use and depression in our sample.

Despite group differences in BDI anhedonia subscores, there were no group differences in the primary measure of trait anhedonia (TEPS) and we did not include a measure of state anhedonia. It is therefore difficult to parse anhedonia from the wider range of depressive or negative symptomatology which differed between the three groups here. Use of additional anhedonia measures such as the Chapman physical and social anhedonia scales (Chapman, Chapman & Raulin, 1976) or the Snaith-Hamilton Pleasure Scale (SHAPS; Snaith, Hamilton, Morley et al, 1995) may have allowed for a more robust assessment of whether there were differences between groups on anhedonia.

As hypothesised, both cannabis and ketamine users exhibited higher schizotypy (or psychosis-like traits; O-LIFE) and higher levels of positive psychosis symptomatology (PQ-B) than controls. Cannabis and ketamine users both had higher scores than controls on two O-LIFE subscales: Unusual Experiences (relating to unusual perceptual experiences, delusional beliefs, etc.) and Impulsive Nonconformity (relating to unstable mood and behaviour).

These findings are broadly in line with previous research which used the Schizophrenia Proneness Instrument (SPI-A; Schultze-Lutter, Addington, Ruhrmann, et al, 2007) to examine cognitive, affective and perceptual profiles of ketamine and cannabis users using a ‘basic symptoms’ approach (Morgan et al, 2012). They found that ketamine and skunk users demonstrated higher levels of attentional and cognitive disturbances than both illicit drug naïve controls and recreational poly-drug users. Chronic ketamine users in particular exhibited the greatest levels of basic symptoms compared with controls, poly-drug users and the cannabis group. Indeed, the ketamine users demonstrated high levels of cognitive

and affective symptoms which were very similar to clinically (SPI-A) assessed prodromal patients who subsequently transitioned to psychosis (Morgan et al, 2012).

Cannabis and ketamine users in Morgan et al's (2012) study scored similarly on symptoms related to cognition, attention and cognitive disturbances as indexed by the SPI-A. They differed on affective symptoms and perceptual disturbances, with the ketamine group scoring much higher on these indexes than cannabis users. In the present study, there were no group differences on the O-LIFE Cognitive Disorganisation subscale. However, both drug groups scored significantly higher than controls on measures of unusual perceptual experiences (O-LIFE Unusual Experiences subscale) and on positive symptoms, as assessed by the PQ-B.

Apart from essential differences in the way that psychosis-proneness was measured in our study compared to Morgan et al's (2012), there were also differences with respect to the groups and their drug use. The cannabis and ketamine groups were better matched in our study; Morgan et al's groups differed more in age and depression. Our cannabis group was on average 6.9 years older than that of Morgan et al (2012) and our ketamine (BDI score  $12.45 \pm 7.5$ ) users were less depressed than theirs (BDI score  $19.20 \pm 10.92$ ). Morgan et al's ketamine users were more depressed than both their cannabis users and controls. In contrast, our study found no difference in depression between the cannabis and ketamine groups (both scoring higher than controls). This finding might relate to the ketamine 'drought' (discussed below) and thus recent changes to drug-taking behaviours in the ketamine group. As ketamine has recently been reclassified both in the UK (now carrying more severe penalties for sale and possession than previously) and also in India, where much of the UK's ketamine supply was until recently produced, this has

led to changes both in public perceptions of the drug's harms as well as a reduction in street-level supply (Nutt & King, 2004; Power, 2014).

Morgan et al (2012)'s ketamine sample were similar in profile to prodromal patients, scoring highly on the following SPI-A subscales: 'Affective-Dynamic Disturbances' (e.g. impaired tolerance of stress, changes in general mood and decreased emotional responsiveness), 'Cognitive-Attentional Impediments' (e.g. attention and short-term memory deficits, difficulties in concentration, slowed down thinking, etc.), and 'Cognitive Disturbances' (e.g. indecisiveness regarding minor decisions, thought interference and blockages, disturbances in immediate recall and in receptive and expressive speech) (Morgan et al, 2012). The ketamine group also scored more highly than all other groups in the study, including the prodromal group, on two subscales relating to unusual perceptual experiences: 'Body Perception Disturbances' (i.e. unusual bodily perceptual experiences) and 'Perception Disturbances' (e.g. hypersensitivity to visual or auditory stimuli, depersonalisation, changes in intensity or quality of perceived stimuli) (Morgan et al, 2012).

The cannabis group in Morgan et al's (2012) study closely matched the ketamine group in scoring highly on the 'Cognitive-Attentional Impediments' and 'Cognitive Disturbances' SPI-A subscales. As previously noted, cognitive-attentional deficits have been linked in previous research to chronic use of both of these drugs (Morgan et al, 2009; Morgan et al, 2012; Solowij, Stephens, Roffman et al, 2002; Crean, Crane & Mason, 2011). The cannabis users also scored much lower than ketamine users on the 'Affective-Dynamic Disturbances and the two 'Perception Disturbances' subscales (Morgan et al, 2012).

In the present study, our ketamine group scored more highly on both the O-LIFE Unusual Experiences and PQ-B (total and distress scores) relative to controls, which

suggests similarities in positive psychosis-like symptomatology to Morgan et al's (2012) ketamine users. It should be noted however that O-LIFE clinical norms have not yet been established and our drug groups had means that were similar to UK-based population norms (Mason & Claridge, 2006). The ketamine drought is a key difference between Morgan et al (2012) and the present study which may have impacted on differences in our ketamine group profile.

Our cannabis users were significantly more depressed than controls, but their mean depression scores were comparable to Morgan et al's (2012) cannabis group. Higher PQ-B and O-LIFE Unusual Experiences subscale scores in our cannabis group compared to controls indicate a degree of positive psychosis symptomatology that was not found in Morgan et al's (2012) cannabis users. Cannabis users in Morgan et al's (2012) study were younger on average and reported using much larger amounts of skunk than our group, which may have influenced differences in their profiles.

Higher scores in both our ketamine and cannabis groups on the O-LIFE Impulsive Nonconformity subscale relative to controls suggest that the drug-using groups had similarly greater tendencies towards impulsive and/or 'non-conforming' behaviour. Interestingly, the O-LIFE Impulsive Nonconformity subscale was positively correlated with frequency of alcohol use in the cannabis group. This highlights the association between impulsivity as both a determinant (e.g. trait impulsivity increasing the tendency to use drugs) and as a potential consequence of chronic drug use (de Wit, 2009). These findings are interesting in light of Mason & Claridge's (2006) argument that a broader construct of psychosis-proneness should account for the clinical reality of overlap between schizophrenia and bipolar symptomatology to include the risk-taking behaviour characteristic of bipolar disorder (Mason &

Claridge, 2006). Research demonstrating that substance abuse is associated with sensation-seeking or impulsivity in non-psychotic individuals, and that lifetime drug misuse or dependence has been found in schizophrenic patients with high impulsive and sensation-seeking personality traits, highlights the importance of this dimension of schizotypy in the association between drug addiction and psychosis (Johnson et al, 1996; Dervaux et al, 2001; Gut-Fayand et al, 2001).

### **Demographics and drug use of the groups**

A main strength of this study is how well the three groups were matched on demographic variables including gender, age, ethnicity, education, and employment, on a premorbid estimate of intelligence, and on use of most other drugs. The two drug using groups also exhibited significantly high levels of dependence on cannabis and ketamine respectively.

Greater use of tobacco in the cannabis group may be because cannabis was mostly consumed on a daily basis as ‘spliffs’ with tobacco, and tobacco use has been found to be associated with cannabis dependence, independently of cannabis use frequency (Hindocha, Shaban, Freeman et al, 2015). The high SDS scores for cannabis dependence in the cannabis group (mean  $7.3 \pm 3.4$ ) suggest that these participants were very concerned about their cannabis use (the cut-off score is three for cannabis dependence; Swift et al, 1998; Hides et al, 2006).

The timing of our study had a significant impact on the selection of ketamine using participants in that all users that we spoke to anecdotally reported a ‘ketamine drought’ which they observed had begun around late 2013 and had continued through 2014, during recruitment for the study. This ‘drought’, the reduction in street-level supply and quality of ketamine over the past several years in the UK, has

also been discussed widely on drug internet forums. Many of the participants we tested reported that prices had trebled within a year, with a widespread reduction in quality and subjectively experienced effects of the drug. Because of the drought, the participants we recruited were not currently using ketamine anything like as heavily as before. Most participants described having experienced a cycle of dependence on the drug prior to the drought, in that they had gradually built up a tolerance to its effects and were therefore using much larger quantities more frequently, with negative impacts on their health, finances and social lives.

A number of studies have shown the potential for ketamine dependency among users, (Morgan, Muetzelfeldt, & Curran, 2009; Muetzelfeldt et al, 2008; Tang et al, 2015). While SDS norms for ketamine users have not been established, a recent study of treatment-seeking ketamine users in China (where ketamine abuse has sharply increased in recent years) found a Chinese version of the SDS (SDS-K) to be a reliable and valid measure of severity of ketamine dependence in this population (Tang et al, 2015). The high SDS scores for ketamine dependence in the ketamine group (mean  $9.55 \pm 2.56$ ), suggest extreme concern about their use of the drug and were particularly interesting in light of the drought. Many participants also said that if the ketamine supply were to revert to previous levels of availability, they would likely return to previous levels of consumption. Greater use of amphetamines and benzodiazepines in the ketamine group might be due to the 'ketamine drought' encouraging use of these other relatively inexpensive drugs which have increased in availability in recent years (DrugScope Street Drug Trends Surveys, 2011 & 2014).

### **Methodological considerations**

This study has methodological limitations characteristic of many studies on recreational drug users (Curran, 2000). Despite general success in matching the groups on demographic and other drug use variables, there may have been other unknown factors which contributed to group differences.

Verification of level of drug use in the samples would need blood samples which were not feasible to take in this study. Urinalysis was used to index general drug use. Self-reported level of drug use may not be accurate as both ketamine and cannabis impair memory and people may underestimate drug use. Future research may benefit from objective measures of chronic drug use (e.g. hair samples) but these are costly (e.g. £90 per hair sample) and are affected by hair treatments (dyes, shampoos, etc.).

The fact that testing was carried out by different researchers may have introduced experimenter bias, possibly influencing self-report measures and task performance. Also, there was some variation in test settings, with a number of participants tested in their own homes. Many of the ketamine participants in particular were tested in more chaotic environments than controls and cannabis users, which may have influenced their performance.

Finally, the PRT and EEfRT tasks are proxies for examining real world decision-making and as such their external validity is as yet unknown.

### **Clinical Implications**

High levels of schizotypy and relatedly positive psychosis-like symptomatology were shown in chronic users of both cannabis and ketamine using questionnaire measures which were resonant of those previously shown using a structured

interview (Morgan et al, 2012). Taken together, these findings suggest that clinical assessments of psychosis symptoms should index use of these drugs, as some symptoms which align with those present in prodromal psychosis may in fact be drug induced. Early intervention assessments in particular should take into account the potential overlap between the cognitive, affective and schizotypal symptom profiles of regular cannabis and ketamine users with those of at risk (or ‘prodromal’) individuals.

A recent exploratory factor analysis found similarities in symptom dimensions between chronic ketamine users and schizophrenia, although extreme psychiatric responses (i.e. drug-induced psychoses) to repeated ketamine use are thought to be atypical in community-based samples of ketamine users (Morgan et al, 2010; Xu, Krystal, Ning et al, 2014). However, as suggested in Morgan et al’s (2012) study, the presence of these symptoms in chronic drug users may be a mechanism by which heavy drug use facilitates transition to psychosis in those with genetic and/or other vulnerabilities.

Given the recent finding that daily cannabis use, particularly of high-potency cannabis, is associated with earlier onset of psychosis in cannabis users, and that increasing numbers of young people are using ketamine and skunk, it is vital that early intervention programmes promote reduction in drug taking and abstinence to determine whether this reduces symptoms classed as ‘prodromal’ (di Forti, Sallis, Allegri et al, 2014; di Forti, Marconi, Carra et al, 2015; McCambridge, Winstock & Hunt, 2007). Educational campaigns regarding the risks of cannabis use, particularly frequent use of high-potency types, are necessary and should particularly target young adolescents, as this is an age when many start experimenting with drugs and

when early prodromal symptoms may emerge (di Forti, Morgan, Dazzan et al, 2009; di Forti et al, 2014).

The present study did not undertake a broader clinical assessment that might shed light on history and patterns of drug use in the respective groups. However the high levels of depression found in our sample of cannabis and ketamine users highlights the wider issue of assessment, treatment and prevention of comorbid mood, anxiety and substance use disorders. While our study was carried out on a non-treatment seeking sample of drug users, research has shown that substance use disorders are more prevalent in individuals with severe mental illness than in the general population, and that such comorbidity is associated with poorer treatment outcomes (Davis, Uezato, Newell & Frazier, 2008; Lai, Cleary, Sitharthan & Hunt, 2015). A number of theories attempt to explain such comorbidity, including the notion that one mental disorder may influence the development of another (e.g. drug misuse contributing to depression), that sustained use of drugs as self-medication or distress relief leads to dependence or addiction, or that multiple disorders share common vulnerability factors (e.g. genetic or socio-economic such as the intergenerational transmission of trauma) (Lai et al, 2015). Further research on comorbidity is needed in order to better understand the nature of the relationship between two co-occurring disorders (whether correlational or causal), which may inform prevention and treatment (Lai et al, 2015).

As discussed, poorer learning on the Probabilistic Reward Task in the cannabis and ketamine users may have indicated poorer reward responsiveness relative to controls. The implications of this possible explanation are that chronic users of these drugs may exhibit deficits in motivated behaviour in daily life, including decreased motivation for non-drug rewards. The cycle of chronic drug use initially increases

the salience of drug rewards while decreasing that of non-drug rewards. Given the relationship of anhedonia to craving and withdrawal symptomatology, further research on hedonic processing in chronic drug users is warranted, as treatment of anhedonia may hold promise for treating the underlying mechanisms of addiction.

### **Conclusion**

The present study compared cannabis dependent, ketamine dependent and healthy control groups on reward processing and prodromal psychosis symptomatology. It revealed mixed findings in terms of the drug groups' reward responsiveness – on the probabilistic reward task, the control group showed greater response bias than cannabis users and controls had greater discriminability than the ketamine group. However there were no significant group differences on the effort-related decision-making task. These results may be partly explained by comorbid levels of clinical depression which were found in both drug-using groups but not in controls. The drug using groups also had higher rates of schizotypal and positive psychosis-like symptomatology than controls. Despite some differences in overall profiles, these findings support previous research (Morgan et al, 2012) in demonstrating the presence of both positive and negative symptoms of prodromal psychosis in chronic users of cannabis and ketamine. Therefore, these findings have clinically important implications for the assessment of at-risk individuals.

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## **Part 3: Critical Appraisal**

## Critical Appraisal

### Overview

This critique serves as a reflection on the process of completing the DCLinPsy thesis. I will discuss my experience working as part of a research group, reflections on recruiting and working with drug-using populations, and how the focus of the research relates to clinical issues. I will also briefly discuss social constructs implicated in research on prodromal symptomatology and psychosis more generally.

### *Working jointly and as part of a research group*

As my research experience prior to training involved working as part of a team of researchers, I enjoyed the opportunity to do the same during the formulation and development stages of the thesis project. Joining forces with my fellow trainee, Lisa Harvey, and receiving input from other researchers working in UCL's Clinical Psychopharmacology Unit (CPU) allowed for initially very broad discussions and ideas about possible projects to become more refined and focused, drawing on the expertise of our supervisors and the CPU team. This process of defining the project and developing a research question and protocol that would be feasible within the constraints of the thesis project was more time-consuming than I initially anticipated, but I appreciated the many meetings and discussions which eventually led to the rationale for the project, focusing on anhedonia and reward processing in drug users.

The initial aim of the project was to build on previous findings by a group of researchers working in the CPU (including several former DCLinPsy trainees) which had demonstrated that frequent cannabis and ketamine users exhibited more psychotic-like symptoms than controls and recreational poly-drug users, and that ketamine users in particular had neurocognitive and affective profiles very similar to

prodromal patients who later developed frank psychosis (Morgan et al, 2012). Initially, Lisa and I chose to focus our research solely on non-treatment seeking cannabis users, with her project relating more to chronic ‘skunk’ use as a model for psychosis and mine focusing on reward processing deficits in chronic users. We initially hoped to combine two quantitative research methodologies – a semi-structured interview and experimental tasks – with the addition of a short qualitative interview which we would devise ourselves. Early on, we planned to use a different semi-structured interview to assess prodromal symptomatology from the one used by Morgan et al (2012), the Schizophrenia Prediction Instrument – Adult Version (SPI-A), which focused on ‘basic symptoms’ present throughout the entire progression from earliest to late prodromal phase. We learned that this tool was not considered a ‘gold-standard’ by researchers in the field, so we initially chose to use the Comprehensive Assessment of At-Risk Mental States (CAARMS), which focuses on ‘attenuated positive symptoms’, typically present in the late prodromal phase, and has been used more widely in clinical settings than the SPI-A. In addition to carrying out the CAARMS with our sample, we each planned to administer one or two computer-based cognitive tasks to assess our respective areas of focus. Our CPU colleagues suggested the ‘probabilistic reward task’ (PRT; Pizzagalli et al, 2005) and ‘Effort-Expenditure for Rewards Task’ (or ‘EEfRT’, Treadway et al, 2009) as possible objective measures of reward processing for my arm of the project, neither of which, to our knowledge, had been used with chronic drug users.

The project shifted focus when we decided to include both skunk and ketamine users as participants, so as to be able to make comparisons of chronic drug users within our study design and to further build on Morgan et al’s (2012) study. We also reluctantly decided to exclude the CAARMS interview, due to concerns about

feasibility. Initially I felt these constraints were frustrating; I had a personal preference for carrying out semi-structured clinical interviews over experimental tasks, based on previous research experience, as I felt the interview process allows for much richer descriptions of participants' experiences and would be more engaging for both participants and myself. However I eventually accepted the need to limit the scope of the project due to concerns about the amount of time we would have needed both to familiarise ourselves with administering the CAARMS and to carry out the interviews. Again, it was useful to have a number of colleagues to advise whilst deciding on this and on the self-report measures we would use, as well as supporting us with statistical analyses after completing data collection.

I appreciated being able to work jointly with Lisa throughout the planning and data collection phases of the project, as this allowed for much discussion and debate between us before then going back to our supervisors and other colleagues for further discussions and feedback. Our conversations were wide ranging, drawing upon our previous experience (mine in non-clinical research and Lisa's from her experience as a drugs worker in central London as well as her past thesis on ecstasy users), our developing knowledge of theory underpinning our research questions (e.g. drug models of psychosis, models of addiction, etc.), our more recent clinical experience during training, and our own life experience. This joint working was also incredibly useful when it came to the recruitment phase, as we could screen potential participants for each other to test.

### ***Recruitment of chronic drug users***

Recruitment was a particular challenge of the research project. Despite the increasing openness in Western societies towards recreational drug use and the

widening of debates around legalisation and regulation of illicit substances, both cannabis and ketamine have been upgraded to Class B drugs in the UK in recent years, carrying severe penalties for their possession and supply. While we knew that it would be possible to recruit participants meeting our eligibility criteria, it was necessary to go about this carefully and to be particularly mindful of confidentiality.

We initially began recruitment via our network of friends and acquaintances, but this yielded too few potential participants so we widened our strategy, placing ads on online forums. This provided a vast number of enquiries, mostly from cannabis users. Following up their queries and screening them proved a challenge, and it soon became clear which ones were more or less motivated to take part. After screening and testing several cannabis users, we realised that our screening criteria needed re-evaluation due to confusion over whether we should be emphasising drug *dependence* as the main criterion or *amount/frequency* of drug consumed. Initially we were somewhat flexible, using both these criteria, but we found out that quite a number of users did not meet the minimum dependence criterion despite consuming cannabis frequently. We decided it would be important to devise firmer criteria focusing on dependence (using the Severity of Dependence Scale, or SDS, Gossop et al, 1992) as the main defining feature of our chronic drug-using samples, over and above frequency or amount of drug consumed regularly.

This decision to define our drug users according to their level of dependence was also influenced by our first trip to Bristol to test a group of ketamine users. These potential participants were friends and acquaintances of one of our contacts and were keen to take part in the study. Prior to this, we had been informed about the ‘ketamine drought’ hitting the UK in recent months, but it was not until we arrived and began speaking to our potential participants that we got a fuller sense of how this

had affected their use of the drug. They reported how the availability of ketamine had reduced sharply beginning around late 2013 and early 2014, and that it continued to be much less accessible. They described how the quality had reduced considerably while the price had shot up from approximately £15 per gram to £40 or more. They shared a similar narrative to explain the drought saying that many of the factories in India which had been producing the drug had been closed and supplies seized by authorities, with much of the current poorer quality supply now coming from China. This was confirmed in several media reports online, which linked the reduced availability to seizures in India and the UK and subsequent governmental reclassification of ketamine in India to its most severe level (schedule X) (Power, 2014). Many of the potential participants we spoke to were frustrated with this situation and wished that the supply would return to pre-drought levels. However, many were ambivalent and also expressed the sense that the drought was a blessing in disguise, as they acknowledged how seriously dependent they had become while it was cheap and widely available, which had, in some cases, severely impacted on their health and functioning. Some spoke about doing up to 7 or 8 grams of ketamine per day at the peak of their dependence before the drought, spending the whole day in their room taking ketamine and not doing much else, struggling with extremely painful 'k cramps' and bladder problems. Several potential participants reported that they rarely took ketamine now since heavy use had contributed to relationship difficulties and had prevented them from pursuing their life goals. Despite the drought however, the majority anecdotally told us that if quality ketamine were currently available to them, they would not hesitate to buy and consume it. This suggested to us that despite the current drought, these individuals

continued to be somewhat dependent on ketamine, which was confirmed in nearly all cases when they were screened with the SDS.

Another challenge with recruitment was the issue of participants' motivation to take part in the study. One aspect of this was the repeated frustration of screening potential participants who would then fail to attend their scheduled testing sessions. This seemed to happen with screened individuals from all three groups (including controls), but perhaps more with the cannabis users. This may have been due to the slightly different recruitment strategy we used for cannabis users, the majority of whom found out about the study via several online classifieds websites, whereas many of the controls and ketamine users were found via snowball sampling. While it is not clear whether the proportion of DNAs we had are considered typical for this type of research project, irrespective of whether participants were drug users or not, this proved not only frustrating (particularly towards the end of the data collection phase) but also may have impacted on findings, given the study's focus on examining motivated behaviour. A further issue related to motivation to take part was the fact that participants were paid for their participation. While paying participants is widespread practice in many types of research, it was interesting that a high proportion of participants from the two drug groups told us prior to testing that they were not volunteering for monetary gain but because they wanted to help further drugs-related research, with one participant even refusing payment upon completing testing. Thus, while the groups were well-matched, there may have been *a priori* differences in reasons for participating that could have impacted on our findings, particularly regarding the motivation-based tasks and measures of anhedonia.

Overall, I found testing the participants to be a very pleasant experience and was struck by the warmth and openness of many of the people I tested. In retrospect I feel it was unfortunate that we could not provide more of a forum for the participants to discuss their experiences given the fact that many of them anecdotally described what they perceived to be very idiosyncratic relationships with drug taking, which seemed to me to be much more complex and ambivalent than could be captured by our measures.

### *Limitations of Study Design*

The study design was naturalistic and single-blind, which may have introduced potential bias based on participant characteristics, as mentioned (e.g. those who were motivated to take part may have had less trait anhedonia), or experimenter effects. Although it is often good practice to have more than one experimenter to reduce demand characteristics, having several people administer the testing protocol may also have introduced an element of bias. The fact that testing took place in different environments may also have influenced our findings. Many of the ketamine users were tested in their homes, which were at times chaotic environments with minor disruptions (e.g. noise, pet dogs requiring attention, etc.). Most of the ketamine users also came from the same group of friends and acquaintances which may have influenced the socio-demographic and drug-use profile of the ketamine group.

One aspect of the design that could have been improved was the assessment of participants' current and past drug use. Our data indicated wide variation in the amount of information obtained from these interviews, which seemed to be a consequence of imprecise interview questions which sometimes neglected key information in bringing together a more complete picture of each individual's pattern

of drug use. This was particularly the case for the ketamine group – upon realising at the start of testing this group that most of the participants’ patterns of ketamine consumption had changed, we agreed to add further questions to our drug use interview which would give us an idea of their habits during periods of heavier use. However, this was hastily decided upon and therefore we did not have a set list of questions regarding past heavy use, and thus the data we were able to analyse regarding past use was limited. The retrospective nature of self-reported drug use was also potentially problematic. Although it is likely that the one-to-one format of the drug use interview encouraged participants to be truthful about their drug, retrospective assessment relied heavily on memory, which may be affected by drug use itself or simply the passage of time (Dragt et al, 2010). Given that research suggests that individuals frequently under-report frequency and amounts of drug use, it is difficult to ascertain how likely this was in our samples and whether there was significant between-group variation. Finally the impact of testing fatigue may have affected results, as the testing protocol was lengthy and the tasks repetitive.

### *Schizotypy and psychosis as constructs*

One significant frustration that I experienced with the project design and methods of inquiry was the need to accept and utilise the constructs of the psychosis prodrome, schizotypy and even psychosis itself. For example, research on schizotypy argues for a range of ‘normal’ trait schizotypy, yet studies employing measures of schizotypy often assume that elevated levels are inherently psychopathological, although more recent research has explored creative or adaptive aspects of what is termed ‘benign schizotypy’. From less psychiatric perspectives (e.g. social constructionist, humanistic or existential), one can argue that these

constructs exist because of the dominance of positivist, medical models of illness and disability within the field of psychological research, and they persist because of social and academic consensus. My clinical experiences throughout training, albeit limited, have thus far exposed me to completely different ways of seeing the world, different not just from my own subjective viewpoint but from the models (e.g. CBT, systemic) which the field of clinical psychology at times so adamantly espouses. While models are useful in guiding therapeutic interventions, I could not shake my sense that the research project was missing important aspects of participants' core concerns and experiences relating to their drug use. Even the literature included in the review seemed to neglect the essential disturbance in the sense of self that may be at root of vulnerability to psychosis, which Nelson, Yung, Bechdolf & McGorry (2008) comment on. They argue that modern psychiatry lacks a means of addressing human subjectivity, quoting Maslow: " 'If the only tool you have is a hammer, you tend to treat everything as if it were a nail.' That is, the subjective has been approached in operational terms..." (Nelson et al, 2008: 382). Reflecting on these issues has reminded me of my initial interest in taking a phenomenological approach to anomalous experience and to those murkier areas of psychological inquiry, like psychosis, that are less amenable to straightforward diagnosis and treatment. Nelson et al's (2008) proposal that research on individuals at clinical high risk for psychosis may benefit from further means of identifying 'self-disturbance' is interesting and provides a novel challenge to future researchers in this field who want to further examine what may be one of the core components of psychotic illness.

To this end, I often finished testing sessions with participants feeling as though an opportunity had been missed to get a much deeper understanding of the context influencing their drug-using behaviour. I think this may have been helped had we

chosen to include a semi-structured interview, which would have encouraged more of a meaningful dialogue about their experiences, which sometimes only happened before or after the testing sessions or not at all. This was particularly the case in my encounters with the ketamine users, as many of them expressed a sense of vulnerability and desire to help others through recounting their painful struggles with ketamine dependence.

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## **APPENDICES**

**Appendix 1**  
**Details of joint thesis**

The thesis was completed as part of a joint project to investigate psychotic-like symptomatology and cognitive functioning in chronic users of cannabis and ketamine.

Two separate theses were completed as a result of the project. They were entitled:

1) Psychotic-like symptomatology and reward responsivity in chronic ketamine and cannabis users

(Alyssa Joye, Trainee Clinical Psychologist, UCL)

2) Ultra high risk for psychosis? Chronic ketamine and cannabis users' performance in attribution assignment and auditory hallucination tasks

(Lisa Harvey, Trainee Clinical Psychologist, UCL)

Both trainees collaborated on the study design and shared participants and data collection.

An outline of each trainee's contribution to the project is as follows:

1) Alyssa Joye: Compiled the testing protocol, including obtaining self-report measures, in collaboration with Lisa Harvey. Piloted initial testing protocol with Lisa and supervisor Val Curran. Placed advertisements for participants on classified websites and screened potential cannabis and control participants. Collected data as outlined in methodology (including two additional computer-based tasks relevant to Lisa Harvey's study – 'Ambiguity of Attribution' and 'White Noise' tasks) from 22 participants (3 controls, 11 cannabis users, and 8 ketamine users), and performed

own data analyses with support from Clinical Psychopharmacology Unit colleagues. Data for 22 participants tested by Lisa Harvey and 16 participants tested by Will Lawn (UCL PhD candidate) was used in analyses.

2) Lisa Harvey: Collaborated on designing testing protocol alongside Alyssa Joye. Piloted testing protocol with Alyssa and supervisor Val Curran. Contacted and screened potential ketamine participants. Collected data as outlined in her methodology for 22 participants (6 controls, 6 cannabis users, and 10 ketamine users). Performed own data analyses on participants she tested in addition to 22 Alyssa Joye tested and 16 Will Lawn tested.

**Appendix 2**

**Approved ethics application form**

UCL RESEARCH ETHICS COMMITTEE  
GRADUATE SCHOOL OFFICE



Professor Valerie Curran  
Clinical and Educational Health Psychology  
UCL

28<sup>th</sup> March 2014

Dear Professor Curran

**Notification of Ethical Approval**

**Project ID: 5402/001: Investigating the determinants and psychological consequences of high-potency cannabis and ketamine use**

In my capacity as Chair of the UCL Research Ethics Committee (REC) I am pleased to confirm that your study has been approved by the UCL REC for the duration of the project i.e. until June 2018.

Approval is subject to the following conditions:

1. You must seek Chair's approval for proposed amendments to the research for which this approval has been given. Ethical approval is specific to this project and must not be treated as applicable to research of a similar nature. Each research project is reviewed separately and if there are significant changes to the research protocol you should seek confirmation of continued ethical approval by completing the 'Amendment Approval Request Form'.

The form identified above can be accessed by logging on to the ethics website homepage: <http://www.grad.ucl.ac.uk/ethics/> and clicking on the button marked 'Key Responsibilities of the Researcher Following Approval'.

2. It is your responsibility to report to the Committee any unanticipated problems or adverse events involving risks to participants or others. Both non-serious and serious adverse events must be reported.

**Reporting Non-Serious Adverse Events**

For non-serious adverse events you will need to inform Helen Dougal, Ethics Committee Administrator ([ethics@ucl.ac.uk](mailto:ethics@ucl.ac.uk)), within ten days of an adverse incident occurring and provide a full written report that should include any amendments to the participant information sheet and study protocol. The Chair or Vice-Chair of the Ethics Committee will confirm that the incident is non-serious and report to the Committee at the next meeting. The final view of the Committee will be communicated to you.

**Reporting Serious Adverse Events**

The Ethics Committee should be notified of all serious adverse events via the Ethics Committee Administrator immediately the incident occurs. Where the adverse incident is unexpected and serious, the Chair or Vice-Chair will decide whether the study should be terminated pending the opinion of an independent expert. The adverse event will be considered at the next Committee meeting and a decision will be made on the need to change the information leaflet and/or study protocol.

On completion of the research you must submit a brief report (a maximum of two sides of A4) of your findings/concluding comments to the Committee, which includes in particular issues relating to the ethical implications of the research.

With best wishes for your research.

Yours sincerely



**Professor John Foreman**  
**Chair of the UCL Research Ethics Committee**

Cc:  
Lisa Harvey & Alyssa Joye, Applicants  
Professor Peter Fonagy, Head of Department



## Amendment Approval Request Form

1	<b>Project ID Number:</b> 5402/001	<b>Name and Address of Principal Investigator:</b> Professor Valerie Curran UCL Dept of Clinical, Educational and Health Psychology Division of Psychology and Language Sciences 1-19 Torrington Place London WC1E 7HB
2	<b>Project Title:</b> Investigating the determinants and psychological consequences of high-potency cannabis and ketamine use	
3	<b>Type of Amendment/s (tick as appropriate)</b>	
	<input type="checkbox"/> Research procedure/protocol (including research instruments) <input checked="" type="checkbox"/> Participant group <input type="checkbox"/> Sponsorship/collaborators <input type="checkbox"/> Extension to approval needed (extensions are given for one year) <input type="checkbox"/> Information Sheet/s <input type="checkbox"/> Consent form/s <input checked="" type="checkbox"/> Other recruitment documents <input type="checkbox"/> Principal researcher/medical supervisor* <input type="checkbox"/> Other *	
	*Additions to the research team other than the principal researcher, student supervisor and medical supervisor do not need to be submitted as amendments but a complete list should be available upon request.	
4	<b>Justification</b> (give the reasons why the amendment/s are needed) 1. The researchers would like to amend the age range of the participant group to include participants up to the age of 55 (ethical approval previously obtained was for the age range 18-35). 2. The researchers also request ethical approval for an advertisement to assist in recruitment of potential participants.	
5	<b>Details of Amendments</b> (provide full details of each amendment requested, state where the changes have been made and attach all amended and new documentation) 1. We would like to extend the upper age limit for potential participants to age 55. The aim of this is to facilitate participant recruitment. 2. While we have thus far elicited interest in the study via word-of-mouth and snowball sampling, we would like to widen our strategy for recruiting participants via advertising in selected, appropriate media (e.g. web-based drug user forums). This would likely speed up the recruitment process and allow us to more efficiently contact and screen potential participants.	
6	<b>Ethical Considerations</b> (insert details of any ethical issues raised by the proposed amendment/s) Ethical considerations are unchanged from the previous application. However participants hear about the study, they will go through the standard screening procedure.	
7	<b>Other Information</b> (provide any other information which you believe should be taken into account during ethical review of the proposed changes)	

**Declaration** (to be signed by the Principal Researcher)

- I confirm that the information in this form is accurate to the best of my knowledge and I take full responsibility for it.
- I consider that it would be reasonable for the proposed amendments to be implemented.
- For student projects I confirm that my supervisor has approved my proposed modifications.

Signature:



Date: 10/10/2014

**FOR OFFICE USE ONLY:**

Amendments to the proposed protocol have been *approved* by the Research Ethics Committee.

Signature of the REC Chair, Professor John Foreman:  .....

Date: *14/10/2014*.



**Appendix 3**

**Participant Information Sheet**



## INFORMATION LEAFLET FOR VOLUNTEERS

Version 1 February 2014

### The determinants and psychological consequences of ketamine and high potency cannabis use

**Investigators:** Lisa Harvey, Alyssa Joye, Will Lawn, Prof. H.Valerie Curran

#### **Purpose of the study:**

To determine the long term effects of high potency cannabis and ketamine use

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends and relatives if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

#### WHAT IS THE PURPOSE OF THE STUDY?

To determine the effects of using different types of recreational drugs upon mental functioning and mood.

#### SOME BACKGROUND TO THE RESEARCH

Many drugs have long term effects; for instance people who drink lots of alcohol often find their memories are not as good as they were. This can often be affected by factors such as the length of time they have been drinking and the quantity that they drink. The present study aims to find out what the long-term effects of using recreational drugs may be on mental state and cognition.

#### WHAT WILL BE STUDIED?

We will ask people who *regularly* use ketamine and cannabi, as well as healthy non-drug using participants, a series of questions about their drug use and their psychological well-being. After these, participants will then be asked to complete a series of computer tasks designed to look at attention and memory.

#### HOW WOULD I BE INVOLVED IF I AGREED TO TAKE PART?

If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason.

If you agree to participate, on the testing day you will come to the Psychopharmacology Laboratories at UCL or, if you do not live locally, the researchers will come to your home. We will collect a urine sample to test for the drug being studied and to screen for use of other drugs; the results will be kept confidential and the sample disposed of at the end of the testing session. You will be paid for participation upon completing the various research tasks. The full testing session will last approximately 2 hours.

#### CONFIDENTIALITY

Any information collected about you will be held in accordance with the 1998 Data Protection Act. All the information that is collected about you during the course of the research will be kept strictly confidential. Your results will have your name and any other details about you removed first so that you cannot be identified from them.

#### **If you would like further information please ask the investigator**

Thank you for reading this leaflet and we hope that you will be able to take part in the study.

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

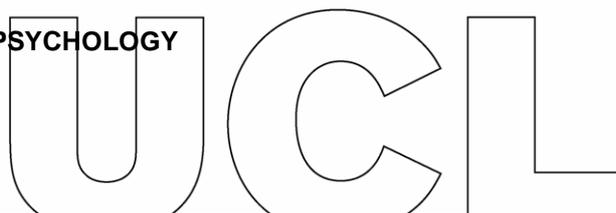
#### Contacts:

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All proposals for research involving human subjects are reviewed by an ethics committee before they can proceed. This proposal was reviewed by the UCL Committee for the Ethics of non-NHS Human Research.

**Appendix 4**  
**Consent Form**



**Consent Form  
Version 1 January 2014**

**CONFIDENTIAL**

**The determinants and psychological consequences of ketamine and high potency  
cannabis use**

Investigators: Prof. Val Curran, Lisa Harvey, Alyssa Joye, Will Lawn.

Please complete the following: *delete as necessary*

1. Have you read the information sheet? YES / NO
2. Have you had an opportunity to ask questions and discuss this study? YES / NO
3. Have you received satisfactory answers to all your questions ? YES / NO
4. Have you received enough information about this study ? YES /NO
5. Which investigator have you spoken to about this study ? .....
6. Do you understand that you are free to withdraw from this study:
  - \* at any time YES / NO
  - \* without giving a reason for withdrawing YES / NO
7. Do you agree to take part in this study? YES/ NO
8. Would you be interested in having your details stored on a database to be contacted for inclusion in further studies? YES/ NO

Signed..... Date.....

**Name (please print) .....**

**Investigator.....**

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[www.ucl.ac.uk/clinical-health-psychology](http://www.ucl.ac.uk/clinical-health-psychology)

**Appendix 5****Generalised Estimating Equations for EEfRT**

### Generalised Estimating Equations for EEfRT

		<i>b</i> Coefficient	SE	<i>p</i>
<b>Model 1</b>	Group:			
	Control vs. Cannabis	0.064	0.1288	0.617
	Controls vs. Ketamine	-0.032	0.1237	0.799
	Gender	0.095	0.1288	0.254
	Trial Number	-0.013	0.0029	<0.001
	Probability	0.338	0.0826	<0.001
	Reward Value	0.266	0.0787	0.001
	Expected Value	0.298	0.1195	0.013
	Baseline Button Press	0.010	0.0174	0.585
	BDI Total Score	-0.007	0.0174	0.249
	Cigarettes/day	-0.010	0.0053	0.052
<b>Model 2</b>	Group:			
	Control vs. Cannabis	-0.014	0.1750	0.935
	Controls vs. Ketamine	0.035	0.1613	0.826
	Gender	0.099	0.0833	0.236
	Trial Number	-0.013	0.0029	<0.001
	Probability	0.339	0.1070	0.002
	Reward Value	0.267	0.0790	0.001
	Expected Value	0.292	0.1189	0.014
	Baseline Button Press	0.010	0.0176	0.589

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BDI Total Score	-0.007	0.0058	0.265
Cigarettes/day	-0.010	0.0053	0.057
Group*Probability			
Control vs. Cannabis	0.090	0.1312	1.095
Control vs. Ketamine	-0.079	0.1234	0.924

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**Model 3** Group:

Control vs. Cannabis	-0.019	0.1953	0.923
Controls vs. Ketamine	0.040	0.1751	0.820
Gender	0.095	0.0832	0.255
Trial Number	-0.013	0.0029	<0.001
Probability	0.335	0.0824	<0.001
Reward Value	0.263	0.0958	0.006
Expected Value	0.304	0.1198	0.011
Baseline Button Press	0.009	0.0175	0.589
BDI Total Score	-0.007	0.0058	0.248
Cigarettes/day	-0.010	0.0054	0.052
Group * Value			
Control vs. Cannabis	0.062	0.1244	0.620
Controls vs. Ketamine	-0.052	0.1007	0.603

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<b>Model 4</b> Group:			
Control vs. Cannabis	-0.061	0.1874	0.744
Controls vs. Ketamine	0.051	0.1725	0.768
Gender	0.099	0.0832	0.233
Trial Number	-0.013	0.0029	<0.001
Probability	0.334	0.0816	<0.001
Reward Value	0.266	0.0788	0.001
Expected Value	0.283	0.1919	0.141
Baseline Button Press	0.009	0.0177	0.593
BDI Total Score	-0.007	0.0059	0.257
Cigarettes/day	-0.010	0.0053	0.059
Group * Expected Value			
Control vs. Cannabis	0.216	0.2238	0.334
Controls vs. Ketamine	-0.139	0.2014	0.491

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<b>Model 5</b> Group:			
Control vs. Cannabis	-0.028	0.1660	0.868
Controls vs. Ketamine	0.029	0.1537	0.850
Gender			
Trial Number	-0.013	0.0029	<0.001

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Probability	0.335	0.0817	<0.001
Reward Value	0.269	0.0814	0.001
Expected Value	0.280	0.1960	0.153
Baseline Button Press	0.009	0.0177	0.593
BDI Total Score	-0.007	0.0059	0.258
Cigarettes/day	-0.010	0.0053	0.059
Group * Reward Value *			
Probability			
Control vs. Cannabis	0.083	0.0882	0.344
Controls vs. Ketamine	-0.054	0.0804	0.504

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**Model 6** Group:

Control vs. Cannabis	0.043	0.1336	0.749
Controls vs. Ketamine	-0.077	0.1258	0.541
Gender	0.073	0.0866	0.397
Trial Number	-0.012	0.0030	<0.001
Probability	0.347	0.0852	<0.001
Reward Value	0.258	0.0800	0.001
Expected Value	0.281	0.1230	0.022
Baseline Button Press	0.012	0.0172	0.482
BDI Total Score	0.002	0.0078	0.781

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Cigarettes/day	-0.010	0.0055	0.078
BDI Anhedonia	-0.049	0.0365	0.178

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