ASSESSING VULNERABILITY TO PSYCHOTIC ILLNESS AMONGST CANNABIS USERS: CORRELATES, DISCRIMINATING FACTORS, AND SCALE DEVELOPMENT

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Table of abbreviations

∆-9-THC	∆-9-Tetrahydrocannabinol
ANOVA	Analysis of Variance
APA	American Psychiatric Association
Appetitive scale	Appetitive scale of the CEQ
Aversive scale	Aversive scale of the CEQ
BASIS- R	Behaviour and Symptom Identification Scale
BPRS	Brief Psychiatric Rating Scale
CBD	Cannabidiol
CEQ	Cannabis Experiences Questionnaire
CEQ-b	Cannabis Experiences Questionnaire brief version
CI	Confidence Interval
CIPD	Cannabis-Induced Psychotic Disorder
Cog-per subscale	Cognitive-perceptual subscale of the SPQ-b
CSCN	Community Sample of Cannabis Naïve participants
CSCU	Community Sample of Cannabis Users
CSQ	Concurrent States Questionnaire
CXS	Interaction term of Cannabis consumption and Stress
DA	Dopamine
DD	Participants with a self-reported Diagnosis of Depression
DFA	Discriminant Function Analysis
Disorganised subscale	Disorganised subscale of the SPQ-b
DSM	Diagnostic and Statistical Manual
EDGE	Enhanced Data rates for GSM Evolution
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
ER	Event Rating, of the most ‘noteworthy event’
ESM	Experience Sampling Methodology
EU	European Union
GPS	Global Positioning System
GROUP	Genetic Risk and OUtcome in Psychosis

GWAS	Genome Wide Association Study
HPA axis	Hypothalamic-Pituitary-Adrenal axis
ICC	Intraclass Correlation Coefficient
ICD	International Classification of Diseases
Interpersonal subscale	Interpersonal subscale of the SPQ-b
Intoxicated scale	Intoxicated scale of the CEQ
KNN	Kth Nearest Neighbour
LOO	Leave-One-Out
MANOVA	Multiple Analysis of Variance
MAR	Missing At Random
MB	Megabytes
MDMA	3,4-methylenedioxy-N-methylamphetamine
MLM	Multi-Level Model
MMU	Manchester Metropolitan University
NEET	Not in Education Employment or Training
NHS	National Health Service
OR	Odds Ratio
OS	Operating System
PANSS	Positive and Negative Syndrome Scale
PCA	Principle Component Analysis
PD	Participants with a self-reported diagnosis of Psychotic Disorder
PE	Frequency of Pleasurable Events
PIS	Participant Information Sheet
PSI	Psychotomimetic States Inventory
QFQ	Quantitative Feedback Questionnaire
SAS	Statistical Analysis Software

SCAN	Schedules for Clinical Assessment in Neruopsychiatry
SCID	Structure Clinical Interview for DSM-IV Axis I disorders
SCL-90-R	Symptoms checklist
SE	Frequency of Stressful Events
SE	Standard Errors
SIM	Subscriber Identity Module
SMS	Short Messaging Service
SNP	Single-Nucleotide Polymorphism
SPD	Schizotypal Personality Disorder
SPQ	Schizotypal Personality Questionnaire
SPQ-b	Schizotypal Personality Questionnaire brief version
SPQ-b-L	Schizotypal Personality Questionnaire- brief Likert version
SPSS	Statistics Package for the Social Sciences
SSQ	Schizotypal States Questionnaire
SSRI	Selective Serotonin Reuptake Inhibitor
THC	Tetrahydrocannabinol
URL	Uniform Resource Locater
VAS	Visual Analogue Scale
WHO	World Health Organisation
WMH-CIDI	World Mental Health-Composite International Diagnostic Interview
WSI	Weekly Stress Inventory

Abstract

Background: Schizophrenia is a pervasive and often debilitating disorder, although vulnerability is not easily assessed. Cannabis has a positive relationship with schizophrenia. To date, it is unknown whether or not this is a causal relationship. Nonetheless, those with vulnerability to psychosis have displayed a differential sensitivity to cannabis.

Aims: There were two main aims to this programme of research: *1)* Contribute to discussions relating to 'causal inference' in the relationship between cannabis and psychosis. *2)* Assess the reliability and validity of the Cannabis Experiences Questionnaire (CEQ) as a measure of psychotic vulnerability based on a differential sensitivity to cannabis.

Methods: Two studies were conducted. The first was a *Cross-sectional investigation* in which two groups of cannabis users were recruited, participants with self-reported depression (n = 85) and participants with self-reported psychotic disorder (n = 48). This investigation also considered data from a community sample recruited as part of other research studies. These consisted of cannabis users (n = 861) and non-users (n = 306). These groups were compared on measures of schizotypy and cannabis induced experience.

The second study was an *experience sampling investigation*, in which regular cannabis users (n = 36), submitted 7 responses per day via a mobilephone, for a period of 14 days. Participants completed measures of: psychotic-like states, stressed states, calm states, drug consumption, stressful and pleasurable events, and aversive cannabis induced experience.

Results: *Cross-sectional investigation:* There was no significant difference between cannabis users with reported depression and reported psychotic disorder in the disorganised or interpersonal domains of schizotypy. The cannabis-using groups of participants displayed a differential sensitivity to cannabis, with those who reported psychotic illness having significantly more aversive cannabis experiences than the community sample (U = 15106.5, z = 3.142, p = .002, r = 0.10) and participants with reported depression (U = 1241.0, z = 3.746, p < .001, r = 0.32) . The most effective means of identifying psychotic vulnerability consisted of a two-step process, firstly utilising assessments of schizotypy and secondly assessments of aversive cannabis induced experience.

Experience sampling investigation: In a dose dependent fashion cannabis predicted increases in interpersonal (*b* = 0.24 95% CI 0.07 to 0.42, *p* = .006) and disorganised psychotic like experience (PLE) (*b* = 0.16 95% CI 0.04 to 0.27, *p* = .006). However, disorganised PLE significantly increased the odds of cannabis consumption (OR = 1.245 95% CI 1.045 to 1.247, *p* = .003). Cannabis positively and significantly predicted 'calm' states in a dose dependent fashion (*b* = 0.23 95% CI 0.07 to 0.39, *p* = .006). Cannabis and stressed states interacted to significantly predict PLEs (*b* = 0.33, 95% CI 0.17 to 0.49, *p* < .001). Aversive cannabis induced experience significantly predicted PLEs both within (*b* = 0.22, 95% CI 0.10 to 0.33, *p* < .001) and between participants (*b* = 0.66, 95% CI 0.06 to 1.27, *p* = .033). Previously documented aversive cannabis experiences significantly predicted propensity to experience stressed states (*b* = 0.15, 95% CI 0.05 to 0.24, *p*= .002).

Conclusion: *Aim 1):* Within a continuum model of psychosis the results of these studies support three mechanisms of a cannabis-schizophrenia interaction; cannabis use causes schizophrenia; schizophrenia causes cannabis use; schizophrenia and cannabis use maintain one another. There is evidence to suggest psycho-social stressors interact with cannabis to induce PLEs. This may indicate that cannabis causes schizophrenia via a cross-sensitisation mechanism. At-risk groups should be warned against using cannabis as a stress coping mechanism.

Aim 2): These results confirm a differential sensitivity to cannabis in those vulnerable to psychotic disorder. This investigation has demonstrated that psychosis vulnerability can be assessed by aversive cannabis induced experience. This investigation has demonstrated concurrent, convergent, and predictive validity of the CEQ as an assessment of psychotic vulnerability. This scale could be useful for drug education programmes and risk assessment in recreational cannabis users; screening for medicinal cannabis prescription; screening for research trials with cannabinoids or other known psychotomimetics; and in the allocation of psychological intervention for cannabis dependence, and (possibly) stress-reduction in those with disorder or at ultra-high risk.

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1. Background

1.1 Introduction

This chapter will serve to contextualise the rest of this body of work within the relevant literature. This investigation examines the relationship between cannabis and psychotic disorder, in addition to contributing to the development of a measure of psychotic vulnerability in cannabis users. In contextualising this research it is necessary to consider literature from distinct domains (e.g. scale development and schizophrenia). Nonetheless, this literature is pertinent in the interpretation of this thesis.

Section 1.2.1 describes schizophrenia and some of the related psychotic disorders. Section 1.2.2 focuses on the schizophrenia spectrum disorder, schizotypal personality disorder and the non-pathological personality trait, schizotypy. Contained within section 1.2.2 is a sub-section which discusses the notion that there are time variant aspects to the purported stable personality trait of schizotypy. Section 1.2.3 is pertaining to assessments of vulnerability to schizophrenia this is separated into four subsections: environmental factors that increase the odds of diagnosis, genetic factors, biological markers, and psychological measures.

One of the principal aims of this thesis is to further the development of a measure. Thus, to contextualise this development process, contained within Section 1.3 is information pertaining to the development of a measurement scale. Section 1.3.1 contains information regarding item generation. Section 1.3.2 discusses the literature regarding the testing of the psychometric properties of a measure including reliability, validity, and factorial structure.

Section 1.4 discusses the psychotomimetic and purported psychotogenic drug cannabis. This section provides insight into the psychological consequence of the pharmacology of an illicit, non-homogenous substance. Section 1.5 provides information about a, cannabis induced illness, which is highly related to schizophrenia: cannabis-induced psychotic disorder. The relationship between cannabis and schizophrenia is examined in section 1.6. Contained within this

section are four subsections pertaining to causality between cannabis and psychotic disorder. Section 1.6.1 considers literature relating to cannabis use as a consequence of schizophrenia. In this section evidence pertaining to the 'self-medication hypothesis' is considered. Section 1.6.2 considers a 3rd (common) factor underpinning the relationship between cannabis and schizophrenia. Section 1.6.3 examines the evidence that both schizophrenia and cannabis interact and maintain one another. Section 1.6.4 assesses cannabis as an independent causal factor in the development of schizophrenia.

Section 1.7 builds on Section 1.6.4 to explore 'plausible' mechanisms by which cannabis may cause schizophrenia. Contained within this section is an examination of the data pertaining to whether the drug has a dopaminergic effect (Section 1.7.1). Section 1.7.2 discusses the plausibility of a gene by cannabis interaction effect. Section 1.7.3 examines the plausibility of cannabis sensitising to psychotic symptoms. Section 1.7.4 examines the literature regarding cannabis and stress interacting to cause psychotic disorder. Section 1.8 discusses the relationship between cannabis, schizotypal state, and schizotypal trait.

Section 1.9 serves to remind the reader of the literature contained within this chapter. This section also highlights the aims of this thesis and earmarks the subsequent sections of this thesis which serve to address these aims. Nonetheless, subsumed within chapters two, three, and, four are distinct aims related to that specific chapter.

1.2 Schizophrenia spectrum disorders, and schizotypal personality

1.2.1Schizophrenia spectrum disorders descriptive features

There are two systems of classification typically used within psychiatry one published by the American Psychiatric Association (APA), the Diagnostic and Statistical Manuals (DSM) and one published by the World Health Organisation (WHO) the International Classification of Diseases (ICD). At the time of writing the 11th revision of the ICD is in a beta draft, with the last corrected update (10th revision) published in an online version in 2010. However, the long awaited fifth update of the DSM has recently been published. Due to the consistent advances in schizophrenia research, this thesis will primarily refer to the most recent diagnostic text, DSM 5 (APA, 2013a).

Schizophrenia is a chronic psychological disorder that is associated with deficits in cognitive, social and occupational function. Schizophrenia is characterised by abnormalities in two (or more) of the following five domains: delusions, hallucinations, disorganised speech, grossly disorganised or catatonic behaviour, and negative symptoms (APA, 2013a, p.99). The symptoms of schizophrenia have been considered to disaggregate into two clusters 'positive' and 'negative' symptoms (APA, 2000, p.299). "The positive symptoms appear to reflect an excess or distortion of normal functions, whereas the negative symptoms appear to reflect a diminution or loss of normal functions" (APA, 2000, p.299). The negative symptoms include features such as affective flattening, alogia, and avolition. The positive symptoms are considered to disaggregate into two further sub-categories: The "psychotic dimension" includes delusions and hallucinations, whereas the "disorganization dimension" includes disorganised speech and behaviour (APA, 2000, p.299).

The incidence rate of schizophrenia in women is slightly lower and typically characterised by a later onset, than it is in men (APA, 2013a, p.102). Onset of first psychotic episode is typically "in the early- to mid-20s for males and in the late-20s for females" (APA, 2013a, p.103). Schizophrenia tends to be a chronic disorder, with only about 20% of people with schizophrenia having a "favourable outcome" and only a few of those are thought to return to pre-morbid level of function (APA,

2013a, p.102). The presence of negative symptoms typically indicates a worse prognosis, these symptoms are often more persistent than positive ones (APA, 2013a, p.102). About 20% of people suffering with schizophrenia have one or more suicide attempt, and unfortunately 5-6% of people suffering with schizophrenia die by suicide (APA, 2013a, p.104).

Numerous different aetiologies have been proposed to explain the mechanism by which someone may decompensate into schizophrenia. These various theories have their grounding in the psychodynamic (e.g. Fromm-Reichmann, 1948), behavioural (Ullman & Krasner, 1975), and cognitive models (Frith, 1992). Nonetheless, any adequate theory of the causes of schizophrenia must be able to explain the more recent wealth of data indicating that it is a heritable disorder (See Sullivan, 2005). The data indicate that there is plausibly a biological basis to schizophrenia. Further, evidence to this effect can be derived from data indicating that people suffering with schizophrenia display neuroanatomical abnormalities, specifically cortical atrophy (ventricular enlargement) (Glahn, et al.,2008). Further evidence for the biological basis of schizophrenia can be derived from data implicating psychopharmacological dysfunction. Dysfunction centralising around the neurotransmitter dopamine (DA) has been consistently implicated in schizophrenia (spectrum disorder) research. Stemming from the observations that antihistamines served to calm pre-operative patients (Delay & Deniker, 1952) a related compound was developed, which is now commonly referred to as typical antipsychotics. Moreover, compounds that elicit dopamine release have been shown to induce psychotic like states similar to schizophrenia (Ellinwood, 1967). It is now known that any antipsychotic which is efficacious in treating positive symptoms serve to have an antagonistic effect on D2 receptors (Sanger, 2004).

Dysfunction in DA activity is thought to be related to disruption to both the ‘mesolimbic’ and the ‘mesocortical’ pathways. The mesolimbic pathway projects from the Ventral Tegmental Area (VTA) to the ventral striatum and the mesocortical pathway projects from the VTA to the frontal cortex. These have been referred to as the subcortical and cortical pathways respectively (Kuepper et al., 2010). It is thought that positive symptoms are as a consequence of hyperactivity of the mesolimbic DA pathway, whereas negative system are as a

result of a diminution of dopaminergic activity in the mesocortical pathway (Lewis & Buchanan, 2002, p.62). Nonetheless, theories of other neurotransmitter dysfunction have been postulated, glutamate is one such neurotransmitter that has been consistently implicated (Javitt, Zylberman, Zukin, Heresco-Levy & Lindenmayer, 1994). Despite the wealth of data indicating a biological basis to schizophrenia, heritability studies fail to explain all of the variance within the population (see Section 1.2.3). Moreover, many environmental factors have been implicated with an increased odds ratio of a diagnosis of psychotic disorder (see Section 1.2.3). Thus, although schizophrenia appears to be a heritable disorder it is highly influenced by environmental factors (e.g. obstetric conditions, cannabis etc.).

There are some disorders which are very closely related to schizophrenia, known as the schizophrenia spectrum disorders. This cluster of disorders include schizophreniform disorder, schizoaffective disorder, schizotypal personality disorder (SPD), paranoid personality disorder and schizoid personality disorder. The symptoms of schizophreniform disorder are “identical” to that of schizophrenia (APA, 2013a, p.97). The two disorders are only distinguishable by the duration of disturbance; an episode of schizophreniform disorder lasts for between one and six months. An episode lasting shorter than this duration is given a diagnosis of brief psychotic disorder, whereas an episode of longer than this equates to a diagnosis of schizophrenia (APA, 2013a, p.97). Approximately two thirds of patients with a diagnosis of schizophreniform disorder progress to develop schizophrenia, and one third recover within the six month period (APA, 2013a, p.98).

Schizoaffective disorder possesses the same characteristics that are associated with schizophrenia. However, in addition to possessing two or more of the criteria for schizophrenia patients suffering with schizoaffective disorder must also display episodes of depression or mania for the majority of the duration of the illness (APA, 2013a, p.106). To distinguish schizoaffective disorder from schizophrenia (which is frequently associated with “mood symptoms and full mood episodes” (APA, 2013a, p.101)), “a major depressive episode must include pervasive depressed mood” (APA, 2013a, p.107). Whereas, “to separate schizoaffective

disorder from a depressive or bipolar disorder with psychotic features, delusions or hallucinations must be present… in the absence of a major mood episode" (APA, 2013a, p.107).

Paranoid personality disorder is characterised by "a pervasive distrust and suspiciousness of others" (APA, 2013a, p.649). In a large epidemiological investigation paranoid personality disorder was the second most prevalent personality disorder in the cohort with 4.41% of the sample meeting criteria (Grant et al., 2004). However, data from the (American) national comorbidity survey indicates that paranoid personality disorder is prevalent in 2.3% of the population (Lenzenweger, Lane, Loranger & Kessler, 2007). Nonetheless, paranoid personality disorder was found to increase the odds of a diagnosis of schizophrenia or other psychotic episode by 3.2 fold. However, when controlling for other sociodemographic factors the increase in odds was non-significant (Pulay et al., 2009). This suggests that although the disorder may be related to schizophrenia, it is feasibly not appropriate to utilise this personality disorder as a prognostic indicator of schizophrenia.

Schizoid personality disorder is characterised by "a pervasive pattern of detachment from social relationships and a restricted range of expression of emotions in interpersonal settings" (APA, 2013a, p.653). In a prospective cohort study people suffering with schizoid personality disorder were found to be less likely to have had a sexual relationship, less likely to be in a relationship at follow-up, and were more likely to prefer to be on their own (Wolff & Chick, 1980). This disorder was shown to be prevalent in 3.13% of the general population (Grant et al., 2004) in one investigation and 4.9% in another (Lezenweger et al., 2007). Schizoid personality disorder was found to increase the odds of a diagnosis of schizophrenia or other psychotic episode by 3.0 (O.R.). However, as before, when controlling for other sociodemographic factors the increase in odds was non-significant (Pulay et al., 2009). Thus, indicating that this disorder may also not be appropriate as a prognostic indicator of schizophrenia.

Schizotypal personality disorder is characterised by "a pervasive pattern of social and interpersonal deficits marked by acute discomfort with….close relationships as

well as by cognitive or perceptual distortions and eccentricities of behaviour" (APA, 2013a, p.655). Two recent epidemiological investigations estimate the prevalence of SPD as 3.3% (Lezenweger, et al., 2007) and 3.9% (Pulay et al., 2009). However, SPD is significantly more prevalent in men (Pulay et al., 2009). SPD was found to increase the odds of a diagnosis of schizophrenia or other psychotic episode by 4.7 (O.R.). Even whilst controlling for sociodemographic factors the odds ratio of 2.1 remained statistically significant (Pulay et al., 2009). Thus, indicating that out of the schizophrenia spectrum personality disorders, SPD displays the greatest predictive ability of schizophrenia. Moreover, medication which has been found to be effective in the treatment of the symptoms of schizophrenia, has also been used to treat the symptoms of SPD (Keshavan, Shad, Soloff, & Schooler, 2004). SPD has been described as the "prototypical schizophrenia-spectrum condition" (Fervaha & Remington, 2013, p.96). These observations amongst others (see Section 1.2.2) are feasibly why schizotypy has received a lot of focus on its relationship with schizophrenia, and the rationale for SPD receiving more attention than the other schizophrenia spectrum personality disorders in this thesis.

1.2.2 Schizotypal personality: disorder and trait

"A personality disorder is an enduring pattern of inner experience and behaviour that deviates markedly from the expectations of the individual's culture, is pervasive and inflexible, has an onset in adolescence or early adulthood, [and] is stable over time" (APA, 2013a, p.645). Personality is arguably a function of environmental (Johnson et al., 2005) and genetic influence (Bouchard & Loehlin, 2001). Although, as of yet precise single-nucleotide polymorphisms (SNP, see Section 1.2.3 for further information) influencing personality are yet to be established (de Moor, et al., 2012). Nonetheless, stable and enduring features of personality have been demonstrated in children as young as 3 years old (Caspi et al., 2003). Suggesting that personality traits are present from a young age, and they persist throughout the lifetime of the individual.

A recent review by Fervaha and Remington (2013) reported converging evidence suggesting that people suffering with schizophrenia and people suffering with SPD

share common neuroanatomical abnormalities, particularly in the medial temporal lobe. The review also found evidence of people suffering with SPD having a larger pre-frontal cortex volume which, the authors suggest, may reflect a “compensatory neuroreserve” (p.103). This may be a factor that could explain why only a small minority of people suffering with SPD decompensate into schizophrenia (See Pulay et al., 2009). In addition to neuroanatomical similarities, SPD and schizophrenia also share common phenomenological, genetic, psychophysiological, cognitive, and pharmacological abnormalities (Siever & Davis, 2004). Nonetheless, assessments of SPD and assessments of a schizophrenia prodromal state indicate that although there is some overlap between the two disorders, they do display discriminant validity (Bedwell & Donnelly, 2005). This indicates that the disorders are distinct disease entities, although they are both highly related.

The assessment of personality through psychometric testing has a long standing history with psychological research (e.g. Hathaway & Mckinley, 1940). Rather like many other aspects of personality, a schizotypal personality (schizotypy) can be assessed through self-report questionnaire. Self-reported schizotypy has displayed validity for both screening for SPD and assessing schizotypal traits in healthy participants (Raine & Benishay, 1995). However, unlike SPD, even a highly schizotypal personality is not pathological. The assessment of schizotypy via self-reports is therefore a useful means by which to make inferences about schizophrenia without the need to recruit a clinical sample. Measures of Schizotypy are frequently used as research tools to differentiate and gradate psychosis-proneness in persons without psychopathology (e.g. Cohen, Buckner, Najolia, & Stewart, 2011). Schizotypal personality trait and research into schizotypal personality disorder has been described as being “of key importance in overcoming methodological weaknesses of schizophrenia research’ (Raine & Lencz, 1995, p3) as “schizotypals tend to be free of the institutionalization and medication confounds that impede schizophrenia research” (Raine, Lencz, & Mednick 1995, p. xii).

Despite the advantages conveyed through the examination of personality traits and disorders they are not without their criticism. DSM IV-TR utilised a multiaxial

system in which personality disorders were considered distinct from other psychological disorders (APA, 2000). However, the appropriateness of differentiating between personality disorder (axis II) and other psychological conditions (axis I) as distinct has been a point of discussion (e.g. Westen & Shedler, 2000; Widiger, 2003). DSM 5 has subsequently moved to a non-axial system as "there is no fundamental difference between disorders described on DSM-IV's Axis I and Axis II" (APA, 2013b, p.1). However, part of the rationale for this move may have been convenience "as the axis system was seen by some clinicians as burdensome and time consuming" (APA, 2013b, p.1). Moreover, the APA (2013a) acknowledges that the consideration of personality disorders in a non-axial model has its limitations as evinced by the inclusion of an alternative multiaxial model for assessment of personality disorder (p.761).

Raine and Lencz (1995) pose a question related to the 'axial debate'; "whether SPD is best construed as a deviation representing an exaggeration of an ostensibly normal personality process which places subjects at risk for schizophrenia, or a major disorder that is much more integrally related to schizophrenia itself" (p.4). With the transition to a no-axial system this question has not become a moot point and at present remains unresolved. Moreover, within the context of personality research this question is particularly poignant as it pertains to another long held and still active debate related to if, and how, someone may decompensate from a high schizotype to psychotic disorder (e.g. Meehl, 1962; Nelson, Seal, Pantelis & Phillips, 2013).

The prevalent model within psychiatry (e.g. APA, 2000; APA, 2013a) is the utilisation of a categorical method differentiating between those mentally ill and those not. "Because of the categorical nature of the DSM …SPD is automatically viewed as a dichotomous entity, so that each patient either is or is not schizotypal" (Lencz & Raine, 1995, p.430). However, personality research has typically utilised a dimensional approach in which schizotypy and schizophrenia exist along a continuum. "Although dimensional systems increase reliability, others suggest that such an approach may be less useful than categorical systems for clinical practice and application" (Kraemer, Noda, & O'Hara, 2004 p.17). Within personality research a fully categorical model is rarely applied as personality research

typically relies on the ability to gradate or rank participants and their traits along a scale.

There have been three principal models proposed to explain the relationship between schizotypy and schizophrenia: the quasi-dimensional approach (which is sometimes also referred to as categorical in nature e.g. Lencz & Raine, 1995, p.430), the “entirely” dimensional or continuum approach (Claridge & Beech, 1995 p.194), and the fully dimensional approach .The entirely dimensional approach, which is influenced by personality theory (see Eysenck, 1960), suggests that healthy people and those suffering with schizophrenia all exist along the same continuum with no differentiation at the point of conversion from healthy to psychotic “except in a purely statistical sense” (Claridge, 1997, p.11). Evidence for this approach can be derived from the observation that both psychotic symptoms and schizotypal traits may disaggregate into a similar factorial structure (see Liddle, 1987; Raine & Benishay, 1995). However, it is worth noting that alternative factorial structures have been postulated (e.g. Mason & Claridge, 2006). High-scoring schizotypes are at an increased risk of decompensating into psychotic illness (Pulay et al., 2009). This indicates a possible continuum between vulnerability and disorder. Nonetheless, this approach has been criticised for not considering “distinctions or discontinuities that might exist between symptoms and traits” (Claridge & Beech, 1995, p.194). This approach has become less popular in recent years (e.g. Nelson et al., 2013), perhaps partly due to the lack of data indicating the point of conversion from high schizotypy to schizophrenia, and the development of genetic and environmental interaction models (e.g. Réthelyi, Benkovits, & Bitter 2013).

One alternative to the continuum model is a quasi-dimensional approach. Meehl (1962, 1990) was one of the central proponents of a theoretical perspective encompassing many aspects of the quasi-dimensional approach. Central to this theoretical perspective is the presence of an underlying genetic susceptibility conferring whether an individual is a schizotype, or to re-phrase a “schizophrenic phenotype” (Rado, 1960 p.87). Meehl (1990) suggests that schizotypes have a genetic vulberability to schizophrenia, a schizogene. Meehl (1990) determined that the schizogene was a dominant gene and thus, this occurs in around 10% of the

general population (p.26). Nonetheless, the conversion from genetic vulnerability (schizotaxia) to schizotype appears to be mediated and influenced by social factors (Meehl 1990 p.50). Meehl suggests that the form and content of a schizotypal trait is determined by social learning, and adverse life events, not heritability (Meehl 1990, p.35). Nonetheless, Meehl (1990) postulated the presence of a single 'schizogene', genetic vulnerability to psychosis was thought to be affected by polygenic 'modifiers' such as being "submissive, hyphohedonic [sic], anxietous, introverted, traumatized, [or] unlucky"(p.53). Although Meehl suggests that a schizogene is a large component of liability, nonetheless Meehl (1990, p.90) also suggests a scenario in which a person not carrying the gene may decompensate. Such a scenario is thought to only occur in instances in which the individual has an exorbitant amount of other (e.g. non-schizotypal) adverse factors. However, decompensated 'non-schizotypes' are said to represent "genophenocopies", as opposed to "true" cases of schizophrenia' (p.67).

Thus, to establish the relationship between schizotypy and conversion to 'true' psychotic mental illness, the quasi-dimensional approach utilises both dichotomous differentiations (schizogene or non-schizogene) and continuums (e.g. severity of symptoms, environmental modifiers). The necessary presence of the schizogene in the expression of 'true' schizophrenia has resulted in it being referred to as "a discontinuous, categorical theory" (Nelson et al., 2013 p.318). Further evidence for the quasi-dimensional model can be derived from heritability studies suggesting a genetic influence on the expression of both schizophrenia (Gottesman, 1991) and schizotypy (Torgersen et al., 2000). Thus, this provides support for the presence of a 'schizogene'. A review of analyses assessing the latent structure of schizotypy suggests that the majority of the research assessed indicated a categorical model (Rawlings, Williams, Haslam, & Claridge, 2008). However, Rawlings et al. (2008) also attempted to address the shortcomings of the previous investigations they reviewed (i.e. small sample size, skewed data, biased samples etc.). Whilst attempting to control for the limitations of previous research Rawlings and colleagues found that the data appears to indicate a dimensional (continuous) distribution. This provides evidence for the presence of a continuum like model between schizotypy and schizophrenia, thus suggesting a fully dimensional model.

The ‘fully dimensional’ model takes influence from both Meehl’s (1990) theory and Eysenck’s (1960) work on personality. This model incorporates the quasi-dimensional model, but includes another continuum related to personality (see Claridge & Beech, 1995, p.194). Within this model the expression of a schizotypal personality is descriptive of an underlying predisposition to psychotic illness. The expression of schizotypal personality traits are non-pathological and construct part of typical individual difference. Some of the factors which might affect the level of schizotypy have been suggested to be: ”personality traits, cognitive style (?creativity) [sic], nervous system type, genetic variation” (Claridge & Beech, 1995, p.194). Within the fully dimensional model, a schizotypal trait increases the individual’s vulnerability to psychosis. Nonetheless, for transition to psychotic mental illness, deleterious environmental factors must be present. The evidence which was suggested in support of the ‘entirely’ dimensional model may also apply to the fully dimensional model. This model explains the similar factorial structure between schizotypy and schizophrenia (Liddle, 1987; Raine & Benishay, 1995), and the increased incidence of decompensating amongst highly schizotypal individuals (Pulay et al., 2009). The model also explains the finding that people with psychotic illness tend to score highly on measures of schizotypy (Camisa et al.,2005). Further evidence for the fully dimensional model can be derived from the overlap, yet significant distinction, demonstrated between schizotypal personality and a psychosis prodromal state (Bedwell & Donnelly, 2005). This model may account for the high prevalence of psychotic-like experience in healthy populations (van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009) and the incidence of cognitive deficits in the same domains as experienced in schizophrenia in healthy schizotypal participants (Moritz, Andresen, Naber, Krausz & Probsthein 1999).

Of the three models outlined, there appears to be the superior body of evidence for the fully dimensional model (Nelson et al., 2013). Moreover, rather than the *one* schizogene proposed by Meehl (1990), most recent research suggests a poly-genic model with plausibly hundreds of SNPs, each conferring a slight additive risk (Purcell et al., 2009). This could indicate that genetic vulnerability exists at gradated intervals which, given the number of implicated SNPs (and the various

permeations of any interactions), could function similarly to a continuum. If the schizogene of the quasi-dimensional model (Meehl, 1990) was replaced with an additive poly-genic 'continuum', this would result in a model similar to the 'fully dimensional' approach. The relevant literature has failed to reach congruence on the exact nature of the relationship between psychoticism and schizotypy and the point at which conversion exists. Nonetheless, the relevant models concur on the fact that there is an inextricable link between psychotic illness and the trait of schizotypy.

Schizotypal trait, and schizotypal state

Schizotypy is commonly assumed to be a stable and enduring personality trait which has demonstrated "moderate" stability (Nestadt et al., 2010, p.1), unlike the symptoms of schizophrenia which are thought to "wax and wane over the lifetime course of a disease" (Noll, 2007, p.156). Some of the literature discussed in this section suggests a mechanism by which one may decompensate from schizotype to psychotic illness (e.g. Meehl, 1990). However, little focus has been paid to the means by which each psychotic(-like) experience may influence the expression of schizotypy or the transition into psychotic breakdown. Moreover, there is a paucity of information pertaining to the factors which may influence the presence of these momentary psychotic-like experiences.

Within an entirely dimensional model, a fully dimensional model, or (plausibly) a poly-genic quasi-dimensional model it is feasible that the traits and states demonstrated in schizophrenia (Chen, Bidwell & Norton, 2006), are also present in schizotypy. Within, these frameworks, if schizophrenia has state and trait properties, it is plausible schizotypy does as well. In addition to a schizotypal trait, there is also arguably a 'schizotypal state'. Rossler, Hengartner, Ajdacic-Gross, Haker, & Angst (2013) determined that over a 30 year follow-up period schizotypy disaggregated into both state and trait factors. Miller, et al. (2002) compared two groups of 'high risk' participants, those who displayed psychotic symptoms during clinical interview and those who did not. Miller and colleagues administered a measure of schizotypy within the same battery of tests, and found that participants that displayed clinical symptoms also had significantly more schizotypal traits. This

is feasibly as a consequence of the effects of personality trait. Nonetheless, in this investigation assessments of symptoms and schizotypy were performed in the same battery. Thus, presumably the participants state may show little variance over such a short period of time. Hence, given that both groups were said to be 'high risk' such an association may also be explained by state processes (i.e. elevations in symptomatology also equated to elevations in schizotypal trait). In a longitudinal investigation, an increase in environmental risk factors resulted in persistence of psychotic experience (Cougnard et al., 2007), thus, indicating that the persistence of schizotypal type experience is in part influenced by environmental factors. The very nature of environmental factors is that they are typically not fixed (i.e. time variant). Thus, if a time variant factor may alter schizotypal trait then schizotypy plausibly has a time variant component.

It has been argued that the presence of a schizotypal trait is reflective of another state the schizophrenia prodromal (Bedwell & Donnelly, 2005). Furthermore, those displaying a prodromal *state* have been shown to display similar cognitive processes to those displaying a schizotypal trait (Barkus et al., 2010). Although, no consensus has developed suggesting schizotypy represents a psychosis prodromal state, schizotypal trait has been found to moderate the association between psychotic like (prodromal) experience and the distress caused by such symptoms (Kline, et al., 2012). Thus, indicating that these two factors are highly related, and within continuum models they are likely to represent varying expression of severity of the same disease process.

Further, evidence for the transitory nature of schizotypy can be derived from observations that SPD can develop after the formative years of personality (e.g. after childhood see Caspi, et al., 2003). "In our clinical work we have come across cases where SPD has become manifest relatively later in life" (Raine & Lencz, 1995, p.5). Moreover, some of the items used to assess schizotypy appear to infer that they have both permanent (e.g. "I am an odd and unusual person", SPQ-b, Raine & Benishay, 1995) and momentary (e.g. "Do you ever suddenly feel distracted by distant sounds that you are not normally aware of?" SPQ-b: Raine & Benishay, 1995) elements. Additionally, some items require the experience to have occurred at a specific level of frequency (e.g. Do you often pick up hidden

threats or put-downs from what people say or do? SPQ-b: Raine & Benishay, 1995). However, there is little information provided by the authors pertaining to what level of frequency is requisite for an increased vulnerability, nor, how each experience may individually contribute to increased psychosis proneness.

However, 'sensitisation' may serve to explain how each psychotic-like experience may contribute to people decompensating (see Section 1.7.3, for further information). Collip, Myin-Germeys and van Os (2008) describe a plausible mechanism of 'sensitisation' in which environmental factors interact over time with genetic/physiological factors to bring about psychotic illness. The notion that environmental factors, some of which typically occur after childhood (such as cannabis use, see Section 1.8), serve to alter psychotic vulnerability diminishes the notion of the stability of schizotypy. Van Os et al., (2009) elaborates on the sensitisation model to suggest that the development from transitory psychotic-like experience, into persistent experience, and to clinical symptoms, is dependent on environmental risk factors. This suggests that by measuring transitory psychotic like experience and its persistence (frequency) this can provide information about both environmental and genetic factors influencing the presentation of psychotic illness (see Section 1.2.3 for further discussion).

There is a developing body of research suggesting that schizotypy may be elevated by environmental factors, such as cannabis (also see Section 1.8), and that these heightened schizotypal states may provide a mechanism for decompensating into psychotic illness (van Os et al., 2009). Nonetheless, it is acknowledged that the majority (75-90%) of psychotic like experiences are typically transitory in nature and persist in only a very small proportion of people (van Os et al., 2009). Van Os et al., (2009) estimated that 8% of the population had psychotic experience, 50% of those individuals (4% of the population) had psychotic symptoms, and 75% of those with psychotic symptoms (3% of the population) decompensated into illness. Thus, this would indicate that transitory psychotic like states are not clinically significant in the majority of cases. However, in instances where these experiences are persistent then they could be indicative of psychotic vulnerability (van Os et al., 2009).

Although it appears that it is the persistent (plausibly trait-like) psychotic-like states which are the most clinically relevant, the momentary evaluation of psychotic-like phenomena is also a worthwhile endeavour. The identification of momentary psychotic like states may allow for an assessment of what constitutes the temporal boundary between a non-clinically relevant transient psychotic-like experience, and a more clinically relevant persistent psychotic-like experience. In the absence of an assessment of what constitutes a transient or persistent experience it is difficult to establish those at the greatest risk. Perhaps one of the most important contributions the assessment of transient psychotic-like states can provide is models of exacerbations of symptomatology in schizophrenia. With prolonged exposure to environmental factors which elevate or contribute to psychotic-like states, these psychotic-like states could plausibly become persistent (e.g. through sensitisation). Within a continuum model of psychosis (see Section 1.2.2, pp. 25-31) environmental factors which increase the persistence of psychotic-like states are also likely to increase the incidence of psychotic symptoms and ultimately disorder. Thus, within such a model the evaluation of environmental factors which increase psychotic-like states can provide inference about the environmental factors influence on psychotic disorder.

Due to their 'transitory' nature (i.e. their moment to moment variance) schizotypal states are difficult to measure. Traditional assessments of schizotypal personality are not appropriate for the measurement of schizotypal states, as the items tend to infer an air of permanence (e.g. "Are you so good at controlling others that it sometimes scares you?" OLIFE: Mason, Claridge, & Jackson, 1995 p.9) or require an amalgamation of previous phenomena (e.g. "Do you often feel 'fed up'?" OLIFE: Mason et al., 1995 p.10). Moreover some of the most commonly used tools for the clinical assessment of psychotic symptoms are not appropriate for the assessment of a schizotypal state. For example the items from the, World Mental Health-Composite International Diagnostic Interview, refer to the 'lifetime' occurrence of psychotic phenomena (WMH-CIDI: Kessler & Üstün, 2004). The Positive and Negative Syndrome Scale (PANSS: Kay, Flazbein, & Opler, 1987), Brief Psychiatric Rating Scale (BPRS: Overall & Gorham, 1962) and Schedules for Clinical Assessment in Neruopsychiatry (SCAN: Wing et al., 1990) are all interview based assessments. Through the use of observations and direct questions during

the interview process these measures make an assessment of momentary symptomatology. However, they are intended for the assessment of clinical not sub-clinical symptoms. Therefore, although they may be adept at highlighting momentary exacerbations in symptomatology, they may not be adept at highlighting momentary exacerbations in psychotic-like symptomatology.

The Structure Clinical Interview for DSM-IV Axis I disorders (SCID) has a non-patient edition (SCID-INP) and assess "current" symptomatology, and so may be better suited to detecting sub-clinical schizotypal states. However, within the context of the measure "current" pertains to whether criteria had been "met at any time during the last month" (First, Gibbon, Spitzer, & Williams 2002, p.26). Thus, invalidating the measures use in the assessment of 'momentary' or transient state like phenomena. Such is the nature of transient phenomena that even slight delays in the assessment procedure may result in alterations of state, even if the state in question is thought to be influenced by stable processes (e.g. personality trait). Therefore, the use of lengthy interview based assessment may distort the temporal boundaries of assessments of momentary phenomena, thus making them inappropriate for assessments of 'state'.

Some self-report measures have been developed for the assessment of psychotic symptoms. The Symptoms Checklist (SCL-90-R, Derogatis, 1975) is a self-report measure that allows the assessment of psychotic symptoms in which the assessor can set the period of response (e.g. one week, one month etc.). However, the SCL-90-R items are related to previously experienced (as opposed to concurrently experienced) phenomena, and so are likely to be assessing the *persistence* of a psychotic state as opposed to a psychotic state per se. The Behaviour and Symptom Identification Scale (BASIS-R, Eisen, Normand, Belanger, Spiro, & Esch, 2004) is a self-report measure however, the anchors ranging from 'none of the time' to 'all of the time' are not appropriate for the momentary assessment of phenomena. Such a measure is likely to be inappropriate for the measurement of a psychotic like state as it is based on retrospective account. A retrospective assessment of a state is likely to be incapable of distinguishing between a rapid cycling state, and a 'state' which has greater stability. Furthermore, due to the undefined time frame of what constitutes 'a state', retrospective measures are

likely to encompass multiple states. Moreover, this undefinable time frame does not lend itself to study design assessing environmental factors which may elicit a schizotypal state.

One such tool that has been developed for the assessment of momentary psychosis-like experience is the Psychotomimetic States Inventory (PSI, Mason, 2008). An elevated score on the PSI has been documented as a result of sensory deprivation (Mason & Brady, 2009). Furthermore, participants that were highly psychosis prone scored significantly higher than those who were not. Thus, those who would be hypothesised to have the greatest propensity to psychotic-like states demonstrated such a response on the measure. Elevations on the PSI have also been documented after participants have been recently aroused from a dream in comparison to when they have been awake for approximately 6 hours (Mason & Wakeerley, 2012). Moreover, elevations in the PSI have been documented as a consequence of a cannabis challenge (Morgan, Rothwell, Atkinson, Mason & Curran, 2010; Schafer et al., 2012; Stokes, Mehta, Curran, Breen, & Grasby, 2009), a ketamine challenge (Freeman et al., 2009; Mason, Morgan, Stefanovic & Curran, 2008), and a salvia divinorum challenge (Ranganathan et al., 2012). Furthermore, following a ketamine challenge increase on scores on the PSI were also associated with pharmacological changes present in psychotic disorder (De Simoni et al., 2012). Taken together, these results provide strong evidence that the PSI is a sensitive and valid (see Section 1.3.2 pp. 51-54) tool for the assessment of momentary psychotic like states.

Later on in this chapter the evidence suggesting that cannabis may elevate a schizotypal trait and state is discussed (Section 1.8 pp. 96-99). However, prior to the discussion of this environmental factors influence on schizotypal state it is necessary to evaluate the literature pertaining to some other areas of research. As discussed in this section transient psychotic like experience may provide information about schizophrenia within several (continuum based) theoretical frameworks. This section has discussed the means by which a schizotypal state can be assessed (amongst other things). However, transient psychotic-like experience is non-pathological and does not provide a good prognostic indicator of

psychotic disorder. The next section will discuss the literature pertaining to assessment of vulnerability for schizophrenia.

1.2.3 Assessing vulnerability to schizophrenia

Factors that increase the odds risk

Given the debilitating nature of the symptoms of schizophrenia and the high suicide rate (APA, 2013a), it is necessary to assess the extent to which psychotic vulnerability can be predicted and disorder ultimately prevented. One means by which psychotic vulnerability can be assessed is by identifying the factors which co-vary with (or in theory precede) a diagnosis of psychotic disorder. One factor that has been shown to increase the odds ratio of psychotic disorder is obstetric complication. In examination of epidemiological data from a Danish cohort, numerous obstetric complications related to behaviour (e.g. non-attendance at a pre-natal clinic), pathology (e.g. maternal influenza), and delivery related events (e.g. harmorrage during delivery, manual extraction) were shown to increase the odds ratio of a diagnosis (to the offspring) of schizophrenia (Byrne, Agerbo, Bennedsen, Eaton & Mortensen, 2007). A meta-analysis of eight studies concluded that three groups of obstetric complications significantly increased the odds ratio of schizophrenia. These were related to difficulties during pregnancy, difficulties during delivery, and non-standard foetal development (Cannon, Jones, & Murray, 2002). It should also be noted that even some seemingly innocuous obstetric conditions such as being born in the winter or in an urban environment have been implicated in an increased odds ratio of schizophrenia (Mortensen et al., 1999). Prenatal stress has also been implicated in increasing the odds ratio of psychotic disorder. However, these effects may not be independent from the other aforementioned obstetric factors (See Clarke, Kelleher, Clancy, & Cannon, 2012).

In addition to the broad range of obstetric complications that may increase the odds ratio of a diagnosis of schizophrenia, there are also factors which occur during childhood which may increase risk. One such example is childhood trauma. Heins et al. (2011) found that childhood trauma (associated with various forms of abuse and neglect) increased the presence of psychotic symptoms in a dose

dependent fashion. Moreover, Heins and colleagues found that patients with a psychotic disorder indicated greater exposure than their non-affected siblings. As the sibling group are first degree relatives they share approximately 50% of the genetic material with the patients. This indicates that the difference between the patient and sibling group is more likely to be as a consequence of environmental factors (as opposed to comparison with a population control group). Hence, the difference between the two groups further emphasises the importance of childhood trauma as an environmental risk factor.

Further evidence comes from Arseneault et al., (2011) who conducted a prospective cohort investigation, and found that childhood trauma predicted adolescent psychotic 'symptoms'. Other childhood factors such as peer rejection, IQ, the internalisation of problems, and abnormal motor development have also been associated with future development of schizophrenia (Cannon, Caspi et al., 2002). Furthermore, social withdrawal in adolescence has been found to be a risk factor for relapse in adults (Robinson et al., 1999). The risk factors which are not unequivocally related to environment could plausibly be reflecting a similar construct to schizotypy or other 'schizogenic' influence (i.e. social withdrawal). Nonetheless, there is a good body of research or rationale to suggest that some of these factors are exerting an independent effect to that of schizotypy (e.g. childhood trauma, see Section 1.7.4).

Other factors not specifically related to childhood, such as an acquired brain injury, have also been related to an increased odds ratio. David and Prince (2005) reviewed data pertaining to brain injury and psychotic symptoms and found that the studies indicate a broad range of purported risk with relative risks (to the population) spanning from 0.2 to 16.3. In Clarke et al., (2012) recent meta-analysis estimate that brain injury increases the odds ratio by1.65. However, the researchers also acknowledge that potential confounders such as substance use may account for at least some of this association. Such a scenario where substance use may result in increased incidence of traffic accident (Movig et al., 2004), resulting in an increased likelihood of acquired brain injury, resulting in an increased likelihood of schizophrenia is a plausible scenario. As outlined in the aforementioned example identifying the independent effect of environmental

factors is a difficult if not impossible endeavour. Thus, an alternative approach to assessing a myriad of different factors is to assess a broader overarching concept, such as stress or the perception of stressful events, or states.

Stressful events have been shown to significantly exacerbate symptomatology (Betensky et al., 2008; Norman & Malla, 1993) and increase incidence of relapse in people suffering with schizophrenia (Doering et al., 1998; Nuechterlein et al., 1994). Moreover, different types of stressors have demonstrated such an effect. For example' an adverse family environment (expressed emotion, see Brown, Monck, & Carstairs & Wing, 1962) has also been associated with increased odds of relapse (Amaresha & Venkatasubramanian, 2012). Furthermore, in comparison to controls people diagnosed with SPD had significantly more adverse life events and experienced more distress as a result of these stressors (Tessner, Mittal & Walker, 2011). In this same study, participants in the control groups also showed an increase in psychosis like symptoms as a result of stressors. Further, evidence for stress' relationship with schizophrenia can be derived from evidence suggesting that the ability to apply coping mechanisms appears to mitigate the psychotomimetic effect of stress. Moreover, there is a neurophysiological difference in event related potentials (P300 wave) between those able to apply such mechanisms and those who cannot (Pallanti, Quiercioli, & Pazzagli, 1997).

People suffering with schizophrenia tend to display both more emotional reactivity to stress than controls (Horan & Blanchard, 2003) and greater subjective stress (Betensky et al., 2008). Furthermore, emotional reactivity and life stressors have been shown to interact to increase psychotic symptoms (Docherty, St-Hilaire, Aakre, & Seghers, 2009). However, it is thought that the impact of stress reactivity on symptomatology may be in-part mediated by familial vulnerability to depressive symptomatology (Kramer et al., 2012). This indicates that the relationship between stress reactivity and symptomatology is influenced by mood, or more specifically genetic vulnerability to mood disorder. This could indicate that the link between stress reactivity and schizophrenia is not an independent process and is in some way influenced by genetic factors. This may also infer that people who develop schizophrenia due to stress related factors are also vulnerable to mood disorder.

Given the subjective and loosely defined nature of what constitutes a ‘stressor’, an exact odds ratio for the effect of ‘stress’ is difficult to generate. Nonetheless, the various data indicate that stressful life events do contribute to the development of psychotic illness. Many of the environmental factors described herein may co-vary with stress and a stress response. However, within the wider context stressful events or psychological stressed states are considered as independent environmental factors (or stressors). It is thought that environmental stressors and innate factors may interact to cause mental illness. Such an association has been referred to previously as a ‘stress-diathesis’ model. Within the realms of schizophrenia one of the pioneers of this model was Meehl (1962). However, as Meehl argued and as the data still suggests genetic factors are the best predictive determinates of psychotic disorder.

Genetic determinates of schizophrenia

Despite the numerous environmental factors that increase the odds of psychotic illness, the one which appears to have the largest effect is familial history (Sullivan, 2005). Prior to the sequencing of the human genome (Lander et al., 2001) familial studies were utilised to elucidate the genetic components of schizophrenia. A meta-analysis of familial studies was conducted by Sullivan (2005). From the studies Sullivan (2005) reviewed there was an increase of 9.8 in the odds ratio of developing schizophrenia associated with having a first degree relative with the disorder. However, given that families often share environments and thus presumably some risk factors it is difficult to disentangle the environmental and genetic effects. To address this, Sullivan also reviewed the data generated by adoption studies, which allow for separation of some of these factors. He found that, in cases where the adoptee had a diagnosis of schizophrenia there was an increase of 5 in the O.R. of the biological parents also having the disorder in comparison to the adoptive parents, providing even stronger evidence for a genetic component.

Another means by which investigators have attempted to assess the heritability of schizophrenia is through the use of twin concordance investigations. Monozygotic twins share the same genetic material however dizygotic twins only share the

same amount of genetic material as a first degree relative. Research from within this domain works on the premise that sets of twins will share a similar environment and thus any discordance between monozygotic and dizygotic twins is indicative of genetic processes. Estimates from a meta-analysis of the twin concordance data indicate that the heritability of schizophrenia liability is 81%, and the effects of environment account for 11% of the variance in a diagnosis outcome (Sullivan, 2005). Although the data from heritability studies indicate a genetic influence they have been criticised as they assume "no interactions among genes or between gene and the environment" (Clarke et al., 2012). That is such models cannot assess the association between psychotic stress sensitivity and mood disorder vulnerability discussed earlier in this section (Kramer et al., 2012). Nor, can the model assess the interaction between stressful life events and psychotic vulnerability. Moreover, the relevant investigations often fail to adequately exert control over the notable differences and similarities in the familial environment which may predict psychotic illness (e.g. stressful life events or obstetric conditions). This could feasibly result in an inflated estimate of the actual genetic involvement.

More recent studies assessing genetic vulnerability have looked at functional polymorphism in single nucleotides (SNPs). Some of these studies were 'candidate gene studies', in which the SNPs were selected on *a priori* hypotheses (Collins, Kim, & Sklar et al., 2012). One such candidate gene is the catechol-O-methyltransferase (COMT) gene, this gene codes for an enzyme that degrades catecholamines such as the neurotransmitter DA (Lachman et al., 1996; for further information on DA see Section 1.2.1 pp. 21-25). A functional polymorphism in the COMT gene has been shown to be significantly related to schizotypy (Stefanis et al., 2004). Thus, indicating that this SNP has convergent validity (see Section 1.3.2 pp. 51-54) as a prognostic indicator of psychotic disorder. However, like many other investigations that have assessed candidate genes (see Sullivan, 2005 for review) these findings have been contradicted by another investigation which has failed to find a significant effect of the SNP (Fan et al., 2005). More than a thousand candidate genes have been assessed in more than a thousand investigations (Allen et al., 2008). However, there is rarely replication of the findings between the investigations and there is insufficient evidence to suggest an

effect of the eight most investigated SNP (Collins, Kim, Sklar, O'Donovan, Sullivan, 2012). These findings suggest that it is inefficient to assess SNP variance based on a priori hypotheses. Moreover, these myriad of investigation contest the notion of Meehl's (1962) hypothesis of a single 'schizogene'. If there is such a gene, this 'holy-grail' of genetics research, is as yet to be identified.

More recently instead of focusing on candidate genes, assessments are being made in genome wide association studies (GWAS), which utilise a systematic interrogation of the entire genome. The GWAS consortium (Ripke et al.,2011) have undertaken a 'mega-analysis' which included more than 50,000 individuals. This analysis identified seven loci which are implicated in schizophrenia and 54 significant SNPs that were subsequently confirmed in two independent samples. However, only approximately 6% of the variance in the data was accounted for by this genetic model. Indicating that the model fails to account for near to the amount of heritability observed in the 'old genetics' (familial) studies (e.g. Sullivan, 2005). This indicates that the model is likely to be missing other significant genetic determinates of diagnoses. Moreover, despite the huge number of participants under consideration, the GWAS consortium acknowledge that the sample is likely to not have sufficient power to model all of the SNPs which confer risk (p.974). The International Schizophrenia Consortium (Purcell et al., 2009) took an alternative approach to modelling the effects of SNPs. The ISC modelled the effects of each of the SNPs assessed with a more liberal p-value threshold ($p<0.5$). Although, this method will likely result in an increased incidence of type one error it does mitigate the influence of failings in statistical power. Utilising this technique the ISC identified 37,655 SNPs each conferring a slight additive risk. However, this only accounted for approximately 3% of the variance in the data.

The investigations of the ISC and the GWAS consortium highlight that there is likely to be numerous SNP's each conferring an additive risk. Moreover, it would appear that samples including vast numbers of people may be necessary to identify a prognostically viable genetic model. Despite the large number of participants and variables included in the two aforementioned GWAS they both fail to account for anywhere near the heritability identified in twin concordance investigations (e.g. 81%, Sullivan, 2005). Clarke et al. (2012) suggest that the

missing heritability “is likely to lie in the environment or gene-environment interaction” (p.597). One recent article has suggested that by combining genetic and epidemiological data (such as exposure to adverse environmental factors) may be the most proficient means to assess heritability and to account for some of the error term (McGrath, Mortensen, Visscher & Wray, 2013). However, such models have yet to be applied in a prognostic capacity.

Biological markers of schizophrenia

Although, the various investigations into genetics are very intriguing, they are yet to elucidate information that has any relevance in the praxis of assessing vulnerability. Due to what has been described as a “hypercomplex” genetic model (Sullivan, 2005, p.617), researchers have sought out other means to identify the schizophrenia genotype through examination of the phenotype. These have been described as biological markers, or ‘biomarkers’. According to the WHO (2001) “A biomarker is any substance, structure or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease” (Introduction section, para. 3). A number of different bio-markers for schizophrenia, have been proposed, these fall within several domains including neuroanatomy, event related potentials, and visual processing (See Allen, Griss, Folley, Hawkins & Pearlson, 2009).

One biomarker falling within the domain of neuroanatomy is ventricular volume. As discussed previously (Section 1.2.1 pp. 21-25) there is an increased incidence of ventricular enlargement (cortical atrophy) in patients suffering with schizophrenia. A recent meta-analysis found consistent enlargement in combined data from thirteen investigations (Kempton, Stahl, Williams, & DeLisi, 2010). This suggests that cortical atrophy may be a distinguishing feature between those with schizophrenia and those without. However, the data indicated that these effects are likely to be neurodegenerative. Cortical atrophy could represent a consequence of, rather than vulnerability to, the disorder. Consequently, assessments of cortical atrophy may be appropriate in identifying those suffering with long-term disorder. However, they are unlikely to be useful in assessment of vulnerability.

One of the most widely investigated biomarkers which falls within the domain of event relate potentials is the P50 suppression response. An event related potential is a small amount of electric current generated in response to a stimuli. These are measurable through an electroencephalogram (EEG) machine, the P50 is the most positive peak in voltage that occurs between 40 and 75 ms after stimuli (Sur & Sinha, 2009).The P50 suppression is one of the most widely investigated bio-markers of schizophrenia (See Allen et al., 2009). The P50 suppression task purportedly assesses the brains ability to filter out irrelevant stimuli (Sur & Sinha, 2009). A recent meta-analysis of the P50's suppression showed a significant difference between patients suffering with schizophrenia and healthy controls (Su et al., 2010).The findings from Su et al. (2010) analyses suggest that the P50 response may be an appropriate means of assessing vulnerability to disorder.

In a search for bio-markers Benson et al. (2012) examined eye-movements in a number of experimental tasks assessing smooth pursuit, fixation maintenance, and free viewing. Patients diagnosed with schizophrenia performed significantly abnormally (e.g. absence of smooth pursuit) on all three tasks in question. Utilising this data Benson and colleagues were able to discriminate between participants with a high degree (87.8%) of accuracy. However, it should be noted that during re-test some of the patient group failed to replicate their abnormal eye movement. This suggests that the task may be prone to changes in environment and thus, may not be truly reflective of schizotaxic vulnerability. Moreover, the investigation assessed participants who had been ill for a substantial period of time (mean 16.9, SD 10.5). Thus, whether or not these findings represent a true phenotype or iatrogenic differences is at present unresolved. Nonetheless, the data indicates that with further investigation the pursuit of eye movement bio-markers may be an appropriate means to assess psychotic vulnerability.

Despite, various biomarkers displaying promising data pertaining to their ability to predict schizophrenia at the moment "no biomarker currently exists" (Weickert, Weickert, Pillai, & Buckley, 2013 p.8). Part of the rationale for Weickert et al. (2013) conclusion is that bio-markers should have some clinical value. At present bio-markers are not as effective at diagnosing schizophrenia as a clinical interview

(Weickert et al., 2013). Furthermore, the prognostic capabilities of bio-markers have not as of yet been established, and it is feasible that some of the bio-markers observed may not be present prior to disease onset. Therefore, these biomarkers may not be useful for indicating vulnerability to schizophrenia onset.

Psychological assessments of psychosis proneness

At present there is insufficient data to generate accurate models to assess psychotic liability through the observation of factors that increase O.R. Neither can psychotic vulnerability be assessed from genetic material which is feasibly as a consequence of the complexity and lack of consensus emanating from the research within this domain. Furthermore, bio-markers although promising avenues of enquiry are not at present capable of being prognostic indicators. Thus, one of the most effective means of assessing psychotic-liability is via assessment of schizotypy (see Section 1.2.2 pp. 25-31).

Researchers have utilised interview based assessments of a psychosis prodromal state to significantly predict which high risk patients decompensated (Miller et al., 2003; Yung et al., 2006). These structured interviews have utilised assessments of psychotic-like phenomena. Unfortunately, these measures are unlikely to be useful for assessment in the general population as these investigations have utilised high risk help seeking participants, who are at an inherently greater risk of decompensating. Moreover, the psychosis prodromal phase reflects a temporary exacerbation in cognitive, and attenuated psychotic symptoms. Due to these symptoms transient nature they may not accurately reflect an individual's inherent 'schizotaxic' vulnerability. The relatively short follow-up periods of the aforementioned investigations (24 and 6 months respectively), and the help-seeking status of the population, therefore suggest that this may not be an appropriate means to assess long-term psychotic liability in the general population.

Interview methods have also been utilised in the assessment of a presumably more stable construct pertaining to psychotic vulnerability: schizotypy (e.g. the structured interview for schizotypy , SIS: Kendler, Lieberman, & Walsh, 1989). Nonetheless, a limitation of interview assessments (and the aforementioned ones

of a psychosis prodromal state) is that they are often time consuming and costly to administer. Thus, interview based assessment are not appropriate for the widespread evaluation of vulnerability, and have more relevance when assessing vulnerability in people known to be at an increased risk (e.g. help-seekers).

Other aspects of personality and behaviour have been evaluated for their ability to predict psychosis. A recent investigation has proposed that social anhedonia, social withdrawal, and positive psychotic like experience significantly interact in the siblings of people suffering with schizophrenia. This interaction has been proposed as a means to "contribute to a better psychosis prediction" (Velthorst et al., 2012,p.293). Nonetheless, at present there is insufficient data to assess these variables as predictors of psychotic illness. Furthermore, social anhedonia and withdrawal are both arguably correlates or feasibly even constructs of schizotypy (Chapman, Chapman, & Raulin, 1976). This could suggest that the factors identified by Velthort et al., (2012) investigation are reflective of schizotypal processes as opposed to an independent influence. Thus, for the exception of the interaction effect this proposed model is assessing broadly similar constructs to other psychological means of assessing psychosis proneness (i.e. schizotypy).

Given the limitations of the other methods of assessing psychotic liability, a lot of research has focused on the ability of self-report measures of schizotypy to predict psychosis. The origins of these assessments are typically rooted in either a fully dimensional or quasi-dimensional approach (Raine, 2006). However, there is often overlap between these two schools of thought with some measures utilising a composite of both approaches (e.g. the Schizotypal Traits Questionnaire: STQ, Claridge & Broks, 1984) The measures which take their influence from the quasi-dimensional model are typically characterised by items that are similar to attenuated symptoms (e.g. 'Have you ever had the sense that some person or force Is around you. even though you cannot see anyone?', SPQ-b: Raine & Benishay, 1995). The assessment of attenuated symptoms in healthy populations often results in highly positively skewed data with a narrow range of responses (infrequent endorsement of items) (e.g Barrantes-Vidal et al., 2013). Several of these measures have referred to DSM criteria for the basis for the items (e.g. Schizotypal Personality Questionnaire, SPQ: Raine, 1991). In contrast the items

from the measures influenced by the dimensional model typically refer to "relatively mild" aspects of personality as opposed to attenuated psychotic symptoms (Mason, et al., 1997, p.24) e.g. Are your feelings easily hurt? (Psychoticism scale: Eysenck, Eysenck, & Barrett,1985).

Many different measures have been utilised to assess schizotypy some of which have been discussed in Mason et al. (1997). A more recent review purportedly assesses the "most important" measures (Fonseca-Pedrero, et al., 2008, p.577). However, neither reviews are exhaustive, particularly since psychosis proneness is still a developing area of research, with new assessments constantly being developed (e.g. Liu, et al., 2013) and old scales being re-developed (e.g. Gross, Silvia, Barrantes-Vidal, & Kwapil, 2012).

As previously discussed, a diagnosis of SPD increases the risk of a diagnosis of schizophrenia (Pulay et al., 2009). However, of greater relevance to predicting disease on-set is whether the personality trait schizotypy can be used to differentiate between those who develop psychotic disorder and those who do not. Shah et al., (2012) utilised structural equation modelling to assess psychotic liability via three of the Chapman scales (Chapman et al., 1978; Eckblad et al., 1982; Eckblad & Chapman, 1983). Within the model, schizotypal personality trait was a significant predictor of diagnosis, indicating that schizotypy accounts for a proportion of variance in psychotic diagnosis. Several subscales of the Schizotypal Personality Questionnaire (SPQ, Raine, 1991) have also been found to significantly predict those who will decompensate to psychotic illness (Salokangas et al., 2013). The data indicated that ideas of reference and lack of close interpersonal relationship were particularly predictive of decompensating. Moreover, in a ten year follow-up investigation, both positive and negative dimensions of schizotypy predicted the development of schizophrenia-spectrum disorders, in addition to both adjustment and social impairment (Kwapil, Gross, Silvia & Barrantes-Vidal, 2013). The data therefore indicates that despite not being an unequivocal indicator of psychotic liability, schizotypy may be a useful means for identifying potential risk to future psychotic incidence.

This section has focused on the means by which liability to schizophrenia spectrum disorder is assessed. The data presented in this section suggests several advantages of psychological assessments of liability over other means of assessing vulnerability. The next section of this chapter will focus on the process by which a psychological measure is developed. This section will provide information on how psychological assessments of personality traits such as schizotypy are created, and tested for reliability, validity and factorial structure.

1.3 Developing and testing psychological measurement scales

1.3.1 Measure development

In any scientific endeavour the act of measurement is central. The precision of the instruments of measurement will undoubtedly affect the interpretability of data and any conclusions drawn. The development and refinement procedure is key to the precision of the measure however, this is often a long, iterative, multi-staged process. For example the SPQ items were derived from the diagnostic criteria contained within DSM III-R (APA, 1987). Reliability, validity and the factorial structure of the SPQ was demonstrated by Raine (1991). The most reliable of these items were selected to be contained within a short version of the scale the SPQ-b (Raine & Benishay, 1995). Through a series of investigations the SPQ and the SPQ-b scoring and factor structure has been further refined to create two new scales (Cohen, Matthews, Najolia, & Brown, 2010; Wuthrich & Bates, 2005).

Sound psychometric measures are contextualised within a theoretical framework. This enables the assessments of the measure to have some bearing on the constructs they purport to measure. The importance of this is evinced by the longevity of the discussions of the quasi and fully dimensional models of schizotypy (e.g. Meehl, 1962; Nelson et al., 2013, also see Section 1.2.2). The various discussions surrounding these models are not limited in their scope to schizotypy, similar debates are taking place within the broader context of personality and its relationship to psychopathology (e.g. Widiger, 2003). When developing a psychological measurement scale the theoretical perspective adopted is of importance in shaping the tool (e.g. Mason et al., 1997 p.21-3). One means in which theoretical perspective can alter the development of a measure is via item development, which is typically the first stage in the process.

There are different ways in which items can be developed. One way is through reviews of the existing scientific literature either from full literature reviews (e.g. Bjordal et al., 1994) or by drawing on key texts (e.g. Poreh et al., 2006). Moreover, from the examination of the literature items can be generated from previously developed measures which are capable of assessing the same or related construct. For example, Doyle et al., (2013) measured subjective effects of drug

administration through a selection of items from; the Psychotomimetic States Inventory (PSI: Mason, 2008); the Clinician Administered Dissociative States Scale (Bremner et al, 1998); and items from a Visual Analogue Scale (VAS: Herbert, Johns & Doré, 1976). The advantage of 'generating' items from other measures is that the items have typically already gone through a developmental process and in some instances there is data pertaining to the validity. In the aforementioned example the PSI has been shown to be reactive to known psychotomimetic drugs, moreover these have been associated with physiological covariates (De Simoni et al., 2012). Nonetheless, the limitation of using items from other scales is the items may be culturally or historically bound in their relevance, for instance the phrase 'muzzy' as used by Herbert et al. (1976) may be ambiguous to younger participants.

Another means by which items can be developed is through consultation with the population on which the tool is to be administered. Streiner & Norman (2002) suggest "whereas clinicians may be the best observers of the outward manifestations of a trait or disorder, only those who have it can report on the more subjective elements" (p.15). Focus groups and interviews with patients or the intended research subjects can be used to elicit a pool of items that reflect the subjective elements of the construct of interest (e.g. Cella et al., 1993; Nassar-McMillan & Borders, 2002). Utilising the target population in item generation can elicit a rich item pool (e.g. Cella et al., 1993). Cella et al. (1993) also adopted another frequently used technique in item generation, interviews with clinicians who have experience of interacting with, observing, and treating people from the population of the measures intended recipients.

Most of modern psychiatry can find its origins in clinical observations (e.g. Freud, 1953; Kraepelin, 1896). Thus clinical observations have influenced the generation of items which are based on symptom criteria set out in the DSM or ICD manuals (e.g. SPQ, Raine, 1991). However, clinical observation also directly influences item generation with Streiner & Norman (2003) suggesting "clinical observation is perhaps one of the most fruitful sources of items" (p.16). However, clinical observations are subject to the interpretation of the clinician, which in part may be guided by; previously outlined criteria; a narrow selection of cases; or limited

available data. An example of where limited data has affected clinical (and theoretical) interpretation is the consideration of schizophrenia as premature dementia, dementia praecox (Kraepelin, 1896). Expert opinion has also been used in the process of item development. For example a Q-sort procedure with expert clinicians and researchers was utilised to assess the factorial structure of a measure (Stirling, Morris, & McCoy, 2012). However, the same criticisms which may apply to the use of clinical observations can be applied to the use of experts.

The various phases of the development of measurement scales may involve several different techniques to generate items (e.g. Cella et al., 1993). Some measures also utilise an amalgamation of different theoretical perspectives in item generation. For example Rawlings and Freeman (1997) adopted items from measures attributed to both the dimensional and quasi-dimensional models. Such an approach may elicit a broad range of ideas relevant to both clinically relevant and non-clinically relevant phenomena. However, the disadvantage of such an approach is that the absence of a clear theoretical model may result in ambiguity in the interpretation of data derived from such measures.

1.3.2 Testing reliability and validity, and examination of the factorial structure

During the development of a psychological measurement scale an important step is the testing of the reliability and validity of the measure. However, neither reliability nor validity are ever unequivocally established. Reliability and validity are not "inherent propert[ies] of the measure, but an an interaction of the scale, the group being tested, and the conditions" (Keszei, Novak, & Streiner, 2010, p.321). Keszei et al., (2010) outline four types of validity: face, content, criterion, and construct. Face validity and content validity are typically the first assessments of validity and they frequently take place during the item development phase. Face validity is the extent to which the items reflect the construct under assessment based on "a subjective judgement of experts" (Keszei et al., 2010, p.322). Content validity is the "degree to which elements of an assessment instrument are relevant to and representative of the targeted construct for a particular assessment purpose" (Haynes, Richard, & Kubany, 1995, p.239). Haynes et al., (1995)

recommend a 35 step process to assess content validity, however, a much more modest procedure has been described elsewhere (Streiner & Norman, 2003, p.19-21).

Criterion validity considers the concordance between the newly devised measure and a well-established measure of the same construct (see McDowell, 2006, p.31). This is typically assessed by performing a correlation between the two measures (see Keszei et al., 2010, p.321). Criterion validity may be further subdivided into concurrent and predictive validity, these are differentiated according to whether temporality can be established, i.e. whether the measure concurs with a current or future state. If the two measures are administered in close temporal proximity this is considered concurrent validity (Keszei et al., 2010, p.321). However, in assessments of predictive validity the new measure is administered in a prospective manner, typically in a follow up study design to assess the relationship between scores on the measure and outcome.

If no appropriate measure exists capable of assessing the construct of interest construct validity is often utilised (Keszei et al., 2010, p.322). When assessing a factor which has no comparable measure validity is established through a process of hypothesis testing in an attempt to amass a body of evidence that suggests construct validity (McDowell, 2006, p.34). When attempting to establish validity in this manner the theoretical perspective adopted is an important consideration as this will effect hypothesis testing.

In the development of self-report measures, there are typically three types of reliability considered: test-retest reliability, equivalent measures reliability and internal reliability (Howitt & Cramer, 2011, p.269; Keszei et al., 2010). In the evaluation of interview based measurement scales intra-rater and inter-rater reliability are important (Keszei et al., 2010). Inter- and intra- rater reliability can be calculated by utilising the intraclass correlation coefficient (Bartko, 1966). This procedure involves estimating the error between each repeated observation (or rating). However, this means of testing test-retest reliability is only appropriate for measures that assess relatively stable constructs. If the construct displays a high

degree of time-variance then Bartko's (1966) method of assessing reliability will likely display a larger error term than the true value.

Test-retest reliability refers to what extent a measure can assess a construct consistently across time. Equivalent measures reliability assesses the extent to which different formats (e.g. fonts) will elicit equivalent data. Test-retest reliability and equivalent measures reliability are evaluations of agreement between two methods. Several different methods have been proposed for the assessment of agreement between methods including tests of correlation, regression models and tests of difference, amongst others (see White & van den Broek, 2004). However, White and van den Broek (2004) recommend the use of the limits of agreement method. Nonetheless, the basic essence of these statistical procedures is to assess the degree to which the data are related or similar, and whether the means significantly differ.

There is another form of reliability that assesses the internal reliability of a measure this is often referred to as internal consistency (e.g. Tavakol & Dennick, 2011). Internal reliability describes the extent to which items of a measure are pertaining to the same related construct. Cronbach's alpha is assessing the correlation between the items on the scale (Tavakol & Dennick, 2011). Typically the outputs generated from statistical packages will suggest items which, when deleted will improve the internal reliability of the measure . However, it should be noted that estimates derived from Cronbach's alpha have been criticised (Cortina, 1993). These criticisms are related to an increase in the number of items increasing the estimates of internal reliability. Moreover, large estimates of alpha do not equate to uni-dimensionality as the presence of multiple underlying factors may be masked by a large number of items or correlation between the underlying factors (Cortina, 1993, p.100).

"Factor analysis can be used to describe the underlying conceptual structure of an instrument" (McDowell, 2006, p.36). Factor analysis can be used to elucidate the underlying structure of the items of a measure. Examination of the factorial structure will elucidate if multiple scales or subscales are present within the measure. The examination of the factorial structure will allow for an assessment of

how many constructs are being assessed within the measure. However, factor analysis will not designate a name nor evaluate the 'nature' of such constructs. Nonetheless, the underlying constructs that are being assessed may be inferred by the grouping and the content of the items. A factor analysis may facilitate the identification of preferable scoring systems for a measure (e.g. Cohen et al., 2010) and may provide inferences to the underlying clustering of symptoms or disorders (see Nelson et al., 2013). Nonetheless, the results elucidated from factor analysis on occasion have shown variance within measures (e.g. Cohen et al., 2010; Raine & Benishay, 1995) and within constructs (e.g. Mason et al., 1995, p.25).

This section has focused on the development of measurement scales, as discussed in Section 1.2.3 (pp. 37-48) such measurement scales are utilised for the assessment of psychotic vulnerability. Nonetheless, as discussed in Section 1.2.3 numerous environmental factors may increase the odds of psychotic disorder. One possible environmental factor is cannabis, given that cannabis may represent one of few preventable environmental factors the relationship between cannabis and psychosis requires further exploration. Nonetheless, prior to the examination of the data pertaining to the relationship between cannabis and psychotic disorder, it is necessary to highlight some of the societal and pharmacological factors which may influence such a relationship. Consequently, some of the factors which may influence cannabinoid consumption are discussed in the next section.

1.4 Cannabis potency, and the British cannabis market

Cannabis is purportedly one of the first cultivated plants (Zuardi, 2006) and archaeological finds of hemp textile can be dated to around 4000 BCE (Li, 1974). Some argue that cannabis has been used for its psychoactive effects for in excess of 4700 years (Jiang et al., 2007). Today cannabis is regarded as the most frequently used illicit substance in Britain (Home Office, 2011). An estimated 7.1% of the central/western European population of 15-64 year olds are thought to have consumed cannabis in the last 12 months (UNODC, 2011). Cannabis is not a homogenous drug. Indeed, the plant contains over 500 different chemical constituents and more than 80 of these are considered to be cannabinoids (Ahmed, et al., 2008; ElSohly et al., 2005; Radwan et al., 2009). Delta-nine-tetrahydrocannabinol (∆-9-THC) is the most abundant cannabinoid and elicits the principal psychoactive effect (Gaoni & Mechoulam, 1964; Mechoulam & Gaoni, 1967). Acute intoxication with∆-9-THC has been shown to elicit psychotic-like experiences (Kaufmann et al., 2010 & see Section 1.5), identifying the chemical as a possible causal or exacerbating factor in the presentation of psychotic illness (see Section 1.6 for further information).

Cannabidiol (CBD) is another of the major constituents of the cannabis plant (e.g. ElSohly et al., 2005). In contrast to ∆-9-THC, CBD appears to play a role in alleviating psychological disturbance. For instance, CBD has been shown to relieve anxiety in healthy participants (Zuardi et al., 1982) and there is evidence to suggest that it could plausibly improve mood (El-Alfy et al., 2010). Furthermore, in a randomised double-blind study, CBD treated the symptoms of schizophrenia as effectively as an antipsychotic but, with fewer side effects (Leweke et al., 2012). The alleviations of psychotic symptoms seen in the CBD group in this study were also significantly associated with increases in endogenous cannabinoid anandamide (Leweke et al., 2012). This indicates that the effects of CBD resulted in alteration of the endocannabinoid system, which may implicate that system in the efficacy of treatment response. Further evidence for the ability of CBD to alleviate psychotic symptoms comes from two studies showing that participants who consumed cannabis with low levels of CBD had significantly more 'positive' schizophrenia like symptoms than participants who typically consumed cannabis with CBD (Morgan & Curran, 2008; Schubart et al., 2011). Moreover, in a similar

study design the group that used cannabis with CBD had significantly less cognitive impairment, thus, feasibly inferring a neuroprotective effect of the cannabinoid (Morgan et al., 2012).

Given the seemingly contrasting relationship ∆-9-THC and CBD have in the presentation of psychotic-like symptoms, the relevant proportion of each chemical typically consumed is of concern. The ratio of ∆-9-THC to CBD appears in part to be influenced by the 'type' (preparation) of cannabis consumed (Hardwick & King, 2008). The vast majority of the preparations of cannabis consumed in the UK today falls broadly into two categories cannabis resin or herbal cannabis with a third preparation (cannabis oil) also detected, but much less prevalent (Hardwick & King, 2008).

Cannabis resin is typically found as a compressed solid block or disc, but can vary in consistency, malleability, viscidity and colour (Scammel & Sind, 2005). Cannabis resin, may in fact, be further subdivided into two preparations, which may be indistinguishable to the naked eye after the refined cannabis product has been pressed (UNODC, 2009, p15). 'Traditional cannabis resin' is often imported with production generally centred in Lebanon, Morocco and Afghanistan (EMCDDA, 2011). 'Herbal cannabis resin' is a processed herbal cannabis product with high potency sinsemilla frequently used in production (Piljman, Rigter, Hoek, Golschmidt & Niesink, 2005). Although, indistinguishable to the naked eye, these forms of cannabis resin typically display dissimilar cannabinoid ratios (Piljman et al., 2005). 'Herbal cannabis resin' displays a profile with greater similarity to herbal cannabis than to 'traditional cannabis resin'.

Herbal cannabis may be further disaggregated into two groups; traditional herbal cannabis, and sinsemilla. Traditional herbal cannabis typically consists of compressed blocks of foliar and floral material (including seeds and stalks) from the *pollinated* female plants, typically originating from countries that have a climate capable of cultivating cannabis growth outdoors without the use of lights or heating equipment (Bone & Waldron, 1999; D. Potter, Clark & Brown, 2008). Meanwhile, sinsemilla consists of the *unpollinated* female plant.

THC is a secretion produced by glandular trichomes (tiny outgrowths from the epidermis of the plant), which are most abundant in the bracts of the female flowers (Hardwick & King, 2008; Kim & Mahlberg, 1997). Thus, the female plants are typically selected as they possess larger amounts of psychoactive chemical. If the male plant is allowed to reach maturity it will produce pollen causing the female plant to divert energy away from THC production into seed production (Knight et al., 2012). Sinsemilla is derived from the Spanish words 'sin' meaning without and 'semilla' meaning seed. Recently sinsemilla has become colloquially referred to as 'skunk', the term skunk however actually refers to a specific cannabis strain; "this strain is said to be one of the first which combines the high THC content of (*Cannabis sativa subspecies sativa*) with the rapid growth cycle and yield of (*Cannabis sativa subspecies indica*)" UNODC, 2009, p11. Nonetheless, the process of categorising herbal cannabis samples can be a challenging endeavour to even the most adept of forensic scientists. As the classification of material as sinsemilla is in part determined by the environment in which the plant is grown (King, 2008, p, 247).

Of the various preparations discussed sinsemilla typically has the highest THC to CBD ratio (Hardwick & King, 2008; D. Potter et al., 2008). Moreover, sinsemilla appears to now dominate the British cannabis market, representing the majority of samples seized (Hardwick & King, 2008; D. Potter et al., 2008) a fact which is confirmed in self-reports (Attha, 2005). Furthermore, a recent meta-analysis has concluded that the mean THC contained within samples of herbal cannabis has increased between 1970 and 2009 (Cascini, Aiello, & Di Tanna, 2012). However, a proportion of this variance may be attributable to the 'freshness' of the sample (Sevigny, 2013). Freshness of the sample could plausibly determine the conversion of THCA into THC (see Baker, Gough, & Taylor, 1982, for further information). However, this remains a matter of conjecture. The increase in freshness of cannabis can be attributed to the increase in domestic production. Quantifying domestic cultivation of cannabis is difficult due to the secretive nature of the enterprise. However, it is highly likely that this is on the increase (Hough et al, 2003; Lloyd & McKeganey, 2010; G. Potter, 2008; Sznitman & Olsson, 2008). Various sources suggest that 50% or more, of the cannabis consumed in the U.K.

is domestically produced (Hough et al., 2003; Leggett & Pietschman, 2008; Sznitman & Olsson, 2008).

To conclude cannabis is the most frequently consumed drug in the UK. The various cannabis preparations may be indistinguishable from the naked eye. Nonetheless, sinsemilla is the most frequently consumed preparation with a large proportion of it being domestically produced. In comparison to other preparations, sinsemilla contains higher levels of a potentially detrimental psychotomimetic chemical (∆-9-THC) and lower levels of a potentially beneficial anxiolytic chemical (CBD). The available data also indicates that this product may be getting stronger, which may be due to advances in botany and selective breeding (G. Potter, 2008).

1.5 Cannabis and acute psychotic reaction

Acute cannabis intoxication is associated with many pleasurable effects including euphoria (Ashton, 1999; 2001), relaxation (Hammersley & Leon, 2006), and feeling ecstatic (Barkus, et al., 2006). Nonetheless, in a small minority of users, cannabis intoxication is associated with a psychotic mental disorder: cannabis-induced psychotic disorder (CIPD) (APA, 2013a, p111). In a comparison of CIPD and alcohol-induced psychotic disorder, CIPD elicited more 'schizophrenia-like' symptoms (Aggarwal, Banerjee, & Singh, et al., 2012). Thus, indicating that out of the two disorders CIPD can be said to be more prototypical of schizophrenia.

Distinguishing between a CIPD and a primary psychotic disorder can be a difficult task. CIPD and primary psychotic disorders yield similar assessments of positive symptomatology (Dawe, Geppert, Occhipinti, & Kingswell, 2011). However, those suffering with CIPD tend to display fewer negative symptoms (Dawe et al., 2011), but more 'neurotic' type psychopathology (e.g. anxiety and social phobia) (Rubio et al., 2012). Nonetheless, the current version of the DSM (APA, 2013a) recommends that the two disorders are best differentiated by the duration of the symptoms experienced (p.113).

Despite the seemingly transient effects of CIPD, it appears highly related to more chronic psychotic illness. In a longitudinal study of patients with a diagnosis of CIPD (mean follow up time 5.9 years), 44.5% patients developed a schizophrenia spectrum disorder (Arendt, Rosenberg, Foldager, Perto & Munk-Jørgensen, 2005). Moreover, 77.2% of participants went on to have another psychotic episode, while only 15.9% of the sample remained out of psychiatric care throughout the follow-up period. Similar findings were also demonstrated by Komuravelli, Poole, and Higgo (2011) who found that the majority of participants with a diagnosis of substance induced disorder (assessed at follow-up) progressed to develop a schizophrenia spectrum disorder. Both schizophrenia spectrum disorders and CIPD display very similar odds rate ratios associated with a familial history of schizophrenia spectrum disorder (Arendt, Mortensen, Rosenberg, Pedersen & Waltoft, 2008). This finding led the authors to suggest that cannabis-induced psychosis and schizophrenia are not distinct clinical entities (p.1269). However, despite this emerging evidence base the latest edition of DSM still considers

cannabis induced disorder a distinct, but related condition to schizophrenia spectrum disorders (APA, 2013a, p.519).

In addition to psychotic disorder, cannabis intoxication may also bring about psychotic-like experience. The administration of ∆-9-THC has been associated with psychotic like experience in healthy participants (Kaufmann et al., 2008). The effects have been shown to be different from schizophrenia, but similar to the psychotic prodromal phase (Koethe et al., 2006). Intravenous administration of ∆-9-THC has been shown to transiently elicit both positive and negative psychotic-like experience in a dose dependent fashion (D'Souza et al., 2004). Moreover, ∆-9-THC significantly increased the presence of core-symptoms and cognitive deficits in participants suffering with a schizophrenia spectrum disorder (D'Souza et al., 2005). Delta-9-THC induced psychotic-like states are alleviated by antipsychotics (Kleinloog et al., 2012; Liem-Moolenaar et al., 2010). Thus, indicating that ∆-9-THC intoxication and endogenous psychoses (e.g. schizophrenia) may have similar neural substrates.

1.6 Cannabis and schizophrenia

Despite the long standing (causal) relationship between cannabis and psychotic reaction the link between cannabis and more chronic psychotic disorder such as schizophrenia is less clear. That is, although there is a link between schizophrenia and CIPD, it is important to establish if cannabis is an *independent* developmental antecedent of schizophrenia. Perhaps most importantly there is a need to assess whether incidence of schizophrenia spectrum disorder may be preventable with the non-initiation or cessation of cannabis use.

To answer this, there is a growing body of longitudinal data suggesting a relationship between cannabis use and chronic psychotic mental illness. Prospective cohort follow-up studies allow for the observation of the temporal relationship of the variables under consideration. A meta-analysis of some of the relevant cohort data has been conducted including data from a cohort of Swedish conscripts (Andreasson, Engstrom, Allebeck & Rydberg, 1987), the NEMESIS cohort (van Os et al., 2002), the Christchurch cohort (Fergusson, Horwood & Swain-Campbell, 2003), and the Dunedin cohort (Arseneault et al., 2002). The results of the meta-analysis indicated that cannabis increased the odds ratio of psychotic symptoms/disorder by 2.34 times (Arseneault, Cannon, Witton, & Murray, 2007).

However, the strengths of the conclusions drawn from this meta-analysis are somewhat reduced by limitations of several of the studies as reviewed by McLaren, Silins, Hutchinson, Mattick, and Hall (2010). For instance, they point out that the Swedish conscript cohort was not assessed for non-clinically relevant psychotic symptoms at baseline. Despite a relatively large sample of respondents (N>4000) the NEMESIS cohort was criticised for a low incidence of clinically relevant psychotic disorder (n=7), resulting in large confidence intervals. The Christchurch cohort was also criticised for the means by which symptomatology was assessed. The Dunedin cohort investigation, however, did not have any direct criticisms levied against it.

There are limitations associated with the more recent investigation of these cohorts. For instance, the Swedish conscript cohort contains more than 50,000

individuals. Several investigations have reported on the outcome of this cohort (e.g. Andreasson, et al., 1987; Zammit, Allebeck, Andreasson , Lundberg & Lewis, 2002), the most recent of which was reported by Manrique-Garcia et al.,(2012). Manrique-Garcia et al. (2012) considered numerous confounders within a regression model (including previous diagnosis, urbanicity, cigarette smoking, evidence of childhood disturbance in behaviour, and social integration), and still showed dose-dependent relationships between cannabis use and the development of schizophrenia, brief psychotic episodes, and 'other non-affective psychoses'. However, some of the information pertaining to childhood social adjustment was gathered retrospectively, and this is likely to be less precise than concurrent assessment. In the substantially more modest Dunedin cohort (N=1037) cannabis consumption before the age of 15 significantly predicted both schizophrenia-like symptoms and a diagnosis of schizophreniform disorder (Arseneault et al., 2002). However, no significant effect of cannabis consumption was noted on a diagnosis of schizophreniform disorder if psychotic symptoms assessed at the age of 11 were included in the model.

The prospective cohort cannot provide unequivocal assurances of a causal model. With the exception of the Dunedin cohort they are frequently incapable of assessing baseline psychotic liability. Given that schizotypal vulnerability may be present from a young age (see Section 1.2.2) it is difficult to establish temporality of the variables (see Section 1.6.4). "An important limitation of many studies is that they have failed to distinguish the direction of association between cannabis use and psychosis" (Frisher, Crome, Martino & Croft, 2009, p.123). The relevant prospective cohort studies suggest an association between cannabis and psychosis. However, this data can be explained by several relevant hypotheses of association.

Gregg, Barrowclough and Haddock (2007) identified in the relevant literature, four hypotheses linking substance use to psychotic disorder. In addition to substance use causing schizophrenia Gregg and colleagues identified three additional routes by which substance use is linked to schizophrenia "substance use is a consequence of schizophrenia; …schizophrenia and substance use share a common origin; and … schizophrenia and substance use interact and maintain

each other" (p.497). Data pertaining to each of these hypotheses will be discussed in Sections 1.6.1 - 4. An appropriate hypothesis should be able to explain; the increased incidence of substance use disorder in people with schizophrenia (APA, 2013a, p.105); the positive association between quantity of cannabis consumed and schizophrenia vulnerability (Zammit et al., 2002); and the association between cannabis consumption per se and schizophrenia (van Os et al., 2002).

1.6.1 Cannabis use as a consequence of schizophrenia

One alternative explanation for the association between cannabis-use and psychosis is that cannabis use is a *consequence* of schizophrenia rather than a cause. This notion has been expressed in several distinct versions of the self-medication hypothesis. Edward Khantzian over the last three decades has developed "the most widely cited" (Kolliakou, Joseph, Ismail, Atakan & Murray, 2011, p.337) theory of self-medication which can find its origins in the psychodynamic school of thought (e.g. Khantzian, 1985; Khantzian & Albanese, 2008; Khantzian & Treece, 1977). Khantzian and Albanese (2008) suggest that the user may experience a beneficial effect of drugs; "[drugs] have the powerful effect of alleviating, removing, or changing human psychological suffering" (p. 2). Moreover, the authors suggested that...

> There is a considerable degree of specificity in a person's choice of drugs… Individuals navigate toward a certain drug because of what it does for them… he or she is drawn to one of the classes of drugs (e.g., stimulants, depressants, opiate analgesics) because they make the individual feel better than anything else (p.2).

Khantzian (2012) discusses some of the factors which may reflect 'human suffering' including self-regulation, feelings, self-esteem, relationships, and self-care. Khantzian (2012) also outlines an argument for how drug use may serve to alleviate the distress caused by the aforementioned factors.

An alternative version of the self-medication model has been proposed suggesting that psychosis prone individuals are drawn to using drugs to alleviate dysphoria associated with adverse psychological events or mood states (Kolliakou et al.,

2011, p.338). However, unlike Khantzian's model this one does not indicate specificity of the substance of (ab)use (i.e. the substance may not make the participant 'feel better than anything else'). Thus, within this model the psychosis prone individual drawn to using substances is more likely to indulge in poly-substance use. In contrast to both these approaches a behavioural approach to self-medication has been postulated which asserts that rather than the substance conveying a benefit to the user, the user consumes the substance as a means of negating aversive events associated with absence of use, such as cravings and withdrawal (Blume, Schmaling & Marlatt, 2000). Nonetheless, the model of self-medication adopted has little bearing on the hypothesis of association outlined by Gregg, et al., (2007) suggesting that cannabis-use is a *consequence* of schizophrenia. Their hypothesis, derived from the literature merely postulates that cannabis use is a consequence of the disorder and do not suggest a beneficial effect of the drug or negative consequence of withdrawal, just a mechanism of association.

The onset of a chronic psychotic disorder is typically characterised by a prodromal state (APA, 2013a, p.102). Furthermore, individuals prone to the development of psychosis may exhibit traits with an affinity to psychotic symptoms (Lupay et al., 2009). Consequently, a person who goes on to develop a psychotic disorder may have been experiencing prodromal symptoms for years prior to onset, and both clinically significant and non-clinically significant 'symptoms' associated with a schizotypal trait since early age. Khantzian suggests that the decision to self-medicate with a particular substance of abuse is predicated upon the pharmacological action of the drug and its ability to alleviate symptomatology or psychological distress. Thus further evidence for the 'self-medication hypothesis' can be derived from the effect of CBD, which has been shown to alleviate psychotic symptoms with comparable efficacy (and fewer side-effect) to an antipsychotic (Leweke et al., 2012). Thus, there is a plausible rationale as to why patients prone to psychosis may choose to consume cannabis. Note though that this mechanism of self-medication derived from CBD does not account for the use of cannabis preparations such as sinsemilla which have been shown to typically have very low levels of CBD (Hardwick & King, 2008).

Further evidence for both Khantzian's model and the model described by Kolliakou et al. (2011) can be derived from the research of Shoval et al. (2007). Shoval and colleagues found that patients comorbid for a substance use disorder and schizophrenia spectrum disorder displayed a trend toward lower levels of depression and fewer psychotic symptoms, in comparison to participants diagnosed with just a schizophrenia spectrum disorder. This may indicate that drug users with schizophrenia could be receiving an alleviation of symptoms as a consequence of their substance use. Moreover, Shoval and colleagues also found that substance use was predicted by comorbidity with anxiety disorders and previous suicide attempts. This could plausibly indicate that the co-morbid patients sought to use drugs to alleviate negative symptoms associated with the schizophrenia prodrome or schizotypal traits. However, several investigations have contradicted these findings. van Dijk, Koeter, Hijman, Kahn and van der Brink (2012) found no significant difference between cannabis users and non-users suffering with schizophrenia in measures of symptoms. Similar findings have also been demonstrated in other cohorts (Boydell et al., 2007). Thus, indicating, that cannabis use may not confer a significant beneficial 'self-medicating' effect in all populations.

Evidence has also been found in support of Kolliakou et al. (2011) model of self-medication. Tosato et al. (2013) compared cannabis users and non-users that had been diagnosed with a psychotic disorder. The cannabis using group displayed fewer depressive symptoms, thus, providing evidence in support of the notion of cannabis use as a mechanism to alleviate dysphoria. Moreover, Tosato and colleagues documented no difference in pre-morbid adjustment between the cannabis- users and non-users. This indicates that there were no observable differences between the two populations. Therefore, the significant difference in depressive symptomatology could plausibly be attributable to cannabis use. Like Tosato and colleagues Katz, Durst, Shufman, Bar-Hamburger and Grunhaus (2010) also documented fewer depressive symptoms in cannabis users with a psychotic disorder in comparison to non-users. Moreover, Katz and colleagues reported that the cannabis using group had lower rates of social withdrawal and stereotyped thinking than non-users, which could implicate that cannabis is conferring a benefit on social skills.

The beneficial effect of drug use may have on a patient's social contact found by Katz et al., (2010) has also been demonstrated in other investigations. Salyers & Meuser (2001) examined patients with a diagnosis of schizophrenia spectrum disorder and found that patients who did not use drugs were more likely to have infrequent social contact and problems in leisure than their drug or alcohol using counterparts. Further, evidence of the social enhancing aspects of drug use has been demonstrated in a qualitative investigation. Patients who had experienced a psychotic episode identified several motivations for use, including a need to conform to social norms with drug taking behaviour (Lobbana et al., 2010). This might suggest that the participants attempted to 'self-medicate' social withdrawal (plausibly experienced as a consequence of a schizotypal personality) by utilising drugs to facilitate social interaction. Further evidence of differences in personality between substance users and non-users can be derived from the investigation of Bizzarri et al., (2009) who explored self-medication with both licit and illicit substances in participants with a mental illness. Bizzarri and colleagues found that participants diagnosed with a substance use disorder displayed greater substance sensitivity, higher sensation-seeking personality traits, and greater incidence of self-medication in comparison to non-comorbid participants. These data provide support for the self-medication hypothesis suggesting that participants co-morbid with a substance use disorder utilised drugs in the alleviation of their symptoms. However, very few of the sample were diagnosed with a schizophrenia spectrum disorder (n=15 for each condition) and multiple substances not just cannabis were considered. Thus, although the data might suggest a differential personality profile between the two groups, there was too little data to suggest whether these differences are present in schizophrenia spectrum disorders or just psychopathology more generally.

An alternative means by which the 'self-medication' hypotheses can be assessed is by assessing self-reported motivations for substance use. In an experience sampling study design the motivation for the majority of cannabis use reported was for the pleasurable effects (86.8%), whereas only a small (14.2%) proportion of cannabis use was as a coping-mechanism (Shrier, Walls, Rhoads, & Blood, 2013). Thus, indicating that the majority of cannabis use cannot be attributable to

either a Khantizian or Kolliakou model of self-medication. However, this study did not utilise participants with a psychiatric diagnosis meaning that these individuals likely display a low incidence of psychosis proneness. Thus, these participants are not likely to be experiencing distressing symptoms that require (self-) medication, and so do not provide a good test of the self-medication hypothesis. Thornton et al. (2012) compared the motivations of participants with diagnoses of psychotic disorder and depression. They found no difference, between the two groups, in the rate cannabis was utilised as a coping mechanism or to alleviate symptoms. The lack of difference between the two groups suggests that they are using cannabis due to similar motivations. Furthermore, Gómez et al., (2013) found that patients who have had a first episode of psychosis did not differ from controls in their self-report motivations for cannabis use. These findings serve to undermine Khantzian's notion that psychological disorders form a unique self-medicating relationship with specific substances.

Although, drug use may correlate with fewer negative symptoms (e.g. depression) and improvements in social functioning, the data do not unequivocally indicate self-medication. Meijer et al. (2012) documented fewer cognitive deficits in cannabis using patients with a psychotic disorder in comparison to non-user patients. Meijer and colleagues attributed the differences they observed to intrinsic differences between the groups. The investigators suggest that the cannabis using group differed as a consequence of them having a lower likelihood of decompensating, which has reached fruition partly as a consequence of using the drug. Within this model the cannabis users had fewer cognitive deficits because they had a lower schizotaxic loading, and had a higher rate of decompensating (than would be expected for their schizotaxic vulnerability) due to the causal effects of cannabis. Within such a framework as that utilised by Meijer and colleagues the association between cannabis use, fewer negative symptoms, and better social functioning, may be explained by cannabis *causing* schizophrenia.

In one of the few longitudinal investigations which has actively sought to test the self-medication hypothesis Henquet et al. (2005) assessed the presence of psychotic like symptoms at baseline (age 14 years), as a predictor of subsequent cannabis use at follow-up (age 24 years). There was no significant effect of

baseline symptoms indicating that within this cohort, participants were not attempting to 'self-medicate' attenuated psychotic symptoms with cannabis. At present there is only limited available data in support of cannabis use being a consequence of psychotic illness. This is plausibly due to the difficulties in making such an assessment (see McLaren et al., 2010). Given the vast number of variables under consideration and the possibility of them interacting (see Section 1.7.2) it is difficult to entirely refute the self-medication hypothesis. Moreover, schizophrenia could plausibly be a neurodevelopmental disorder (see Clarke et al., 2012). If this does prove to be the case then it would be implausible to attempt to establish temporal priority and consequently most commonly accepted definitions of causality (see Section 1.6.4) of cannabis use over psychotic vulnerability.

1.6.2 Common factors shared between cannabis use and schizophrenia

Another explanatory model outlined by Gregg et al. (2007) to explain the link between cannabis use and schizophrenia suggests that the two share a common factor. This is also referred to as the 3rd factor model of association. This model postulates that the association between cannabis and schizophrenia is underpinned by a third factor which the other two variables share in common. When considering cannabis as a causal factor of schizophrenia one of the most difficult notions to dismiss is the possibility of a common factor or factors, which may account for the association between the two variables. One of the reasons why this notion is so difficult to dispel is that numerous different factors may underpin the association, some of which may be unobservable. In this section some of the possible common factors will be discussed. Nonetheless, given the numerous known and (in all likelihood) unknown variables that are associated with both schizophrenia (see Section 1.2.3) and cannabis consumption (e.g. availability, societal factors etc.) it is implausible to consider all of these factors.

Chambers, Krystal, and Self (2001) suggest that schizophrenia and drug addiction may share a common aetiology in the dysregulation of dopamine and glutamate signalling. It is proposed that this mechanism may predicate those prone to schizophrenia to develop an addictive disorder more regularly than healthy individuals. This model may explain the association between cannabis use and

substance use *disorder*, but it fails to explain the association between incidence of cannabis use (i.e. non-pathological use) and psychotic disorder. A common factor which could plausibly increase the incidence of substance *experimentation* (the propensity to try an illicit substance) and psychotic disorder is 'openness to experience'. Openness to experience is characterised by having a broad range of interests, and a tendency to be daring (McCrae & Costa, 1987, p.87).

Ross, Lutz and Bailley (2002) found that the presence of positive schizotypal 'symptoms' is predictive of an increase in openness to experience and the presence of negative 'symptoms' is predictive of a significant decrease. Indicating that vulnerability to schizophrenia (schizotypy) is feasibly, related in part, to the same mechanisms which determine the personality trait openness to experience. Flory, Lynam, Milich, Leukefeld and Clayton (2002) observed that cannabis abuse was associated with high openness to experience, as assessed by a measure of the five factor model of personality. Moreover, the effect of openness to experience being associated with cannabis abuse was not homogenous across substance abuse, with no such relationship established for alcohol. Thus, there exists converging evidence to suggest that one such common factor linking cannabis and the positive symptoms of schizophrenia is a propensity to be open to experience.

Given the findings of Ross et al. (2002) it would follow reason that individuals displaying positive symptoms are more likely to be a drug abuser and individuals with more negative symptoms less so. Partial support for this comes from a study by Compton, Furman and Kaslow (2004), who reported that cannabis users had significantly fewer negative symptoms than non-users, however no significant difference in positive symptoms was observed. Schaub, Fanghaenel, Senn and Stohler (2008)found no significant difference in either positive or negative symptoms between moderate cannabis users, daily cannabis users or cannabis abstainers, thus providing no support for the theory. However, a meta-analysis of nine studies performed by Talamo et al. (2006) found that individuals co-morbid with schizophrenia and substance use disorder were significantly more likely to have more positive symptoms and fewer negative symptoms. In this instance causality is (once again) difficult to establish as the pharmacological action of the

substances in question (including cannabis) may independently result in the release of DA (see Section 1.2.1) in the human striatum (Bossong, et al., 2009) which in turn could elicit more positive symptoms (Kapur, Mizrahi & Li, 2005). Nonetheless, taken together, these studies provide some evidence that openness to experience may be a shared factor between substance experimentation and psychotic propensity.

Another example of a common factor is the presence of attention deficit hyperactivity disorder (ADHD) like symptoms. Cassidy, Joober, King and Malla (2011) found that retrospective assessments of childhood ADHD predicted inability to abstain from cannabis use in patients with a psychotic illness. As the presence of ADHD-like 'symptoms' were thought to precede the diagnosis of a psychotic disorder, it is feasible that these 'symptoms' may be reflective of neurodevelopmental differences of those able to abstain and those not. Support for ADHD-like 'symptoms' as a third factor linking psychotic disorder with cannabis use can be derived from investigations that have demonstrated an association between childhood inattention; and a psychosis outcome (Erlenmeyer-Kimling et al., 2000); and drug use (van Emmerik-van Oortmerssen et al., 2012). Furthermore, schizotypy is a known correlate of ADHD (Keshavan, Sujata, Mehra, Montrose, & Sweeney, 2002). Thus, the data provides evidence in support of ADHD-like 'symptoms', acting as a common factor associating both cannabis use and schizophrenia. The data also indicates that such an association may plausibly be as a consequence of neurodevelopmental abnormalities.

Evidence for many other different common factors have been suggested including; hedonic response influenced by ventral striatal activation (Cassidy, Lepage, Harvey & Malla, 2012); sensation-seeking (Zhornitsky et al., 2012); social anhedonia (Zhornitsky et al., 2012); and childhood abuse (Compton et al., 2004). However, whether or not these factors are truly independent of psychotic disorder and substance use is difficult to establish. For example, abnormality in ventral striatal activation could be a key component in the presentation of positive psychotic symptoms (Lewis & Buchanan, 2002). Thus, if such abnormalities are development antecedents of the disorder they are unlikely to exert a truly independent effect on drug use. Thus, in the aforementioned example it would

appear most plausible that this abnormality is primarily, or even causally, associated with schizophrenia and that the drug use association is a secondary effect. Nonetheless, whilst it is highly likely that cannabis use and schizophrenia share some common factors, this does not dispel the possible action of other mechanisms of association, as outlined by Gregg et al., (2007).

1.6.3 Schizophrenia and cannabis synergistically maintain one another

The third possible hypothesis outlined by Gregg et al., (2007) suggests that drug use and schizophrenia display a synergistic relationship wherein cannabis and schizophrenia can possibly prime for, and maintain, one another. Out of the four hypotheses suggested by Gregg and colleagues this is feasibly the most difficult to assess. “As yet, however, there have been no empirical investigations of bidirectional models” (Gregg et al., 2007, p.505). The rationale for this is that to assess such a relationship it is necessary to assess temporally sequenced data at various time points. The ability to test for such a possible hypothesis typically falls beyond the remit of cross-sectional research, although one novel case study may be able to provide limited data in support. In this instance, a 38 year old male patient suffering with psychotic disorder surreptitiously smoked cannabis whilst taking part in an imaging study (Voruganti, Slomka, Zabel, Mattar & Awad, 2001). During the imaging procedure the participant requested to take a break as they were experiencing distress. During a short break the participant used cannabis. The participant returned in a “relaxed and jovial” state, and completed the imaging procedure (p.174). However, the following day during a scheduled assessment the participant presented with an exacerbation of symptomatology.

In Voruganti et al. (2001) case study the participant’s distress, was alleviated by the use of cannabis. However, despite experiencing alleviation of distress the following day the participant experienced an exacerbation of symptoms. This could plausibly indicate that cannabis provides temporary relief of distress and/or symptomatology. However, this relief is short lived and could come at the cost of exacerbation, which in turn could feasibly lead to more cannabis use. Further evidence for a synergistic relationship can be derived from research utilising an experience sampling (see Section 3.2.1) repeated measures study design.

Henquet et al., (2010) compared patients with a psychotic disorder with a control group on assessments of psychotic-like symptoms, mood, and cannabis use. They found that the patient group experienced significantly more psychosis-inducing and mood-enhancing effects of cannabis in comparison to controls. This indicates that the patients may be using cannabis for the mood enhancing aspects of the drug. However, this comes at a cost of exacerbation of symptoms. Henquet and colleagues describe this as feasibly underpinning a "vicious circle of deleterious use" (p.447).

Another investigation has provided data relating to a bi-directional effect of cannabis and schizophrenia. Hides, Dawe, Kavanagh and Young (2006) followed up a group of patients who had recently experienced the onset of psychosis. Cannabis consumption predicted psychotic symptoms in a dose dependent fashion however, psychotic symptom severity in turn predicted cannabis consumption. This data indicates that distressing symptoms may increase the likelihood of cannabis use and cannabis use the likelihood of symptoms, this resembles the vicious deleterious circle suggested by Henquet et al., (2010).

Due to the methodological difficulties associated with trying to observe the temporal relationship between symptomatology and cannabis use very few investigations have assessed this notion. Nonetheless, this hypothesis may explain why those who are psychosis prone may use cannabis more frequently than those non-prone.

1.6.4 Cannabis use as a causal factor of schizophrenia

Cannabis use has been shown to elicit psychotic-like reaction in healthy participants (e.g. Koethe et al., 2006) and exacerbate symptoms of people suffering with schizophrenia (e.g. D'Souza et al., 2005). Cannabis use is also associated with an acute psychotic illness, which is related to schizophrenia (see Section 1.5). Moreover, cannabis use has been consistently associated with a significantly earlier age of onset of non-cannabis induced psychotic disorder (e.g. Barrigón et al., 2010; Katz et al., 2010; van Dijk et al.,2012). Furthermore, this effect is thought to be stronger for cannabis in comparison to other drugs of abuse

(Large, Sharma Compton, Slade & Neilssen, 2011). As compelling and consistent these findings are, they do not 'prove' the existence of a causal mechanism.

Bradford-Hill (1965) recommended that several conditions must be satisfied in order for causal inference. Bradford-Hill (1965) suggests causality can be inferred from considering the weight of the evidence of; strength of association; consistency (across investigations); specificity; coherence; biological gradient; experimental evidence; analogy; temporality; and plausibility. "These guidelines provide a framework for the analysis of whether cannabis use is causally associated with psychosis" (McLaren et al., 2010, p.11).

The epidemiological data presented in Section 1.6 suggests that there is good evidence for the strength of association between cannabis use and schizophrenia. Moreover, the association has been displayed quite consistently across the majority of cohort based investigations (see McLaren et al., 2010). However, one of Bradford-Hill's suggested criteria is clearly not easily defined within this context. The criterion of specificity suggests that a given population will develop the disorder when introduced to the causal factor (i.e. cannabis). However, the factors that may constitute this population are difficult to determine (see Section 1.2.3). In addition to numerous different environmental and developmental factors which may increase the risk of a diagnosis of schizophrenia, there are plausibly hundreds of SNP's each conferring an additive risk (see Section 1.2.3). Given these myriad of factors precisely identifying the population in which specificity can be demonstrated is at present impossible. Moreover, due to these numerous factors it is likely that schizophrenia can have multiple pathways to causation. Thus, even once the necessary population has been identified, there are likely to be incidence of the disorder which occurs in the absence of cannabis use. Consequently, it has been suggested that specificity should be dropped from these guidelines (Howick, Glasziou, & Aronson, 2009).

Nonetheless, Bradford-Hill (1965) suggests that specificity may be observed by assessing the "specificity in the magnitude of the association" (p.297). Thus, specificity can be assessed by judging the magnitude in increases in O.R. in comparison to some of the other (feasibly) causal factors. Arseneault et al. (2002)

in assessments of the O.R. for psychotic like symptoms found that strong psychotic symptoms at 11 years old increased the O.R. 5.16 fold, however cannabis use by age 15 increased the O.R. 6.56 fold. However, in assessments of the O.R. of an outcome of schizophreniform disorder the presence of psychotic symptoms at age 11 had more than 5 times the magnitude of effect of cannabis consumption. In another investigation, cannabis dependence (O.R. 2.94) has demonstrated a greater O.R. on an outcome of psychotic symptoms in comparison to dependence on other drugs (+/- cannabis dependence) (O.R. 2.29) (Johns et al., 2004). Caution should be adopted in comparison of odds ratios as this will in some regards be dependent on the scales under assessment. However, as the independent variables discussed are dichotomous as opposed to continuous, the comparison still holds meaning (as long as the measures are viable assessments of the constructs). Thus, the data indicate that cannabis use may hold specificity of magnitude over some other constructs with regards to psychotic-like symptoms, but plausibly not diagnosable schizophrenia spectrum disorder.

Little data is available to test the coherence for a causal relationship. Frisher, Crome, Martino and Croft (2009) compared estimates of the prevalence of cannabis use with estimates of the prevalence of schizophrenia. Frisher and colleagues reasoned that, if a causal model can be adopted then incidence and prevalence of schizophrenia should display a positive relationship with cannabis use. However, examination of patient records of 2.3% of the population of the U.K. did not elucidate such a hypothesised increase, despite this encompassing a period of time with a theorised increase in cannabis consumption. There was no significant change in incidence of schizophrenia or psychoses. In fact, the data indicated a *decrease* in the prevalence of schizophrenia and a *decrease* in the prevalence of psychoses in the latter years of the data submission period, as incidence of cannabis consumption increased. Further evidence against the presence of coherence can be derived from research with an Australian cohort. Degenhardt, Hall and Lynskey (2003) demonstrated no significant increase in the incidence of schizophrenia, and no consistent pattern of decrease in the age of onset, despite theorised increase in prevalence and incidence of cannabis use. Thus, there is no available data to suggest a coherent model of association.

There are however, data available suggesting a biological gradient or what may also be referred to as a dose-dependent effect. If cannabis causes schizophrenia then it would stand to reason that a greater exposure to cannabis should increase the odds of a diagnosis. This notion has been demonstrated in various cohort based studies (Henquet et al., 2005; Manrique-Garcia et al., 2012; van Os et al., 2002).Moreover, a dose dependent effect has also been demonstrated in relation to within-participant variance in psychotic-like symptoms in a longitudinal investigation (Van Gastel, Schubart, Kahn & Boks, 2010). Furthermore, a dose dependent response was demonstrated in relation to frequency and onset of psychotic relapse in a patient group (Linszen, Dingemans, & Lenior, 1994). A biological gradient has also been demonstrated by Baskak et al., (2012) who found a negative relationship between temporal proximity to last cannabis use and assessments of schizotypy.

However, other investigations have failed to replicate evidence of a biological gradient. Schaub et al. (2008) compared three groups of participants suffering with schizophrenia, no difference was found between those cannabis naïve, 'moderate' cannabis users, or daily cannabis users in assessments of psychotic symptomatology. Barrowclough, Emsley, Eisner, Beardmore, & Wykes (2013) compared patients with a psychotic disorder who were either cannabis users or users of other drugs. Barrowclough and colleagues did not document an effect of cannabis consumptions per se, or dose of cannabis on positive symptomatology. Intriguingly the cannabis using group displayed significantly fewer negative symptoms. Nonetheless, Barrowclough and colleagues did find a dose dependent effect of cannabis on assessments of functioning. Thus, this indicates that cannabis may confer a beneficial effect to the user, serving to dispel the notion that cannabis causes schizophrenia.

At present the data appears to indicate that there is some evidence of a biological gradient in the relationship between cannabis and schizophrenia. Nonetheless, the significance of such a relationship is unclear due to the number and breadth of social (e.g. changes in maternal marital status) and genetic (e.g. child's gender) factors that have been associated with cannabis use and cannabis use disorder (see Hayatbakhsh, Najman, Bor, O'Callaghan & Williams, 2009). Several of these

factors may also influence the expression of schizophrenia (see Section 1.2.3) thus the evidence of a dose dependent response has been brought into question. “Where confounding factors covary with the exposure of interest in a quantitative fashion (as they often will) then spurious dose–response associations will be apparent” (Macleod, 2007, p.405). An example of the non-independence of one of these factors can be derived from the prospective cohort study of Kuepper, van Os, Lieb, Wittchen, and van Os (2011) who found that both urbanicity and cannabis use interact to significantly predict psychotic symptoms.

There is a body of evidence which suggests that numerous different factors may increase the O.R. of a psychotic disorder (see Section 1.2.3). Some of these factors may be seen as analogous to cannabis in the respect that they are environmental factors (e.g. urbanicity) which appear to increase the odds ratio of schizophrenia. However, these factors have not provided sufficient evidence to assert a causal inference (e.g. urbanicity; Pedersen & Mortensen, 2006; Vassos, Pedersen, Murray, Collier & Lewis, 2012). Thus, there is a body of evidence suggesting that analogous factors may cause schizophrenia. However, the weight of evidence in support of these factors as causally associated with schizophrenia is typically comparable to cannabis (see Clarke et al., 2012).

As it would not be ethical to induce chronic illness, there is a paucity of experimental evidence that may provide causal inference in the relationship between cannabis and psychotic disorder. Nonetheless, there is a wealth of experimental data indicating that cannabis may cause psychotic like reaction in healthy participants and exacerbation of symptoms in people diagnosed with psychotic disorder (see Section 1.5 and also see D’Souza, Sewell, & Ranganathan, 2009 for review). Moreover, there are data indicating that the same drugs used in the treatment of schizophrenia may be proficient in ameliorating acute psychotic (and psychotic like) states induced by cannabis (see Crippa et al.,2012 for review). However, there is a vast difference between inducing and ameliorating temporary psychotic like states and causing chronic psychotic illness. The experimental evidence from temporary psychotic like states allows causal inferences to be made, but are far from sufficient to attribute causality to; schizophrenia.

Experimental study design is proficient at establishing temporality, there is a clearly demonstrated effect of ∆-9-THC preceding exacerbations in psychotic symptoms. However, out of the confines of the laboratory, one of the more difficult of Bradford Hill's (1965) recommendations to establish is temporality. Temporal priority is established by examining the sequence of occurrence of events to ascertain which of the events precedes which. Utilising the Christchurch cohort Fergusson, Horwood, and Ridder, (2005) attempted to use structural equation modelling to account for unobserved confounders, which might include factors such as neurodevelopmental differences. Despite controlling for unobserved effects, cannabis still exerted an influence on an outcome of psychotic symptoms inferring between a 1.6 and 1.8 fold increase in odds. The model may even account for a schizotypal state (see Section 1.2.2) or gene by environment interaction effect in the residual (see Henquet, DiForti, Morrison, Kuepper & Murray, 2008). However, such a modelling technique may not elucidate time dynamic effects at a micro- (or macro-) level of the time dynamic under observation. For example, synergistic maintenance may be taking place at a moment to moment basis, which could result in a macro-level effect of cannabis on psychotic symptoms at time of assessment. Nonetheless, such a scenario is only likely to come to fruition where the effect of cannabis on psychotic symptoms is greater than the effect of psychotic symptoms on motivations to consume cannabis. Thus, Fergusson et al., (2005) provides a good argument for cannabis consumption having an independent causal effect on the presentation of psychotic *symptoms*. However, psychotic *disorder* was not assessed. This provides evidence of cannabis 'causing' psychotic symptoms. However, this is a finding that has been replicated in numerous experimental investigations (see D'Souza et al., 2009).

Some studies can provide information in regards to cannabis' temporal priority over psychotic disorder. Allebeck, Adamsson, and Engström (1993) examined medical records to identify patients that had at some point in their lifetime received a diagnosis of cannabis use disorder and schizophrenia. The majority of the cases (69%) initiated pathological cannabis use prior to the onset of psychotic symptoms. These findings were supported by Sevy et al. (2010) who reported that the majority of patients they assessed with a dual-diagnosis of cannabis use

disorder and schizophrenia, had the onset of the cannabis use disorder prior to the onset of positive symptoms. Moreover, within this sample cannabis use was also associated with an increase in severity of positive symptoms. Linszen et al. (1994) also found that in the majority of their sample (96%) cannabis abuse preceded the onset of a schizophrenia spectrum disorder. The findings of Allebeck and colleagues, Sevy and colleagues, and Linszen and colleagues suggest; that the onset of a cannabis use disorder has the appropriate temporal sequencing to promote a psychotic disorder. However, it should be noted that, although, this association has been documented in cannabis abuse, this does not account for the association between non-pathological cannabis use and schizophrenia. Moreover, the aforementioned investigations have demonstrated evidence of priority over positive symptomatology, but not a pre-morbid state.

In terms of elucidating the effect of temporal sequencing and more broadly causality the findings of Hambrecht & Hafner (1996; 2000) reveal an association which has gained some acceptance (e.g. see Gregg et al., 2007 p.505); the presence of multiple models of association. Hambrecht & Hafner (1996) assessed temporal priority in patients with a psychotic disorder. They found drug abuse preceded symptoms in 27.5% of cases; symptoms preceded drug use in 37.9% of cases; and they occurred within the same month in 34.6% of cases. These findings suggest that different groups of participants could plausibly have different models of association. This provides support for each model of association outlined by Gregg et al., (2007); schizophrenia as a consequence of cannabis use; cannabis use as a consequence of schizophrenia; and a common factor and / or synergistic maintenance of the factors. Although, Hambrecht & Hafner looked at drug use per se, the most frequently used drug in the sample was cannabis (88% of respondents). Hambrecht & Hafner (2000) undertook further analysis and elucidated that cannabis abuse typically preceded the onset of positive symptoms, however, the onset of prodromal symptoms disaggregated into the three groups described previously. By extending their investigation to assess the onset of the prodrome Hambrecht & Hafner have attempted to establish temporality over the onset of the disorder as opposed to the onset of clinically relevant symptoms. This adds further weight to the notion that several different models of association may be at work.

As discussed in Section 1.2.3, schizophrenia is heavily influenced by both genetic and developmental factors. There is also evidence suggesting schizophrenia may have both neurodevelopmental and neurodegenerative components, related to both structural and pharmacological abnormalities (Gupta & Kulhara, 2010). Thus, the influence of this purported "progressive neurodevelopmental disorder" may be exerted from a very young age (Rapoport & Gogtay, 2011, p.251). An example of such could be expressed in the affinity between schizophrenia and schizotypal personality traits which are thought to be stable from a very young age. Cannabis use onset will not typically occur before adolescence or early adulthood (e.g. 16 years old; Hayatbakhsh, Williams, Bor & Najman, 2013). Thus, cannabis use initiation typically occurs a substantial period of time after the on-set of neurodevelopmental abnormalities, obstetric complications, or the formation of personality. If these factors that occur early in life are found to be causally related to the development of schizophrenia then disentangling the temporal priority of cannabis on disease onset becomes even more onerous.

1.7 ‘Plausible’ mechanisms by which cannabis might cause schizophrenia

Bradford-Hill (1965) postulated several recommendations for causal inference (see Section 1.6.4). This section is dedicated to assessments of plausibility, the means by which cannabis could cause schizophrenia. Assessments of plausibility are however, difficult to establish in fact, Bradford-Hill suggested that plausibility “is a feature I am convinced we cannot demand. What is biologically plausible depends upon the biological knowledge of the day” (p.10). Thus, this is not a requisite of a causal inference and will be impart limited by inadequacies and lack of coherence in data pertaining; to genetic and environmental susceptibility (see Section 1.2.3 pp. 37-49); and more broadly the aetiology of schizophrenia (see Section 1.2.1 pp. 21-25). Nonetheless, given the available data several plausible mechanisms have been proposed. This section seeks to assess some of the available data pertaining to a selection of these mechanisms. This section will assess the plausibility of cannabis inducing psychotic disorder through; a dopaminergic mechanism of action; a gene by environment interaction effect; a sensitisation effect; and an interaction (cross-sensitisation) with stress. It is important to note that these mechanisms of action may be viewed as independent mechanism. However, the most likely mechanism of action consists of a combination of factors. For example, a genetic influence may interact with cannabis, and both cannabis and genetic factors may also interact with other environmental factors (e.g. stress). Through, a process of sensitisation this interaction of factors may result in a change in response amplitude and psychotic disorder. The pharmacological expression of these interactions of variables could be a disruption of dopaminergic function.

1.7.1 Dopamine

One plausible mechanism by which cannabis can induce both an acute psychotic state (i.e. D’Souza et al., 2004) and potentiate for chronic psychotic disorder involves the neurotransmitter dopamine. It is thought that a dysfunction in dopaminergic function is a central component in the expression of schizophrenia (see Section 1.2.1). Cannabinoids are known to elicit their principal psychoactive effect through the cannabinoid receptor CB1 (Pertwee, 2006). Cannabinoid

receptors are known to be present in many areas of the brain (Herkenham et al., 1990). Some of these areas including the cerebellum (Picard, Amado, Mouchet-Mages, Olié & Krebs, 2008), the basal ganglia (Perez-Costas, Melendez-Ferro, & Roberts, 2010), the hippocampus (Harrison, 2004) and the pre-frontal cortex (PFC: Salgado-Pineda et al., 2007) have previously been implicated in psychotic disorders.

The cerebellum has been associated with dysfunction of the mesolimbic and mesocortical pathways (see Section 1.2.1) via its effects on the midbrain (Nopoulos, Ceilley, Gailis & Andreason, 2001). The basal ganglia is modulated by the VTA which is central to both mesolimbic and mesocortical pathways (Perez-Costas et al., 2010). Moreover, as the PFC forms part of the cortex it is invariably associated with the mesocortical pathway. Thus, given the presence of the CB1 receptors the notion that they may be modulating DAs function in these regions is a plausible mechanism. Consequently, a theory encompassing cannabis' psychotomimetic and psychotogenic effects as mediated by dopamine has a body of converging evidence.

There are a number of naturally occurring chemicals that bind to the CB1 receptor, the best known of these endogenous cannabinoids (endocannabinoid) is anandamide. Anandamide is thought to be metabolised more quickly than ∆-9-THC, and to have a milder psychoactive effect (Scherma et al., 2008). Nonetheless, it is thought to play a crucial role in reward processing and DA release (Cheer, et al., 2007). In animal models, ∆-9-THC has been shown to elicit DA release in the medial prefrontal cortex (Chen, Paredes, Lowinson & Gardner,1990) and nucleus accumbens, with these effects being attenuated by a CB1 antagonist (Cheer, Wassum, Heien, Phillips & Wightman, 2004; Tanda, Pontieri & Chiara, 1997). These findings implicate a dopaminergic action of the endocannabinoids within humans and a dopaminergic action of ∆-9-THC within animal models.

In human participants Bossong et al., (2009) demonstrated a dopaminergic action of ∆-9-THC in several human striatal sub-regions. In the case study described in section 1.6.3, the surreptitious consumption of cannabis resulted in an increase in

dopaminergic activity (Voruganti et al., 2001). Further, evidence of the dopaminergic action of cannabis is evinced by the ability of DA antagonists to alleviate the symptoms of intoxication (Liem-Moolenaar et al., 2010). Moreover, Greenwood et al., (In press) have demonstrated that cannabis users display N-methyl-D-aspartate receptor (NMDAr) dysfunction. Although the NMDA-r is primarily associated with the neurotransmitter glutamate, antagonism of the NMDA-r appears to increase the availability of dopamine in the cortex (particularly at D1 receptors), although the mechanism by which this occurs (and indeed its clinical significance) remain matters of conjecture (see for example Smith et al., 1998 and Deakin, Lees, & McKie, 2008).

There is also behavioural evidence for a link between cannabis and DA activity. For instance, cannabis has been shown to alter attentional salience processing (Bhattacharyya et al., 2012), the dysfunction of which has been attributed to dopaminergic processes (Kapur et al., 2005). Furthermore, it is thought that dopaminergic activity plays a central role in addiction (Wise, 2008), and cannabis has been associated with psychological and physical dependence and withdrawal (See Maldonado, Berrendero, Ozaita & Robledo, 2011 for review). Nonetheless, a recent review examining cannabis as a typical drug of dependence concluded that it does not display a profile of DA alteration consistent with other addictions (Ghazzaoui & Abi-Dargham, in press). This finding suggests that if cannabis is eliciting DA release then this may be occurring; in an atypical manner; in only a small group of users; or not on a consistent basis.

Support for a cannabis dopaminergic pathway to psychotic reaction has not been consistently demonstrated in humans. For instance, in one post mortem investigation there was evidence of dopamine dysfunction in participants who had a provisional diagnosis of schizophrenia (Dean, Bradbury, & Copolov, 2003). However, there was no significant difference in DA transporter binding in controls / patients who had THC metabolites in their blood in comparison to those without recent cannabis use. Another study showed that a group of patients who had suffered with their first psychotic episode displaying cannabis dependence did not differ in their D2 receptor binding from non-cannabis using patients (Safont et al., 2011).Chronic cannabis users also do not demonstrate a reduction of striatal

D2/D3 receptor availability, as would be consistent with abuse of a dopaminergic substance (Albrecht et al., 2013). This finding has been replicated in other investigations (Urban et al., 2010; 2012). However, these investigations demonstrated significant alterations in DA function in a subset of users who had initiated use prior to 18 years old. This finding may explain the lack of consensus in the literature relating cannabis' effects to those of a typical drug of addiction. Plausibly, the findings of Urban et al (2010; 2012) indicate that age of initiation or duration of use may be mediating factors in the dopaminergic effect of cannabis.

Results of imaging studies have also failed to support the notion of cannabis as a DA agonist. Neither, Barkus et al. (2011) nor, Stokes et al., (2009) found an elevation in striatal DA release as a result of a ∆-9-THC challenge, despite the presence of psychotic-like symptoms. Stokes and colleagues suggested that the data indicates that striatal DA release is unlikely to be the mechanism of association between cannabis and schizophrenia (p.186). However, in a subsequent re-analysis of their data Stokes et al., (2010) did elucidate evidence of dopaminergic activity in both frontal and temporal gyri. These areas are associated with decision making and auditory perception respectively (Stokes et al., 2010, p.1526). Alterations of dopaminergic activity in this area could explain disruptions in cognition and the presence of hallucinatory or delusional experience. Nonetheless, elevated dopaminergic activity in the cerebral cortex did not correlate with assessments of psychotomimetic experience. Thus, although Stokes and colleagues have demonstrated some evidence of dopaminergic activity as a consequence of cannabis, it is not yet clear whether this might be clinically relevant in the expression of psychotic symptoms.

In a recent imaging study an inverse relationship was demonstrated in DA synthesis capacity in the striatum and cannabis use with cannabis users meeting criteria for dependence (Bloomfield et al., in press). This finding indicates that cannabis may serve to *reduce* the brains capacity to create DA within this area. It is thought that people suffering with schizophrenia have an increased availability of DA in the striatum (Kegeles et al., 2010). This may indicate that cannabis does elicit DA release. However, if DA release is occurring (or has occurred) it is unlikely that cannabis is potentiating for a sensitised dopaminergic system.

Therefore, this is unlikely to be the pathway to psychotic disorder. Furthermore, Bloomfield et al., (in press) did not find a relationship between an altered dopaminergic system and the presence of cannabis-induced psychotic-like symptoms.

Research in humans implicating a dopaminergic pathway between cannabis and psychosis is still in its infancy (see Stokes et al., 2010, p.1521) and, as discussed in this section, the evidence is far from definitive. The prospect of DA release mediating the psychotomimetic and psychotogenic effects of cannabis is certainly feasible. However, even if cannabis is a DA agonist, it is not yet clear, whether this reflects a primary or secondary process. That is, DA release could represent the pharmacological expression, as opposed to the mechanism per se. Thus, other plausible mechanisms of action may or may not incorporate an association between cannabis and cortical and sub-cortical DA release.

Given that genetic factors appear to be the most powerful determinates of psychotic disorder (see Section 1.2.3) it is feasible that those who experience the dopaminergic effects of cannabis already have a pre-existing vulnerability. This is supported by the research of Kuepper, Ceccarini et al., (2013), who found no dopaminergic response to a ∆-9-THC challenge in healthy controls. However, there was evidence of dopaminergic activity in the striatal sub-regions of patients and first degree relatives. This could suggest that the dopaminergic action of cannabis is only present in those at greatest genetic risk. This is known as a gene and environment interaction.

1.7.2 Gene and Environment interactions

Another plausible mechanism by which cannabis might cause schizophrenia involves an interaction between genes and the environment. This model suggests that genetic and environmental factors may interact to bring about psychotic disorder. As discussed in Section 1.2.3 schizophrenia appears to have a high degree of heritability, and yet genetic models fail to account for much of the variance in the data and often yield inconsistencies. These inconsistencies could

plausibly be attributable to the models' inability to model an interaction between gene and environment.

The Catechol-O-methyltransferase (COMT) gene has a functional polymorphism: Valine (Val) and Methionine (Met). It is thought that the genetic expression influences DA's availability in the Pre-Frontal Cortex, with Val homozygotes presumably having the lowest synaptic DA levels, resulting in greater availability of DA at the receptor (Chen et al., 2004). Caspi et al., (2005) looked at genetic vulnerability within the COMT gene, which they found moderated the influence of (adolescent) cannabis use on the development of schizophreniform disorder. Once again utilising the Dunedin birth cohort (Arseneault et al., 2002), 953 individuals were genotyped. Caspi and colleagues observed no significant effect of genotype, or adolescent cannabis exposure per se. However, a significant interaction effect between the two variables *was* observed. Specifically, of the early initiates into cannabis use 4.2% of the Met homozygotes went on to develop schizophreniform disorder, in contrast 13% of the Val homozygotes developed the illness. The adjusted O.R. of the interaction effect between adolescent cannabis use and geneotype showed that, whilst Met homozygotes had only a slightly elevated chance of developing schizophreniform disorder over cannabis abstainers (1.1 OR), Val/Met heterozygotes were at a greater risk (2.5 OR), and carriers of two Val alleles were at the greatest risk (10.9 OR). This finding shows that the phsychotogenic effects of cannabis is moderated by the Val allele of the COMT gene.

Further evidence of an interaction effect between the COMT gene and cannabis has been demonstrated in animal models (O'Tuathaigh, et al., 2012). Evidence of a cannabis COMT interaction effect has also been demonstrated in a naturalistic environment. In an ESM study Henquet et al., (2009) considered 31 patients with psychotic disorder and 25 healthy controls. The data from the participants were pooled and split into those with low schizotypy (n=14) and those with high schizotypy (n=42). Henquet and colleagues found that the Val carriers who were high schizotypes showed an increase in hallucinatory experience as a consequence of cannabis use. However, no such effect was found in the low schizotypes, or the high schizotypes who were Met homozygotes. This finding was

also repeated in an experimental investigation (Henquet et al., 2006), providing additional support for the COMT gene as a modulating factor in the psychotogenic effects of cannabis. However, given that this effect appears restricted to a subset of psychosis prone individuals it is feasible that other mechanisms may also explain the relationship between cannabis and schizophrenia.

Several studies have failed to replicate Caspi et al. (2005) findings. One such study is Zammit et al. (2007) who found no significant interaction effect in a cohort of 493 patients with schizophrenia. The findings remained consistent even when participants were differentiated at age of first cannabis use. However, in this study, participants were differentiated on the basis of being over the age of 18 at first cannabis use and this information was reliant upon retrospective accounts. Caspi and colleagues found the most significant effect when differentiating participants on the basis of whether they had initiated use prior to 15 or had become monthly users by 18 years of age. Furthermore, the inclusion criteria were based on the participant's accounts at that age. The lack of a significant interaction in this study could therefore be accounted for by, the adoption of a different criteria and retrospective assessment, in determining 'the early onset of cannabis use'.

Zammit, Owen, Evans, Heron and Lewis (2011) once again failed to replicate Caspi et al. (2005) findings in a prospective cohort study, cannabis use was assessed at age 14, with no difference in psychotic experience, after a two-year follow-up period, found on the basis of COMT genotype expression. However, cannabis use may have a neurodegenerative effect associated with chronicity of use (Arnone et al., 2008), which may not have been present at time of evaluation (age 16). Thus, this may account for the lack of significant findings in Zammit et al. (2011) investigation.

Pelayo-Téran et al., (2010), looked at the interaction between cannabis use and polymorphism in the COMT gene and its effect on age of onset of psychosis. In a non-cannabis using control group; Val homozygotes had a significantly earlier age of onset; with Met homozygotes displaying a later age of onset; and heterozygotes displaying an intermediary profile. In the cannabis using group there was no significant difference on age of onset based on COMT polymorphism. Thus, the

data may indicate that, in this instance, the cannabis COMT interaction may serve to alter the delay effect conferred by two Met alleles. The research of Pelayo-Téran and colleagues brings into question which functional polymorphism of the COMT gene is most susceptible to the deleterious effects of cannabis.

Costas et al., (2011) also found a 'reverse association'. They found that Met homozygotes had twice (2.07 OR) the probability of lifetime prevalence of cannabis consumption, however age of cannabis initiation was not controlled for. Despite age initiation being an important determining factor in Caspi et al., (2005) investigation. The exact effect of not differentiating participants according to early or late onset of use is difficult to determine. Unfortunately, this makes it difficult to draw comparison with the findings of Caspi and colleagues. Costas et al., (2011) discuss the possibility of a 'flip-flop' association whereby biological, environmental, or methodological factors may be considered the putative explanation. The investigations of Costas and colleagues, and Pelayo-Téran and colleagues *do* suggest a modulating effect of the COMT gene on cannabis. However, the 'reverse association' of the Met allele indicates that at present our current understandings of the genetic factors which predispose to schizophrenia are not adequate.

In conclusion, a gene / environment interaction based on the COMT gene and adolescent cannabis use does appear plausible. However, given the inability of subsequent studies (Costas et al., 2011; Pelayo-Téran et al., 2010; Zammit et al., 2007; Zammit et al., 2011) to replicate Caspi et al., (2005) findings what, if any, interaction exists is, at this moment, difficult to establish. At present there is no definitive evidence mapping out specific genomes that confer susceptibility to schizophrenia, and research within this domain is often marred by an inability to replicate findings (see Section 1.2.3). Henquet et al., (2008) in a review of gene *x* cannabis (environment) interactions summarises that genetic and environmental influence "...are more likely to underlie the complex interactions between cannabis and psychosis, whereby multiple variations within multiple genes—rather than one single genetic polymorphism— may set an individual's vulnerability at birth to develop later psychosis" (p.1117). This notion is evinced by several SNP's displaying a significant interaction effect with cannabis including the NRG1 gene

(Han et al., 2012), the FAAH gene (Arias et al., 2010), the AKT1 gene (Di Forti et al.,2012; van Winkel, 2011), and a three-way interaction between the AKT1 gene, the COMT gene and cannabis (van Winkel, 2012). A cannabis gene interaction, possibly via a DA pathway (for example COMT SNP), is perhaps the most plausible model available to suggest how cannabis might cause schizophrenia. Nonetheless, further information is required to elucidate the mechanism by which each cannabis use may contribute to the expression of psychotic experience, psychotic symptoms and psychotic disorder. Such a mechanism has been proposed in sensitisation.

1.7.3 Sensitisation

Sensitisation refers to the repeated exposure to stimuli, which results in an enduring alteration in response amplitude. Although there is compelling evidence that schizophrenia is influenced by genetic factors, numerous environmental stressors also increase the odds ratio of decompensating (see Section 1.2.3). However, it is not thought that any of these factors are completely deterministic of psychotic disorder (Clarke et al., 2012).Van Os et al., (2009) suggests that in a continuum model of psychotic disorder (see Section 1.2.2); 8% of the general population have psychotic-like experience; 50% of them (4% of the general population) experience psychotic symptoms; and 75% of them (3% of the general population) develop psychotic disorder. Although van Os and colleagues found the presence of psychotic experience to be relatively common, for some people, these transitory experiences persist, leading to clinical relevance. Van Os and colleagues suggest that repeated exposure to deleterious environmental factors in childhood/adolescence may be a significant contributory factor to chronic psychotic disorder. Given cannabis' propensity to elicit transitory psychotic-like experience (see Section 1.8 & 1.6.4) exposure to cannabis may constitute one such environmental factor. Van Os and colleagues suggest that this may take place by a process of sensitisation, defined by Collip, Myin-Germeys, and Van Os (2008) as "the observation that individuals who are exposed repeatedly to an environmental risk factor may develop progressively greater responses over time, finally resulting in a lasting change in response amplitude" (pp. 220-1).

A process has been described whereby neurochemical sensitisation, thought to be underpinned by the release of DA into the ventral tegmental area, plays a role in decompensating in vulnerable people and the course of the disorder (Lieberman, Sheitman, & Kinon, 1997). Lieberman et al., (1997) describe sensitisation as consisting of both an induction and expression phase. Lieberman and colleagues suggest that the induction phase is thought to be underpinned by DA release into the ventral tegmental area (VTA). However, a more recent review has argued that multiple cortical and subcortical regions (including the VTA) may be implicated as is the neurotransmitter glutamate at the NMDAr (Vanderschuren & Kalivas, 2000). Irrespective, both DA release in the VTA and inhibition of the NMDAr have been implicated in psychotic break down and the expression of positive and negative symptoms (Lieberman et al., 1997; Lisman, Pi, Zhang & Otmakhova, 2010; Morgan, Mofeez, Brandner, Bromley & Curran, 2004). Some of the same neural networks and transmitters are also thought to underpin the second phase of sensitisation expression (Vanderschuren & Kalivas, 2000).

Lieberman et al., (1997) describe the development of schizophrenia within a three stage process. The first stage requires genetic vulnerability and / or neurodevelopmental abnormalities. The second stage occurs during adolescence or early adult hood wherein repeat exposure to a stressor results in repeated release of DA in the VTA. The third stage consists of “structural neuronal changes” which results in clinically relevant disorder (p.216). Although the neurochemical process described by Lieberman and colleagues may represent the underlying mechanism, the process of sensitisation can be seen expressed in behaviour, affect and cognition (Collip et al., 2008).

Further evidence for a process of sensitisation in psychotic disorder can be derived from the investigation of Dominguez, Wichers, Lieb, Wittchen and van Os (2011), who found that the greater the persistence of sub-clinical psychotic experiences, the greater the transition to psychotic disorder. Moreover, this was found in a dose dependent fashion. Furthermore, Cougnard et al., (2007) elucidated an additive effect of environmental stressors that combined with psychotic-like experience to contribute to persistent and feasibly clinically relevant psychotic ‘symptoms’. A model of sensitisation could explain why schizophrenia

appears to have both neurodevelopmental and neurodegenerative features (Gupta & Kulhara, 2010). The neurodevelopmental features may be represented by genetic factors, and the neurodegenerative features could be as a consequence of sensitisation.

Animal models have been shown to sensitise to cannabis. Behavioural sensitisation has been demonstrated as a consequence of having repeat doses of ∆-9-THC (Cadoni, Pisanu, Solinas, Acquas & Chiara 2001; Rubino, Viganó, Massi & Parolaro, 2001). Furtheremore, behavioural sensitisation to ∆-9-THC has been found to correspond with alterations in DA transmission (Cadoni, Valentini, & Chiara, 2008). However, other investigations have failed to replicate these findings (Arnold, Topple, Hunt & McGregor, 1998; Varvel, Martin & Lichtman, 2007). The evidence suggesting a sensitising effect of cannabis is at present sparse. Animal models suggest a possible mechanism of sensitisation. However, such a response has not been demonstrated consistently and may not extrapolate to humans.

In human subjects, cannabis users have demonstrated an increased activity in the ventral striatum in response to a non-drug reward (Nestor, Hester, & Garavan, 2010). This activation significantly and positively correlated with life-time cannabis exposure. This indicates that cannabis may sensitise to non-cannabis related events: cross-sensitise. Similarly as demonstrated in Nestor et al., (2010) investigation, in animal models the prior administration of cannabis has been shown to cross-sensitise to amphetamine (Gorriti, Fonseca, Navarro & Palomo, 1999), and morphine (Cadoni et al., 2008). However, cannabis does not appear to cross sensitise with cocaine (Arnold et al., 1998).

The data regarding sensitisation of cannabis in animal models is inconsistent as is the information pertaining to cannabis' ability to elicit dopaminergic activity (see Section 1.7.1). The incongruence in the data suggests that a process of sensitisation may not fully explain the relationship between cannabis and psychotic disorder. However, there is evidence to suggest that cannabis may cross-sensitise to other drugs (e.g. Cadoni et al., 2008) or experimental conditions (Nestor et al., 2010). Due to the ethical implications, It is difficult to assess a mechanism of sensitisation in experimental studies utilising human subjects.

Within the confines of the laboratory it is difficult to observe a lasting change in response amplitude as a consequence of cannabis administration. However, it is easier to assess a process of cross-sensitisation. Through the use of statistical models it is possible to assess if variables may combine to elicit an effect size larger than the sum of the parts. Although, this may not demonstrate the neurological or mechanistic substrate of sensitisation it will allow for inference to be made as to whether response amplitude is altered as consequence of the presence of both factors. The interaction between these factors may be explained by genetic interaction processes, such as a gene *x* gene *x* cannabis interaction effect (van Winkel, 2012). Nonetheless, these interactions have also been taken as evidence for cross-sensitisation (Kuepper et al., 2010).

1.7.4 Cross-sensitisation between cannabis and stress

Sensitisation represents a plausible mechanism by which cannabis may cause schizophrenia. However, assessing such a mechanism is a difficult task in human subjects in naturalistic environments (see Section 1.7.3). Nonetheless, there is evidence to suggest that cannabis may cross sensitise to other rewards (Nestor et al., 2010) and there is also evidence to suggest that cannabis may cross-sensitise (interact) with stress.

There is a well-established relationship between stress and psychotic disorder. For instance, patients suffering with Post-Traumatic Stress Disorder (PTSD) who are also 'positive' schizotypes tend to have more trauma related symptoms and a greater spectrum of PTSD symptomatology (Marziller and Steel, 2007).In comparison with positive schizotypes and controls, negative schizotypes have also been shown to display a significant increase of DA into the striatum as a result of psychosocial stress (Soliman et al., 2008). Furthermore, negative schizotypes have been shown to have "greater stress-induced striatal and limbic deactivation" (Soliman, 2011, p.184). In an experience sampling investigation (see Section 3.2.1) patients suffering with a psychotic illness have been shown to have an increased stress reactivity in comparison to controls (Myin-Germeys, Van Os, Schwartz, Stone & Delespaul, 2001). Moreover, psychosocial stress has been shown to elicit DA release in the PFC in none-prone individuals (Lataster et al.,

2011). Thus it appears that the expression and maintenance of psychotic symptomatology are in some part influenced by stress (see Sections 1.2.3 & 3.1 for further discussion). However, the means by which cannabis interacts with stress is less clear.

One of the most often cited motivations for cannabis use is the relief of dysphoria, this is an agent to relieve psychological distress (Gregg et al., 2007). Based on this premise, and the observations that cannabis has anxiolytic properties (Zuardi et al., 1982), it would appear that cannabis has a beneficial effect on psychological stress. Nonetheless, cannabis and the endocannabinoid system appears to play a complex role in stress related disorders (Neumeister et al., In press). Cannabis increases cortisol release in a dose dependent fashion in both frequent and non-frequent users (D'Souza et al., 2008; Ranganathan et al., 2009). However, these affects are blunted in habitual users, which could plausibly indicate sensitisation, a change in response amplitude. In animal models, the endocannabinoid system has been shown to regulate response to aversive stimuli (Häring, Grieb, Monory, Lutz & Moreira 2013). If these results extrapolate to humans then stimulation of the cannabinoid system may result in an exaggerated response to aversive stimuli.

There is emerging evidence to suggest an interaction between cannabis and psychological stress on a psychosis outcome. In animal models, stress was a necessary requisite for cannabis to elicit striatal DA release (Littleton and Maclean, 1975; Maclean and Littleton, 1977). However, observing an interaction between stress and cannabis is more difficult in humans, one of the reasons being stress is more difficult to define and induce. In a laboratory setting in human subjects, Δ-9-THC significantly increased the skin conductance response in regards to intensely and moderately fearful faces, but not neutral faces (Fusar-Poli et al., 2010). This indicates that cannabis was serving to exacerbate the physiological stress response, but only when exposed to a psychological stressor (i.e. a fearful face). Cannabis and stress were interacting to result in an increase in response amplitude.

In non-experimental investigations, urbanicity has been consistently implicated as a contributory factor in presentation of psychotic illness (Vassos, Pedersen,

Murray, Collier & Lewis, 2012). It is thought that this could be reflective of the presence of social processes, such as 'social capital' (Krabbendam & van Os, 2005). Social capital has been shown to have a strong relationship with stress and stress-coping mechanisms (Gächter, Savage, & Torgler , 2011). Kuepper et al., (2011) in a prospective cohort study demonstrated a significant interaction effect between cannabis and urbanicity on the development of psychotic symptoms. Thus, suggesting that some of the environmental stressors conferred by an urban environment are interacting with cannabis consumption. This provides further support for the notion of a cannabis stress interaction effect.

Childhood abuse or trauma is another psychological stressor which appears to have an independent effect on psychotic disorder (Sheffield, Williams, & Blackford, Heckers 2013), and interacts with cannabis on a psychosis outcome. Harley et al., (2010) found that both cannabis and childhood trauma contribute independently, and interact significantly, to predict psychotic symptoms. Houston, Murphy, Adamson, Stringer and Shevlin (2008), and Houston, Murphy, Shevlin, and Adamson (2011) found no significant main effect of cannabis on psychotic disorder. However, a significant interaction effect between cannabis and childhood trauma increased the odds of a diagnosis of psychotic disorder. This indicates that cannabis and psychological stressors may interact to confer a risk greater than the sum of the parts. However, the validity of Houston et al., (2011) findings have been questioned (Daly, 2011). Daly (2011) attempted to address the shortcomings of previous investigations by adjusting for baseline psychotic symptoms. After adjustment, there was no main effect of sexual abuse, cannabis, and no interaction effect between the two on hallucinatory experience.

In analysis of another dataset whilst controlling for baseline psychotic experience, Murphy, Houston, Shevlin & Adamson (2013) did demonstrate a significant interaction effect of cannabis and childhood trauma on psychotic disorder. This finding has been further replicated in independent Greek, Dutch, and English cohorts (Konings et al., 2012; Sideli et al., 2012), although was not replicated by Kuepper, Henquet, Lieb, Wittchen and van Os (2011). Taken together, these findings suggest that if cannabis and psychological stressors interact there are feasibly other factors which are important determinates of psychotic susceptibility.

The research of Alemany et al., (2012) may help account for some investigations failing to document a significant interaction effect. Alemany and colleagues documented no significant main effects of cannabis or childhood abuse on psychotic-like experience irrespective of the participant's COMT functional polymorphism. However, a significant interaction effect of cannabis and childhood trauma was documented in all groups. The Val carriers displayed significantly more psychotic-like experiences as a consequence of this interaction effect, whereas Met homozygotes displayed significantly fewer. Vinkers et al., (2013) undertook a similar analysis to Alemany and colleagues. Vinkers and colleagues documented a significant threeway interaction effect between COMT polymorphism, cannabis and childhood abuse. The data also indicated that Val homozygotes were the most susceptible. This indicates that the interaction between cannabis and stress may be in part modulated by polymorphism of the COMT gene.

Intriguingly, in a recent review of pharmacological interventions for the treatment of the acute effects of cannabis, propanolol (and rimonabant) were thought to be the most effective (Crippa, et al., 2012). Propanolol is a beta-blocker which lowers heart rate and has been used in the treatment of stress related disorder (Brunet et al., 2008). This indicates that, rather than the treatment of dopaminergic dysfunction associated with antipsychotic drugs, feasibly the best means of attenuating acute cannabis induced psychotic episode is via the amelioration of the physiological and psychological stressed state. This provides further evidence for stress playing a central role in the psychotomimetic effects of cannabis.

Parakh and Basu (2013) suggest that the interaction between cannabis and environmental stressors is a necessary requisite in cannabis 'causing' psychotic disorder. Activation of the Hypothalamic-Pituitary-Adrenal (HPA) axis (physiological stress response) by cannabis may not in itself be pathological. However, the data indicates that feasibly, when the physiological stressed state is elicited in combination with a psychological stressed state this could elicit both DA release in cortical and subcortical regions and bring about psychotic reaction. At present cross-sensitisation could represent a plausible mechanism by which

cannabis may cause schizophrenia (see Collip et al., 2008; Henquet et al., 2008; Kuepper et al., 2010; van Os et al., 2009 etc.). Nonetheless, alternative mechanisms have been suggested, such as that based on cognitive disruption (Meijer et al., 2012) or primary action of the CB1 and the cannabinoid system (Emrich, Leweke, & Schneider, 1997) (see Parakh & Basu, 2013 for further information). The discussion of these alternative mechanisms goes beyond the scope of this literature review. However, it is feasible that *multiple* different plausible mechanisms of association have a causal influence on psychotic disorder (e.g. Myin-Germeys & van Os, 2007).

As discussed previously (Section 1.2.1 pp. 21-25) schizophrenia has a well-established relationship with several other disorders. SPD is the "prototypical schizophrenia-spectrum condition" (Fervaha & Remington, 2013, p.96). Given that schizotypy has been utilised to elucidate information about schizophrenia (see Section 1.2.2). Schizotypy can also provide inference about the consequence of cannabis use on psychotic disorder. Thus, the next section will discuss the relationship between cannabis, schizotypal state and schizotypal trait.

1.8 Cannabis, schizotypal state and schizotypal trait

In Section 1.6 various hypotheses regarding the relationship between cannabis and psychotic disorder were discussed. However, this association can be further assessed by examination of data pertaining to the relationship between cannabis and schizotypy. Both Schizotypal personality trait and schizotypal state are highly related to schizophrenia (see Section 1.2.2 pp. 25-31). Schizotypy is commonly viewed as a stable and enduring personality trait that is thought to reflect an individual's propensity (both genetic and psychological) to develop psychotic disorder. This notion has led some researchers to look at the relationship between cannabis and schizotypy to contribute to the causal debate (e.g. Mass, Bardong, Kindl & Dahme, 2001).

Many investigations have demonstrated a significant elevation in schizotypy in cannabis users in comparison to drug naïve controls (e.g. Dumas et al., 2002; Fridberg, Vollmer, O'Donnell & Skosnik 2011; Mass et al., 2001; Skosnik, Spatz-Glenn & Park., 2001 etc.). Given the purported stability and early development of schizotypy, this may indicate that a schizotypal personality trait predisposes an individual to use cannabis, which is a view adopted by some investigators (Mass et al., 2001). However, other investigations, such as that of Bailey and Swallow (2004) have drawn different conclusions. Bailey and Swallow (2004) also documented an elevated schizotypal trait in positive, negative and disorganised domains in cannabis users. However, they concluded that this effect may have been a consequence of a schizotypal personality trait predisposing to drug medication, or due to the acute psychotomimetic effects of the drug. The interpretation of the association between cannabis and schizotypy holds relevance not only for the cannabis schizophrenia causality debate, but also implications for models of schizotypal vulnerability.

As stated above, some studies have noted elevated schizotypy levels in cannabis users in comparison to controls. In addition, some research has demonstrated that current cannabis users score higher than past cannabis users on measures of schizotypy (Dumas et al., 2002, Skosnik et al., 2001). There may be an intrinsic difference between cannabis users who persist and those who cessate use. However, factors that underpin cessation are poorly understood (Dekker et al.,

2008) and there is no known evidence to suggest what, if any, differences exist between these two groups. If there is no fundamental factor that might predict cessation then this could plausibly indicate that the significant difference between the current and past cannabis users is as a consequence of the acute effects of cannabis.

Anglin et al. (2012) found that cannabis use prior to 14 years old predicts SPD independently of the presence of psychotic symptoms at baseline. This appears to indicate that adolescent cannabis use has temporal priority over schizotypal symptomatology. This implicates a causal relationship between cannabis and SPD. Unlike some of the other investigations Baskak et al. (2012) were capable of assessing the temporal relationship between cannabis and schizotypy. Baskak and colleagues found that former cannabis users scored significantly higher than cannabis-naïve participants, in positive, negative, and disorganised domains of schizotypy. Within the positive domain this was associated with a dose dependent effect. Moreover, in analysis of temporal proximity to cessation it was elucidated that more recent cannabis use was positively and significantly associated with elevations in positive and negative dimensions of schizotypy.

Further evidence of cannabis' (or more specifically Δ-9-THC) ability to elevate schizotypy can be derived from the research of Morgan and Curran (2008). Individuals' frequently using cannabis with high levels of ∆-9-THC and no CBD (as assessed by hair-analysis) had significantly higher positive schizotypal traits than both non-users and users with ∆-9-THC and CBD in their system. The decision to consume cannabis containing solely Δ-9-THC or Δ-9-THC and CBD, may be influenced by numerous factors (e.g. geographical location: D. Potter et al., 2008). However, it is highly unlikely that this decision will be influenced by schizotypal personality, particularly considering that microscopic examination and detailed forensic examination is required to accurately identify preparations that contain CBD (see Section 1.4). Thus, it would appear that the findings of Morgan and Curran are as a consequence of ∆-9-THC ability to elevate schizotypy, and CBD's ability to attenuate these effects.

Nonetheless, there are contrasting data suggesting that cannabis does not cause elevations in schizotypy. Schiffman, Nakamura, Earleywine and LaBrie (2005) found a significant difference in schizotypal trait between cannabis users and non-users. However, Shiffman and colleagues, utilising a retrospective measure, elucidated that these schizotypal traits occurred significantly earlier than first cannabis use. Although, there are methodological limitations to retrospective assessment, the findings of Shiffman and colleagues appear to implicate a non-causal relationship between cannabis and schizotypy.

Fridberg et al., (2011) assessed chronic cannabis users and non-cannabis users on assessments of schizotypy and other non-pathological personality traits. The cannabis using groups scored significantly higher on assessments of schizotypy and, this was in a dose dependent fashion. This suggests a biological gradient, which is one of the requisite factors (see Section 1.6.4) to suggest that cannabis may cause elevations in schizotypy. Intriguingly, the cannabis using group also differed from controls on other aspects of personality (conscientiousness, agreeableness etc.). This finding may reflect intrinsic differences between cannabis users and non-users which predispose to cannabis use.

However, the notion of intrinsic differences between cannabis users and non-users was not supported by the findings of Linscott (2008). He found significant elevations in schizotypy in cannabis users in comparison to non-users, but no significant difference in the latent structure of schizotypy. This finding indicates that the cannabis using population are exhibiting a high, but not abnormal schizotypal personality profile. Nonetheless, Esterberg, Goulding, McClure, and Compton (2009) have demonstrated that indices of cannabis, alcohol and nicotine use have been associated with positive and disorganised dimensions of schizotypy. Thus, substance use/misuse more generally has been associated with schizotypy which does not indicate specificity (see Section 1.6.4).
At present, the relationship between cannabis, schizotypal trait, and schizotypal state remains unresolved. Like so many other domains associated within schizophrenia (see Section 1.2.3, 1.6 & 1.7) the data is inconclusive. Thus, there is a need for further research to highlight the relationship between cannabis, schizotypy and schizophrenia.

1.9 Summary of the chapter and the aims of this body of research

This chapter has discussed some of the relevant literature pertaining to schizophrenia (Section 1.2.1 pp. 21-25), schizotypal personality disorder, schizotypal personality trait, and a schizotypal state (all Section 1.2.2 pp. 25-37). This chapter has also discussed the relevant literature pertaining to assessing psychotic vulnerability (Section 1.2.3 pp. 37-48) and the development of a psychometrically sound measurement scale (Section 1.3 pp. 49-54). Section 1.4 (pp. 55-58) has provided a summary of the status quo of the cannabis market and its relationship with psychotic reaction. Section 1.5 (pp. 59-60) has discussed some of the literature relating to cannabis-induced psychosis. This chapter also summarised some of the available data pertaining to a causal association between cannabis and schizophrenia (Section 1.6 pp. 61-79), in addition to a section devoted to the assessment of plausible mechanisms (Section 1.7 pp. 80-95). Finally, this chapter examined the data pertaining to the relationship between cannabis, schizotypal state and schizotypal trait (Section 1.8 pp. 96-98).

This thesis contains three research chapters each of which have distinct aims. Chapter 2 and Chapter 3 consider data derived from distinct groups of participants, collected with distinct methodologies. However, further analyses of the data derived from both of these investigations are considered in Chapter 4. The aims of Chapter 2 (Section 2.1.1 p.105), Chapter 3 (Section 3.1.1 pp.164-65), and Chapter 4 (Section 4.1.1 p. 261) are discussed later on in the thesis. However, this thesis as a whole body of research possessed two primary aims. An assessment of whether or not the aims of the individual chapters and the thesis as a whole have been achieved is considered in the fifth and final chapter.

The literature discussed within this chapter should serve to contextualise the individual chapters, along with contextualising the two principal aims of this body of research:

1. To contribute to discussions relating to ‘causal inference’ in the relationship between cannabis and psychosis
2. To assess the reliability and validity of a measure of psychotic vulnerability based on a differential sensitivity to the psychotomimetic effects of cannabis

The first aim of this thesis is addressed in Chapter 3, which assesses the temporality of various variables of interest. Within a continuum model of psychosis, analyses in Sections 3.3.3 (pp. 217-26), 3.3.5 (pp. 230-34) and 3.3.6 (pp. 234-38) assess converging evidence for the; self-medication hypothesis; a causal model of association; and a synergistic model of association (see Section 1.6 pp. 59-79). This chapter also allows for the assessment of a plausible mechanism of association. The plausibility of a cannabis stress interaction effect is assessed in Sections 3.3.3 (pp. 217-26) and 3.3.4 (pp. 227-29).

The second chapter contributes to the second primary aim of this thesis. This chapter tests the notion of a differential sensitivity to cannabis in those vulnerable to psychosis. The fourth chapter serves to fulfil the second primary aim of this thesis, which is achieved by assessing evidence for the predictive validity, convergent validity, and concurrent validity of a measure of cannabis induced experience. In addition, contained within the chapter are assessments of internal reliability and data pertaining to test-retest reliability.

The previous section (1.8) of this chapter has elucidated a paucity of understanding about cannabis' relationship with psychotic disorder and schizotypal trait. The next chapter attempts to further the understanding of cannabis' impact on schizotypal trait, whilst simultaneously assessing whether psychosis proneness confers a differential sensitivity to cannabis.

2. Cannabis induced experiences, schizotypal traits and their relationship to self-reported diagnoses of psychotic mental illness and depression

Brief overview

This chapter is one of several research chapters contained within this thesis. This particular chapter seeks to further elucidate the relationship between cannabis use, psychotic disorder and schizotypy, whilst simultaneously assessing a differential sensitivity to the drug based on psychosis proneness. This aim is achieved by examining group differences between cannabis users; from a community sample; with reported depression; and with a reported psychotic disorder. Contained herein is a brief introduction which contextualises this investigation (Section 2.1 pp. 102-05). After the introduction there is a description of the methodology utilised in this investigation (Section 2.2 pp. 106-17). The results of this investigation are contained within Section 2.3 (pp. 118-45). Section 2.3.1 (pp. 118-121) is concerned with the assessment of the assumptions of the subsequent analyses and Section 2.3.2 (pp. 121-125) and 2.3.3 (pp. 126-7) describes the participant's characteristics. Section 2.3.4 (pp. 127-31) and 2.3.5 (pp. 131-33) compares the groups of participants on measures of schizotypy and cannabis induced experience. Sections 2.3.6-8 (pp. 134-145) assesses the participants within a regression model to test for predictors of group-membership (i.e. diagnoses). The results of the investigation are discussed within Section 2.4 (pp. 146-59).

2.1 Introduction

Cannabis and psychotic disorder have a well-established link (see Section 1.6.4 pp. 72-9), nonetheless whether cannabis causes schizophrenia is still a matter of debate. To assist in answering this question researchers have looked at the relationship between cannabis and schizotypy (e.g. Mass et al., 2001). Schizotypy is purportedly a stable and enduring personality trait which is thought to represent psychotic vulnerability (see Sections 1.2.2 pp. 25-31 & 1.2.3 pp. 45-8). Schizotypal trait has been shown to be elevated in current cannabis users in comparison to former cannabis users and people who are cannabis naïve (Dumas et al., 2002; Skosnik et al., 2001). However, there is data indicating that there may be state aspects to this purportedly stable trait (see Sections 1.2.2 & 1.8 pp. 96-8).

Assessing which factors predispose individuals to psychotic disorder is a current and ever expanding area of research (see Section 1.2.3). One of the least resource intensive means of assessing psychotic vulnerability is via self-report assessments of schizotypy. Nonetheless, given that schizotypy may have state elements and cannabis may induce psychotomimetic states (see Section 1.8), assessments of psychosis proneness utilising schizotypy may not truly reflect 'schizotaxic' liability in cannabis using populations. This is evinced from the frequent occurrence of psychotic like states in the healthy population and the infrequency that these states are clinically relevant (van Os et al., 2009). Thus, it is proposed that within this population other means of assessing psychotic vulnerability should be adopted.

It has been proposed that the "genetic risk for psychotic disorder might be expressed in part as sensitivity to the psychotomimetic effects of cannabis" (Eisenberg, 2010, p.32). There is some data which supports this notion; in a prospective cohort study the Genetic Risk and Outcome in Psychosis investigators (GROUP, 2011) compared patients with a psychotic disorder, their siblings, and healthy controls. In comparison to the control group, the sibling group displayed significantly more positive and negative aspects of schizotypy. This had a positive linear effect with dose of cannabis. Moreover, a similar effect was documented between the sibling and patient groups, but only within the domain of positive symptomatology. Thus, suggesting that a differential sensitivity to the

psychotomimetic effects of cannabis is partially determined by genetic vulnerability.

In a naturalistic experience sampling investigation (see Section 3.2.1 pp. 166-70) Henquet et al., (2010) found that, patients suffering with a psychotic disorder had elevations in their positive symptoms as a consequence of cannabis use. However, no such relationship was demonstrated within controls. In another experience sampling investigation cannabis induced significantly more psychosis-like experiences in psychosis prone participants, in comparison to those thought to be at a low risk (Verdoux, Gindre, Sorbara, tournier & Swendsen, 2003). In a further naturalistic investigation cannabis consumption induced psychotomimetic experience with more marked effects in those psychosis prone (Mason et al., 2009).

A measure has been developed to record and quantify cannabis induced experiences; the Cannabis Experiences Questionnaire (CEQ). The CEQ comprises of a checklist of pleasurable, aversive, and after-effects of cannabis intoxication. Item generation consisted of several phases (see Section 1.3.1 pp. 49-51 for further information on item generation). Initial literature searches were undertaken of user's self-report data, and clinical description of; cannabis induced psychosis; and amotivational syndrome. Qualitative investigation in the form of structured interviews were then undertaken with cannabis users (N = 62). The participants were asked to comment on; the familiarity of the items generated from the literature searches; a description of any familiar phenomena identified; any previous good and bad cannabis experiences and how these impact on the individual; any cannabis induced experiences not already generated.

Although, the CEQ is typically administered as a self-report measure (e.g. Bloomfield, et al., in press; Stirling et al., 2008 etc.) it has also been administered as an interview to a clinical population (Di Forti et al., 2009). The CEQ has undergone several factor analyses, which have yielded two different scoring systems (see Stirling et al., 2008; Barkus & Lewis, 2008). Moreover, a third scoring system also appears to be in use, although it is unclear whether this is derived from statistical procedures (Greenwood et al., In press). However, the

most recent factor analysis on the most comprehensive dataset has yielded a three factor solution (Stirling unpublished data, see Appendix 1). Research has consistently demonstrated a highly significant relationship between aversive cannabis induced experiences and positive, negative, and psychotic dimensions of schizotypy (Barkus & Lewis, 2008; Barkus, Stirling, Hopkins & Lewis 2006; Stirling et al., 2008, Morris, [unpublished data]). Moreover, in a small pilot investigation, (N = 16) in-patients who had a diagnosis of cannabis induced psychosis had significantly more aversive cannabis induced experiences than a community sample (Stirling, 2011).

The CEQ has been administered and re-administered at an approximate 2 month interval to a sample of 65 cannabis users. The three subscales of the CEQ displayed a highly significant positive correlation (all $p < .001$, $r > .75$) (Stirling, unpublished data). Thus, indicating test-retest reliability. In a recent investigation Greenwood et al.(In press) found significant differences between short-term and long-term cannabis users on the CEQ. Short-term cannabis users displayed significantly more pleasurable and aversive cannabis experiences. This could indicate that these experiences may be attenuated in long term use. This may suggest a time variant component to this measure. However, it may reflect a decrease in vulnerability with time as the sample transit past the age at which psychotic breakdown is most common (see Section 1.2.1 pp. 21-25). Evidence for this can be derived from a comparison of the mean age of the short term cannabis users (20.9 years) and the long term cannabis users (39.9 years).

2.1.1 Aims of the chapter

There is a significant positive relationship between cannabis and schizotypy. However, whether this relationship is causal and the significance of this particular association to schizophrenia remains a matter of conjecture. The literature indicates that people with psychotic vulnerability may display a differential sensitivity to cannabis. However, the utility of such an observation has yet to be assessed and requires further enquiry. This investigation seeks to address deficiencies in the literature, by fulfilling the following three aims:

1. To assess variance in schizotypal trait related to cannabis use and reported mental illness (see Section 1.8 for rationale pp. 95-98).
2. To assess the presence of a differential sensitivity to the psychotomimetic effects of cannabis in those with psychotic illness (see Section 2.1 for rationale pp. 101-03).
3. To assess the utility of assessments of cannabis induced experience and schizotypal trait as predictors of psychotic illness in cannabis using populations

2.2 Methodology

2.2.1 Study design

A cross-sectional study design was utilised to compare four different groups of participants: a community sample of participants who were cannabis naïve (CSCN), a community sample of cannabis users (CSCU), a sample of cannabis users with a self-reported diagnosis of depression (DD), and a sample of cannabis users with a self-reported diagnosis of psychotic disorder (PD). A cross-sectional study design will allow for inferences to be made about differences in the populations from which the groups originate. Comparison will be drawn between these independent groups of respondents, on assessments of schizotypal personality (Section 2.3.4 pp. 127-31). Comparison will also be drawn between the three cannabis using groups of respondents (CSCU, DD and PD) on indices of cannabis use (Section 2.3.2 pp. 121-25) and cannabis induced phenomena (Section 2.3.5 pp. 131-33). In Sections 2.3.6-8 (pp. 134-45) the scales of the CEQ and the SPQ-b will be assessed as predictors of group membership.

2.2.2 Participants

Inclusion and exclusion criteria

All participants had to be over the age of 18 to take part in the investigation. The criterion was used to increase homogeneity between groups, given that schizophrenia for example typically first presents itself “in the early- to mid-20s for males and in the late-20s for females” (APA, 2013a, p.103). The imposition of such a criterion also circumvents a possible methodological issue of obtaining consent. For participants under the age of 16, dual consent should be sought from both the participant and those with parental responsibility (BPS, 2008 p6). However, as this investigation utilised internet based research dual consent would be difficult to procure and validate. No participant under the age of 18 years was recruited to the DD or PD group. However, 35 participants under 18 years old were recruited in cohorts 2 and 3 (see Table 1), 32 of which were in the CSCU group. Their data were excluded from the analysis.

Participants were excluded from the PD and DD groups if they self-reported a diagnosis of a mental illness of an unequivocally biological aetiology (e.g. epilepsy). As it is unclear how such mental illness may influence the expression of schizotypy and cannabis induced experience. Participants were also excluded if they had a psychological disorder of a purely exogenous origin. There was however, one exception applied to the PD group of substance-induced psychotic disorder. In addition to this exclusion criterion and the inclusion criterion outlined above the respondents were also subjected to further inclusion and exclusion criteria specific to their group status. Participants in the cannabis naïve group (CSCN) were excluded if they reported having ever consumed cannabis.

The groups of cannabis users (CSCU, DD and PD) were subject to a further inclusion criterion of a minimum of one lifetime use of non-synthetic unadulterated (except for with tobacco) cannabis. Synthetic cannabis use and cannabis consumed in suspension (e.g. Sativex, GW Pharmaceuticals) were not considered sufficient for eligibility. Participants were eligible for inclusion in the PD group if they reported at any point in their lifetime receiving a diagnosis of; schizophrenia; schizoaffective disorder; schizophreniform disorder; delusional disorder; drug induced psychotic disorder; brief psychotic disorder; shared psychotic disorder or psychotic disorder not otherwise specified. Participants were included in the DD group if they reported at any point in their lifetime having received a diagnosis of depression. Participants were however, excluded from the DD group if they had received a diagnosis of any of the disorders requisite for inclusion in the PD group, bi-polar mood disorder, or cyclothymia.

It is of importance to note that the CSCU group and CSCN groups were not specifically asked to document any previous mental illness. Thus, it is feasible that within these groups there will be a population rate incidence of mental illness, hence, they are referred to as a ‘community sample’. The mental illness of primary interest, schizophrenia, has a lifetime prevalence rate of approximately 0.3%-0.7% of the population (APA, 2013a, p.102). Given the large sample of respondents it is anticipated that in the event of several individuals being misattributed to the CSCU or CSCN groups this would not produce a significant effect. Moreover, the effect of misattributing participants to the CSCU or CSCN groups will likely result in the

analyses being more conservative, minimising group differences. Moreover, the analysis contained in Section 2.3.8 has taken further steps to control for incidences of unreported or undiagnosed (psychotic) mental illness.

Recruitment

Community Sample

The two groups of community respondents (CSCN and CSCU) were derived from data collected from previous investigations (i.e. not as part of this PhD). A total of 1167 participants were recruited in five different cohorts, between the years of 2004 to 2009. The amalgamated dataset consists of 861 individuals with experience of cannabis exposure and 306 without. The various cohorts, the recruitment strategies employed and procedure are described in greater detail elsewhere. Cohort one is considered in Barkus, et al., (2006); cohorts two, three and four are considered in Stirling et al., (2008); cohort five is considered in Morris (Unpublished data).

Table 1
Indicating the number of cannabis users and non-users recruited in each community sample cohort

	Cannabis naïve	Cannabis user	Total
Cohort 1	38	99	137
Cohort 2	71	141	212
Cohort 3	27	105	132
Cohort 4	28	51	79
Cohort 5	142	465	607
Total	306	861	1167

Cohorts one and two were recruited by posting notices requesting participants around a university campus. The notices invited interested individuals to contact a researcher for a questionnaire, which was distributed to the respondent. The paper questionnaires were returned anonymously in a post box on campus or via the mail in a pre-paid envelope.

The third cohort was recruited by an email distributed by a Dutch college. The email directed interested individuals to an electronic version of the questionnaires

hosted on the college's intranet. Within this cohort non-student respondents were also recruited by a snowballing technique. The participants invited people from within their social network to complete 'hard copies' of the questionnaires which were mailed back in pre-paid envelopes. The fourth cohort was recruited to provide test-retest data on the CEQ, however, only one of their data entries is considered herein. Similarly to the Dutch cohort this sample utilised electronic methods to recruit university students. However, non-student adults were also recruited through various (non-online) social networking groups e.g. a film/book club. Irrespective of electronic or non-electronic recruitment, participants completed 'hard-copies' of the various measures.

In the fifth cohort a variety of recruitment techniques were utilised. Advertisements were placed via a number of media including radio, mass email distribution systems, and web-based advertisements. Additionally (online) social network snowballing in the same vein as applied by Stirling, Morris and McCoy (2012) were employed. All participants in the fifth cohort were directed to a website which contained study information and a link to a web-based questionnaire, in a very similar manner to the method of collecting data utilised for the clinical respondents.

Clinical respondents

A total of 413 participants initiated a data entry, of those 299 participants progressed to the final page of the measures and thus were retained in the data set (see Section 2.2.6 pp. 115-17). No system of imputation was adopted consequently, 70 participants that had not completed all items pertaining to one of the scales/subscales were excluded. Of the 229 remaining participants, 22 were excluded as they did not report a diagnoses of depression or one of the psychotic disorders under consideration and 56 were excluded as they did not report a diagnoses of a mental illness. Please note that due to recruitment methods (i.e. attempts to recruit clinical respondents) these participants were not deemed eligible for inclusion in the community sample groups. Fifteen participants were excluded from the DD group as they had also reported a diagnosis of bi-polar mood disorder. A further three participants were also excluded, two of whom reported a diagnosis of epilepsy and one of whom reported heavy metal poisoning.

After inclusion and exclusion criteria were applied 85 participants remained in the DD group and 48 in the PD group.

To facilitate recruitment numerous study advertisements were placed in strategic locations in both virtual (see Appendix 2) and physical environments (see Appendix 3). Advertisements were distributed to the service users of mental health charity the African and Caribbean Mental Health Services, Manchester. Advertisements were also placed in magazines/newsletters, distributed by national mental health charities MakingSpace, and Rethink (formerly the National Schizophrenia Fellowship). MakingSpace also promoted the study directly to their service users via their care co-ordinators. Rethink further promoted the study through their website, Facebook page and Twitter service.

Internet based self-help and social networking website ‘Schizofriend.me’ promoted the study by direct messaging to their service users. Study information was also distributed by the research network Schizophrenia Research Forum. Discussion forums directed at people suffering with mental health problems (and their family members) ‘Psychforums.com’ and ‘Schizophrenia.com’ facilitated the posting of study information in their forum section. Mental health information website Psyweb.com promoted the study via their website alongside an article detailing the background of the investigation.

In addition to organisations pertaining to mental illness distributing study information, some pertaining to drug use also helped. Drugsforum.com an organisation providing recreational drugs information and a medium for discussions posted information to their users. Two cannabis lobbying groups the UK Cannabis Internet Activists, and CLEAR: Cannabis Law Reform, carried study information on their website in addition to articles detailing the background of the research.

2.2.3 Measures

Basic demographic information and mental health (Appendix 4)

All participants provided basic demographic information (i.e. age and sex). Clinical respondents additionally provided a synopsis of their current and past mental health, including summary information about current and past pharmacological and psychological treatments and frequency of medication adherence. Each of these six items consisted of two parts; the first is a dichotomous, 'Yes' or 'No' answer e.g. 'I am currently receiving treatment for a nervous / psychological disorder'; the second part is an open ended text box e.g. '(If previous answer was YES) What nervous / psychological disorder(s) are you being treated for?' The only item which did not take this form was regarding medication adherence frequency (ie. If you are/were taking medication, did/do you take your medication as often as the doctor or pharmacist told you to?), which was scored on a five-point scale ranging from 'Rarely or never' to 'Always or almost always'.

Schizotypal Personality Questionnaire- Brief

All participants completed the SPQ-b (Raine and Benishay, 1995). The SPQ-b contains 22-items, which represent the most reliable items from the Schizotypal Personality Questionnaire (Raine, 1991, Raine and Benishay, 1995). The SPQ-b contains statements such as 'Sometimes I'm sure that other people can tell what I'm thinking'. Each item allows for only a dichotomous response either 'Yes' or 'No'. The SPQ-b provides a total schizotypy score and three subscale scores. The subscales contain items pertaining to cognitive-perceptual deficits, interpersonal deficits and deficits of (dis)organisation.

The Cannabis Experiences Questionnaire (See Appendix 1 for items)

The CEQ currently (version 8) comprises of four sections, the first records cannabis use history relating to; frequency of use; total amount consumed; environment of consumption; expenditure; age at first use; and type of cannabis used. The second section is in regards to drug use other than cannabis. The third

and fourth sections comprise a checklist of cannabis induced experiences and form the substantive part of the questionnaire. The third section (43-items) relates to the concurrent effects of the drug (experiences the participant has whilst intoxicated). The fourth section (12-items) is a checklist of after effects of cannabis (experiences the user has after initial intoxication has subsided). Various means of scoring the CEQ have been employed (see Barkus and Lewis, 2008; Stirling et al., 2008). However, the current investigation will utilise the method of scoring derived from the most recent Principal Component Analysis (PCA) conducted by John Stirling in 2010. This was conducted on the largest combined database of respondents available.

The 2010 PCA is not published elsewhere, thus the associated pattern matrix has been included in Appendix 1. This analysis indicated that the items disaggregated into three factors scoring an eigenvalue larger than two. This three factor solution was confirmed by the associated scree plot (see Appendix 1). The first factor accounted for 25.46% of variance and contained 20 items with a unique factor loading greater than 0.4. Three of these items originated from section four pertaining to the after effects. These items were labelled the aversive scale and contained experiences that most users would typically find unpleasant e.g. Feeling fearful. The second factor accounted for 10.33% of variance and contained 16 items (> 0.4 factor loading). These items were labelled the appetitive scale and contained experiences that most users would typically find enjoyable e.g. Feeling ecstatic. The third factor accounted for 6.46% of variance and contained 10 items (>0.4 factor loading), 7 of which originated from the section pertaining to after effects. These items were labelled the intoxicated scale and contained experiences associated with the effects after the prominent psychoactive effects have subsided e.g. feeling generally slowed down.

Please note that since the questionnaires original development the measure has evolved and as a consequence several of the cohorts described above have completed previous versions. The version completed by Cohort 1 and the majority of Cohort 2 had no section two and a substantially reduced section one thus no information about other drug use was collected and only minimal information about cannabis consumption was recorded. Cohort 3 completed a version of the CEQ

translated into Dutch. In this cohort due to ethical restrictions section two was not included as part of the questionnaire. Cohort 4 completed both sections one and two, however, the information contained in section two has not been retained. Consequently, there are only complete datasets of information from section 2 of the CEQ (Other drug use) for Cohorts 5 and the clinical respondents. Despite the CEQ now being in its eighth version throughout its development the substantive part of the questionnaire (the checklists of experiences) have remained consistent.

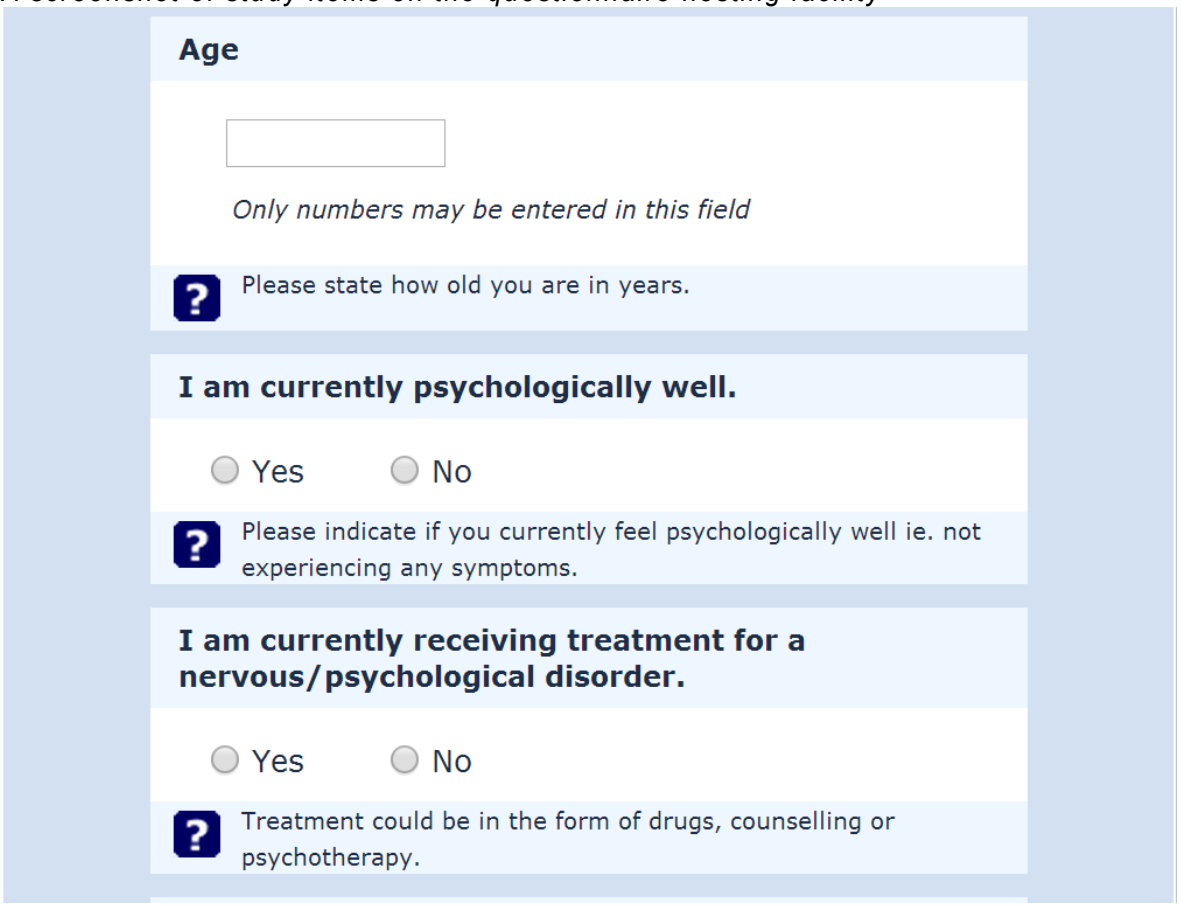
2.2.4 Pilot Study

A piloting procedure was undertaken to determine the suitability of the website design and item presentation. Ten participants (female n =7) were opportunistically recruited from a psychology student undergraduate population. These participants accessed the various pages of the website and completed the measures presented. The participants were then requested to comment on ease of access; ease of interpretation; clarity of presentation; and item presentation.

The feedback received from the participants was broadly very positive. Nonetheless, as a result of the piloting additional information was added to a help box underneath the majority of items presented (see Figure 1). This information was added to help facilitate clarity of interpretation of the items. The format of the display of section 2 of the CEQ (other drugs used) was also altered as a result of the piloting. Initially this section was displayed as a series of branched items with participants requested to state in separate open text boxes each drug (other than cannabis) that they had ever consumed. This method was deemed by the pilot participants to be too laborious and subsequently was replaced with a checklist of some of the most commonly consumed drugs (See Appendix 5).

Figure 1

A screenshot of study items on the questionnaire hosting facility



2.2.5 Procedure

Respondents were given the opportunity of participating electronically or in a 'paper and pen' format, however, none of the hard-copy data returned was eligible for inclusion (see Section 2.2.2 pp. 106-08). Thus, all the clinical respondents (DD and PD) completed the measures 'online' consequently only this procedure will be discussed. Participants were directed to the research group's website via various means (see Section 2.2.2). The website, which was hosted on an internal server, contained; a participant study information sheet (Appendix 6); information detailing the background to the research (Appendix 7); information about other on-going research; information about the ethical approval of the investigation (Appendix 8); the researchers contact details (Appendix 9); and a consent form (Appendix 10).

At the bottom of the consent form was a button to affirm consent, this opened up a 'pop- up' window containing the questionnaire. On the first screen of the 'pop-up' window was a notice requesting any participants who had not affirmed consent to

return to the previous window and do so. This page also briefly summarised some of the study information presented previously (Appendix 11). Participants then clicked a button at the bottom of the window to open up the next page, which contained the items pertaining to demographic information and the mental health questionnaire (Appendix 4). Once this measure was completed the SPQ-b was presented next, with the CEQ presented last (see Appendix 1). Once these items were completed participants were forwarded on to a page expressing the researcher's gratitude. All the submitted data was stored on an internal server, behind a protective firewall.

2.2.6 Ethical considerations

Risks and safe-guarding of participants

The procedure was approved by the MMU research ethics committee, and was also granted approval by RETHINK's ethics committee. To offer an avenue of support to any participant experiencing distress, a list of information groups and support services aimed at addiction, drug use, and mental health were presented on the website. Two participants reported directly to the researcher experiencing distressing symptoms (e.g. suicidal ideation), although they did not suggest that it was as a consequence of participation in the research. In these instances further information regarding support pertaining to those participant's specific issues was forwarded on to them.

Research ethics in a virtual setting

Application of research ethics in an online setting is a complex one in which traditional ethical conventions may not easily be applied, one such example is the right to withdraw. As the participant transitioned through the process of completing the various measures, the participant's data from the previous pages were retained in a database. Thus, allowing for the storage of partial data. There was a button at the bottom right of the screen which automatically erased any partial data submitted. However, in the instance where the participant did not press this button

but, instead navigates away (closes the browser) before the final page, this is taken as withdrawal of their data. Thus, partial data was removed from the dataset.

In an effort to increase response rate and to promote honest and accurate responses participants were offered complete anonymity. However, because of the poorly defined notion of what constitutes a virtual identity after data submission participants were not offered the right to withdraw. If for instance a pseudonym is commonly utilised on a forum page this could reasonably be considered an individual's identity, and thus asking the participants for a pseudonym is not appropriate. Moreover, in the event that a participant wishes to withdraw their data, to do so via electronic means would have resulted in them inadvertently identifying themselves. To further protect anonymity and confidentiality 'cookies' (small identifying pieces of information) were not sent to a participant's computer as these could be used to 'reconstruct' the participants response (at the point of the data's origin).

As cookies were not utilised access to the measures could not be restricted, which presented a challenge for ensuring consent had been given. By simply typing in the URL of the hosted measure it was possible to access it without seeing the consent form or participant information sheet. However, several steps were taken to ensure that this possibility was highly improbable. The research group's purpose built website acted as a gateway in-between any linked pages (e.g. external websites containing advertisements) and the questionnaire. This ensured that there was only one link to the measures posted in a public forum (that attached to the consent form). The URL for these measures was unmemorable and contained a long sequence of alphabetic characters, numbers, and punctuation. This URL was not distributed, placed in Google listings, or (knowingly) linked from another page. Furthermore, on the first page of the hosted measures participants are requested not to proceed unless they have affirmed consent (see Appendix 11).

To further ensure participant confidentiality data was stored on an in-house server. Via the 'in-house' storage of data the robust and regularly updated university

firewall is utilised to prevent malicious attack. However, more importantly this method ensures that the data is never stored outside of the EU and thus, is always subject to the stringent EU data protection laws. If data is stored on servers outside of the EU explicit consent should be sought (from the participant) and established prior to the exportation of data, with the exception of companies with licenses from the Safe Harbor Framework (International Trade Administration, 2013).

2.2.7 Statistical procedures adopted in the analysis

In this investigation no system of imputation was utilised, this was done to ensure that group differences were not minimised or maximised. The results were generated using data analysis software SPSS 19.01 (IBM). Prior to undertaking meaningful analyses of the data, they were assessed for the requisite assumptions applicable to various statistical analyses (Section 2.3.1). As is often convention, the analyses contained within this investigation utilised a *p*-value of less than 0.05 to indicate statistical significance. With the exception of instances when multiple comparisons are made in which case a Bonferroni correction is utilised to adjust alpha to an acceptable level. Utilising Chi^2 and Kruskal-Wallis tests the various groups were assessed for differences in (basic) demographic data and self-reported cannabis related behaviour (Sections 2.3.2). Utilising a Chi^2 test comparison was also drawn between respondents who reported diagnoses of mental illness on data relating to their mental health (Section 2.3.3).

Utilising Kruskal-Wallis, Jonckheere-Terpstra, and Mann-Whitney tests the four groups of respondents (CSCN, CSCU, DD, and PD) were compared for differences on assessments of schizotypy (Section 2.3.4 pp) and assessments of cannabis experiences (Section 2.3.5). The data was assessed in a forced entry multinomial regression model to assess the variables as covariates of group membership (2.3.6). This analysis was also utilised to elucidate any group differences when; an interaction between cognitive-perceptual deficits and aversive cannabis experiences were considered (Section 2.3.7); and undiagnosed or unreported mental illness is controlled for (Section 2.3.8).

2.3 Results

2.3.1 Assessing the assumptions of the analyses

This section considers the variables which must be assessed for statistical assumptions including; SPQ-b total score; SPQ-b cognitive-perceptual, interpersonal and disorganised subscales; CEQ aversive, appetitive, and intoxicated scales; and several indices of cannabis use.

Assessing the distribution of the indices of cannabis use

Participants responded to interval and scale items pertaining to frequency of cannabis use, weekly expenditure, number of lifetime uses, and age. Histograms were generated and the distribution of the data was examined. The results of a Kolmogorov-Smirnov test of distribution indicate that for all the variables under assessment in each of the three groups the data are significantly non-normally distributed (See Appendix 12). Furthermore, no transformation would correct the distribution due to the differences in distribution between the three groups (i.e. positive and negative skew). Moreover, a Levene's test of homogeneity of variance indicates that for weekly expenditure and age the variances were significantly different for the groups under assessment (see Appendix 13). Therefore, analyses considering these variables will utilise non-parametric statistical techniques.

Assessing the distribution and homoskedasticity of the schizotypal personality questionnaire-brief

The SPQ-b consists of three subscales pertaining to cognitive-perceptual, disorganised, and interpersonal disruption, the sum of which provides a total score on the SPQ-b. The CSCN, CSCU, DD and PD group were assessed independently for homogeneity of variance on each of the SPQ-b subscales and total. In no instance did Levene's *F* attain significance at < .05, thus the variances between the groups are presumed to be homogenous (See Appendix 15).

In addition to an inspection of histograms the data was tested for skewness by a Kolmogorov-Smirnov test. The CSCN and CSCU groups displayed significantly positively skewed data on all three SPQ-b subscales and total score (see Appendix 14). In contrast the DD group displayed a significant negative skew on the cognitive-perceptual and interpersonal subscale. However, this group displayed a significant positive skew on the disorganisation subscale. However, the SPQ-b total score was not found to be non-normally distributed. The data from the participants who had received a diagnosis of a psychotic disorder (PD) displayed negatively skewed data in the three subscales and SPQ-b total score.

Comparison between the four groups suggested equal homogeneity of variance, providing support for one of the assumptions of parametric analysis. Nonetheless, each of the groups submitted significantly skewed data. In this instance a transformation is not appropriate as the associated histograms suggest; the CSCN and CSCU groups have positively skewed data, the PD group displays slightly negatively skewed data, and the DD group submitted both positively and negatively skewed data. Hence, non-parametric statistical methods were utilised when comparing groups on these variables (section 2.3.5).

Assessing the distribution and homoskedasticity of the Cannabis Experiences Questionnaire

Homogeneity of variance was assessed between the cannabis using groups. The three groups were found to be none homogenous in the aversive, appetitive and intoxicated scales (Appendix 17). Nonetheless, an assessment of the assumptions of normality was undertaken for the three scales of the CEQ. A Kolmogorov-Smirnov test was used to assess normality of distribution (Appendix 16), in addition to an inspection of histograms in the three independent groups on all three of the CEQ scales.

The CSCU group displayed a positive significantly non-normal skew on the aversive, appetitive, and intoxicated cannabis experiences scale. The DD group also displayed a positive significantly non-normal skew on the aversive cannabis

experiences scale, and the intoxicated scale. However, the DD groups' distribution on the appetitive scale was not found to be significantly non-normal and displayed a slightly negative skew. The PD group also displayed a positive significantly non-normal skew on the aversive, appetitive, and intoxicated scales. Consequently the data are assumed to violate the assumptions requisite for parametric statistical analyses.

Assessing the assumptions of a logistic regression model

The SPQ-b *total score*, alongside the CEQ scales, was initially assessed for the assumptions of the multinomial logistic regression model; linearity and non-multicollinearity. In an alternative model the CEQ scales not found to violate assumptions, were also assessed with the SPQ-b's *subscales*. In a logistic regression model the notion of a linear relationship between the 'independent' (predictor) variables is violated. "The assumption of linearity in logistic regression, therefore, assumes that there is a linear relationship between any continuous predictors and the logit of the outcome variable" (Field, 2009, p.273). Following the procedure described by Field (2009, p.296) the predictor variables were assessed for linearity with their logit values.

The DD and PD groups were compared against the CSCU as the reference group. The non-significant p-values of the interaction between the SPQ-b total, aversive, and intoxicated scales and their respective log values indicate that the assumptions of linearity have not been violated. However, in comparison of the CSCU group and the DD group there was a significant relationship between the appetitive scale and its log indicating non-linearity between the variables (b = -0.15, Wald χ^2 (1) = 9.82, O.R.0.86, 95% CI 0.79 to 0.95, p = .002). This indicates that in consideration of the comparison of the CSCU and DD group the appetitive variable is not appropriate for a linear log regression model. However, this variable was not shown to have a non-linear relationship when comparing the HCU and PD groups. However, in comparison of the PD and DD group the interaction between the appetitive scale and its log was significant, suggesting a non-linear relationship (b = 0.19, Wald χ^2 (1) = 10.37, O.R.1.22 95% CI 1.08 to 1.37, p =.001).

One approach to address the non-linear relationship would be to transform the data. However, given that the data within the PD and CSCU group indicates linearity (between the variable and its own log) this will necessitate the transformation of data that has met the assumptions. Moreover, within the context of a logistic regression the data is already subject to transformation. However, appetitive experiences are not the phenomena which are of primary interest, thus the scale will be dropped from regression models.

Utilising group membership (CSCU, DD, & PD) as an outcome variable the aversive and intoxicated scales and the SPQ-b total score were assessed within a linear regression model for multicolinearity (Field, 2009, p.297). The associated tolerance and variance inflation factor (VIF) fall within the parameters recommended by Mernard (1995) and Myers (1990) respectively (see Appendix 18). Moreover, the associated variance proportion table did not indicate more than one independent variable having a high proportion of effect on the lower eigenvalues (see Appendix 19).

The SPQ-b subscales were also assessed in a model including the cognitive perceptual, interpersonal, and disorganised subscales as well as the interaction between the subscale and its own log. The interaction between the cognitive-perceptual, disorganised, and interpersonal subscales and their respective log values were non-significant indicating that the assumptions of linearity have not been violated. The aversive and intoxicated scales and the SPQ-b subscales were also assessed within a linear regression model for multicolinearity (Field, 2009, p.297). The associated tolerance and variance inflation factor (VIF) fall within acceptable parameters (Mernard, 1995; Myers, 1990) (see appendix 20). Moreover, the associated variance proportion table did not indicate more than one independent variable having a high proportion of effect on the lower eigenvalues (see Appendix 21).

2.3.2 Participant characteristics

The sample consisted of 85 people who had received a (self-reported) diagnosis of depression (DD). The DD group had a mean age of 30 years (SD 10.83)

consisted of 49 males and 36 females. The sample also contained 48 participants, who reported receiving a diagnosis of a psychotic disorder, PD. This group consisted of 33 participants with a self-reported diagnosis of schizophrenia, 6 who reported psychosis not otherwise specified, 6 who reported schizoaffective disorder, and 3 who reported drug (cannabis) induced psychosis. The PD group had a mean age of 36 years, 27 of the group were male and 21 female.

The community sample of cannabis users (CSCU) (n= 861) had a mean age of 23 years (SD 6.12), and contained 393 males, 465 females, and 3 participants who opted not to state their gender. The other group consisting of a community sample of cannabis naïve participants (CSCN) (n=306) had a mean age of 22 years (SD 7.62), and contained 80 males, 225 females and 1 participant who did not state their gender. There was a significant difference in the distribution of males and females between the four groups (CSCU, CSCN, DD, and PD) (χ^2 (3) = 48.60, p<.001). However, there was no significant difference in the distribution of males and females between the three cannabis using groups (χ^2 (2) = 5.96, p=.051). Trend gender differences in the CSCN and CSCU groups may be due to the recruitment of psychology students, which have a higher proportion of females (Department for Education and Skills, 2007). If only the clinical respondents are considered (DD and PD) there was no significant association of group and gender (χ^2 (2) = 0.24, p=.88).

Table 2

Indicating the number of current and former cannabis users recruited in each cohort

Cohort / Group	Current user	Past user
3	65	40
4	30	21
5	243	222
Community Sample of Cannabis Users total	338	283

The cannabis using groups (CSCU, DD, and PD) significantly differed in the preparation of cannabis that they typically consumed (χ^2 (6) = 74.24, p < .001) (Table 4). The majority of the CSCU group typically consumed sinsemilla. However, in the DD and PD groups traditional herbal cannabis was the most frequently consumed preparation. This could potentially reflect an aversion in

these groups to the most commonly consumed, most potent (relative ∆-9-THC to CBD ratio), and theoretically most detrimental preparation; sinsemilla (D'Souza, et al.,2004, Hardwick & King, 2008). The participants also significantly differed in whether they reported that they were a current or former cannabis user (χ^2 (2) = 29.17, p < .001). The majority of the CSCU and DD group were current cannabis users. In contrast the majority of the PD group were former cannabis users. It is feasible that the psychologically deleterious effect of the substance, on the PD group, has resulted in a greater incidence of abstinence.

No data was collected pertaining to the CSCU group's social context of use, but intriguingly the PD and DD groups significantly differed. A greater proportion of the PD group tended to use cannabis in solely social situations more frequently than their counterparts. This could feasibly be as a consequence of the PD group utilising cannabis to mitigate the social withdrawal vulnerability conferred by their schizotaxic liability. Such an effect has been documented by other investigations (e.g. Salyers & Meuser, 2001) and is discussed in Section 1.6.1. In contrast a greater proportion of the DD group tended to use cannabis alone. Participants also documented the time of day that they tended to use cannabis. Unfortunately, the frequency of participants in each group is insufficient to perform a Chi^2 test between all three groups. Nonetheless, such a test can be performed comparing the CSCU and PD groups (excluding the DD group). There was a significant association between the CSCU and PD groups on the time of day cannabis was used (χ^2 (2) = 48.71, p < .001). The majority of participants in the PD group tended to use cannabis both during the day and night time, whereas the most frequent time of use in the CSCU group was solely at night.

Participants also responded to interval and scale items pertaining to frequency of cannabis use, weekly expenditure, number of lifetime uses, and as discussed previously age. Due to the data violating assumptions (see Section 2.3.1) non-parametric statistical methods, a Kruskal-Wallis ANOVA were employed to determine group differences. The p-values indicate that there are significant differences between the CSCU, DD and PD groups on assessment of; age; the frequency of their cannabis use; and weekly expenditure on cannabis; and age of first use (see Table 3). Despite research indicating that age of cannabis initiation

may be a significant determinant of psychotic mental illness, the mean ranks indicate that the participants in the CSCU group were initiated younger than their DD and PD counterparts (Arseneault et al., 2002; Veen, et al., 2004). There was also a significant difference between the number of self-reported lifetime uses between the PD and DD group.

Table 3
Comparing age and indices of cannabis use in groups of participants

					Kruskal-Wallis		
		CSCU	DD	PD	DF	*H*	p- value
Age	Mean rank	460.66	687.08	822.70	2	114.063	**<.001**
	Median	21.0	27.0	33.0			
Frequency of use	Mean rank	509.74	245.79	374.56	2	73.352	**<.001**
	Median	4.0	1.0	2.0			
Weekly Expenditure	Mean rank	389.24	529.54	464.06	2	32.076	**<.001**
	Median	2.0	4.0	3.0			
Number of lifetime uses	Mean rank	No data	68.64	52.45	1	5.938	**.015**
	Median		1000	300			
Age of first use	Mean rank	435.15	524.94	525.39	2	13.961	**.001**
	Median	16.0	16.0	17.0			

The data indicates that the CSCU group used cannabis more frequently than the clinical respondents. However, their expenditure was substantially lower this may reflect an increase in price between the two data collection periods (community sample, 2004-9; clinical respondents, 2011-3). The PD group had significantly fewer lifetime uses than the DD group, which is feasibly a reflection of an adverse response to the drug.

Table 4
Comparing further indices of cannabis use between groups of participants

		Group				
		CSCU (%)	DD (%)	PD(%)	Chi^2	DF
Type of cannabis used**	Cannabis resin	151 (26.4)	10 (12)	8 (17)		
	Sinsemilla	300 (52.5)	31 (37.3)	8 (17)		
	Traditional herbal cannabis	104 (18.2)	35 (42.2)	24 (51.1)		
	Any/Don't know	16 (2.8)	7 (8.4)	7 (14.9)		
	Total / Test statistic	571	83	47	74.24	6
Current or past user**	Current	338 (54.4)	69 (81.2)	18 (37.5)		
	Past	283 (45.6)	16 (18.8)	30 (62.5)		
	Total / Test statistic	621	85	48	29.17	2
Context of use*	Socially	No data	11 (12.9)	18 (38.3)		
	On your own		12 (14.1)	4 (8.5)		
	Both		62 (71.3)	25 (53.2)		
	Total / Test statistic		85	47	11.43	2
Time of day used	Day	127 (16.5)	2 (2.4)	4 (8.3)		
	Night	536 (69.6)	37 (43.5)	19 (39.6)		
	Day & Night	107 (13.9)	46 (54.1)	25 (52.1)		
	Total	770	85	48		
Frequency of cannabis use	Everyday	140 (16.6)	45 (57)	15 (37.5)		
	More than once a week	149 (17.6)	13 (16.5)	8 (20)		
	About once a week	69 (8.2)	7 (8.9)	5 (12.5)		
	About once or twice a month	175 (20.7)	11 (13.9)	2 (5)		
	A few times each year	168 (19.9)	2 (2.5)	5 (12.5)		
	About once a year	71 (8.4)	1 (1.3)	3 (7.5)		
	About once or twice ever	73 (8.6)	0 (0)	2 (5)		
	Total	845	79	40		
Weekly Expenditure	<£2.50	302 (44.1)	15 (17.6)	14 (31.1)		
	£2.50-£5	86 (12.6)	9 (10.6)	3 (6.7)		
	£5.01-£10	70 (10.2)	14 (16.5)	6 (13.3)		
	£10.01-£15	43 (6.3)	6 (7.1)	3 (6.7)		
	£15.01-£20	72 (10.5)	9 (10.6)	9 (20.0)		
	>£20	112 (16.4)	32 (37.6)	10 (22.2)		
	Total	685	85	45		

*p<.01 **p<.001

2.3.3 Comparing those with reported depression and those with reported psychotic disorder

All clinical respondents (DD and PD) completed an additional questionnaire which pertained to their current and previous mental health. Those diagnosed with depression (DD) and those diagnosed with a psychotic disorder (PD) did not differ significantly in their self-assessment of currently being psychologically well (see table 5). However, the PD group were significantly more likely to be currently taking medication than the DD group (χ^2 (1) = 21.10, p<.001). This is feasibly as a result of the PD population receiving a maintenance dose of medication, which is a common course of treatment for schizophrenia (NICE, 2010, p.98). The majority (68.8%) of the PD group had a (self-reported) diagnosis of schizophrenia. The data reflects the differences in the courses of the two clusters of disorders. Schizophrenia tends to run a more chronic course, with only "a small number of individuals reported to recover completely" (APA, 2013a p.102). This is evinced in the data with members of the PD group being significantly more likely to be currently receiving a non-pharmacological (psychological) treatment (χ^2 (1) = 4.29, p=.038). Nonetheless, participants in the PD and DD group did not differ significantly in their previous experience of taking medication or receiving a non-pharmacological treatment for their mental illness (see Table 5). Neither did the participants significantly differ in their self-reported medication adherence (Kruskal Wallis, U=1458, *Z*=-1.06, p=.29).

The results of the comparisons contained within this section indicate that the two groups do not differ significantly in their previous experiences of medication and non-pharmacological intervention, on the indices under assessment. However, the PD group were significantly more likely to be currently taking medication and receiving psychological intervention. Nonetheless, there was no significant difference between the DD and PD group on the self-reported assessment of being currently psychologically well. Thus, indicating that the increased likelihood of current intervention in the PD group is a consequence of the chronicity of the disorder, as opposed to greater incidence of acute illness.

Table 5
Comparing current and previous mental health of participants with reported depression and reported psychotic disorder

		Group		Chi^2
		Depression Diagnosed (%)	Psychosis Diagnosed (%)	
Currently psychologically well?	Yes	51 (60)	26 (54.2)	
	No	34 (40)	22 (45.8)	
	Total / χ^2	85	48	0.43
Currently taking medication?* **	Yes	38 (44.7)	41 (85.4)	
	No	47 (55.3)	7 (14.6)	
	Total / χ^2	85	48	21.10
Currently receiving a non-pharmacological treatment?*	Yes	19 (22.6)	19 (39.6)	
	No	65 (77.4)	29 (60.4)	
	Total / χ^2	84	48	4.29
Previously taken medication?	Yes	68 (81)	35 (74.5)	
	No	16 (19)	12 (25.5)	
	Total / χ^2	84	47	0.75
Previously received a non-pharmacological treatment?	Yes	59 (70.2)	33 (68.8)	
	No	25 (29.8)	15 (31.3)	
	Total / χ^2	84	48	0.03

*p<.05 **p<.01 ***p<.001, All degrees of freedom =1

2.3.4 Cannabis use, Diagnosis and differential schizotypal trait

Analysis contained within this section contributes to one of the primary aims of this chapter: To assess variance in schizotypal trait related to cannabis use and reported mental illness. As the data was found to be non-normally distributed (see section 2.3.1 and Appendices 14 & 15) a non-parametric alternative to analysis of variance, a Kruskal-Wallis test, was performed. The CSCN, CSCU, DD, and PD, groups were compared for differences on the three SPQ-b subscales and the total score. The four groups significantly differed in their scores on the cognitive perceptual subscale (H (3) = 40.92, p < .001), interpersonal subscale (H (3) = 76.60, p < .001), disorganised subscale (H (3) = 72.31, p < .001), and SPQ-b total (H (3) = 79.68, p < .001) (see Table 6).

A linear effect (by the definition of the phrase) between the groups is not hypothesised as they are categorically and substantively different. For example, there may be differences in schizotypal personality between the CSCN group and the CSCU group. However, these variances are substantively, physiologically, and theoretically different from the variances that will be displayed between the DD and PD groups. Moreover, a linear effect may presume that the differences

between the lowest scoring group and the second to lowest scoring group, is twice the difference of the lowest scoring group and the third lowest scoring group. Thus, a true linear effect between the groups would be an unreasonable hypothesis to address. However, some would argue that if the DD group were omitted with sufficient data a true linear effect may be observed within a continuum model of psychosis and schizotypal personality (See Section 1.2.2). Nonetheless, a reasonable hypothesis to test would be one asserting that the groups will display a distinct profile on the SPQ-b with the CSCN, CSCU, DD and PD groups scoring the lowest to highest in that respective order.

Table 6

Measures of central tendency on the SPQ-b by participant groups

		Group			
		CSCN	CSCU	DD	PD
Cognitive-Perceptual	Mean (SD)	2.50 (2.3)	2.53 (2.0)	3.00 (2.1)	4.44 (1.8)
	Median	2	2	3	5
Interpersonal	Mean (SD)	2.87 (2.3)	2.73 (2.3)	4.74 (2.5)	4.92 (2.3)
	Median	3	2	5	5
Disorganised	Mean (SD)	1.54 (1.7)	1.94 (1.7)	3.15 (1.8)	3.08 (1.8)
	Median	1	2	3	3
SPQ-b total	Mean (SD)	6.91 (4.8)	7.20 (4.8)	10.89 (5.4)	12.44 (4.8)
	Median	6	6	11	13

One means in which this notion of a distinct profile, in a distinct order can be tested is through a Jonckheere-Terpstra non-parametric test. A significant trend in the data was noted the median score on the cognitive perceptual subscale significantly increased between the CSCN, CSCU, DD, and PD groups in that respective order, $J = 235661.50$, $z = 3.77$, $r = 0.10$, $p < .001$. A significant trend indicating an increase in the median was also noted between the groups for the interpersonal subscale $J = 240924.50$, $z = 4.57$, $r = 0.13$, $p < .001$, disorganised subscale $J = 260633.50$, $z = 7.703$, $r = 0.21$, $p < .001$, and SPQ-b total $J = 252171.00$, $z = 6.27$, $r = 0.17$, $p < .001$. Although statistically significant the associated effect sizes (r) suggest only a small linear effect of group on schizotypal personality (Cohen, 1988).

Tests of difference in schizotypal trait between two groups of participants

The groups significantly differed in the three SPQ-b subscales, and SPQ-b total. The results of the Jonckheere-Terpstra test suggest a distinct profile of response between the four groups in a distinct (hypothesised) order, albeit with only a small effect size. However, to make inferences pertaining to significant differences between specific groups the non-parametric equivalent of an independent t-test was performed; the Mann-Whitney test. As each pairwise comparison will utilise four variables, a multiple comparison (Bonferroni) adjusted alpha of < .0125 will be utilised.

The CSCU group were tested in a pairwise comparison with the CSCN group for differences in the SPQ-b. The two groups did significantly differ in scores on the SPQ-b disorganised subscale, with the CSCU group scoring significantly higher than the CSCN group, see Table 6 and Table 7. Other investigations have demonstrated an elevated schizotypal personality score in cannabis users in comparison to none cannabis users (e.g. Dumas et al., 2002; Skosnik et al,. 2001). Nonetheless, the effect size is only small accounting for 1.21% of the total variance. However, this was limited to solely that subscale as the two groups did not significantly differ in the cognitive perceptual subscale, the interpersonal subscale, or the SPQ-b total score.

Table 7
Pairwise comparisons of a community sample of cannabis users and a community sample of non-cannabis users on assessments of schizotypy

	CSCN Mean rank	CSCU Mean rank	U	*Z*	Effect size *r*	*p*-value
Cognitive-perceptual	576.42	586.69	129413.50	-0.464	-0.01	.643
Interpersonal	602.78	577.32	125985.00	-1.147	-0.03	.251
Disorganised	**523.83**	**605.38**	**11.3321.50**	**-3.719**	**-0.11**	**<.001**
SPQ-b	568.74	589.42	127064.00	-0.924	0.03	.355

In a pairwise comparison, the DD group were assessed with the CSCU group for differences in the SPQ-b. The two groups did not significantly differ in the cognitive perceptual subscale, after a Bonferroni correction for multiple testing. However, the DD group scored significantly higher than the CSCU group on the

interpersonal, and disorganised subscales, and SPQ-b total score (see Tables 6 & 8). Nonetheless, the effect size indicates only a small effect accounting for 4.84%, 3.61% and 4% of the total variance respectively. The lack of statistical difference in the cognitive-perceptual subscale may be as a consequence of the cannabis use in the CSCU group. This notion may be tested by comparing the cannabis naïve group (CSCN) with the DD group (U = 11088.50, z = -2.10, p < .035, r = -0.11). The significant difference suggests that cannabis use is diminishing the differences between the CSCU group and the DD group, or that a Bonferroni correction resulted in the adoption of too conservative a p. value.

Table 8
Pairwise comparisons of a community sample of cannabis users and cannabis users with a reported diagnosis of depression on assessments of schizotypy

	CSCU Mean rank	DD Mean rank	U	Z	Effect size *r*	*p*-value
Cognitive-perceptual	**467.86**	**530.58**	**31740.50**	**-2.043**	**-0.07**	**.041**
Interpersonal	**454.71**	**663.83**	**20414.50**	**-6.798**	**-0.22**	**<.001**
Disorganised	**457.78**	**632.74**	**23057.50**	**-5.732**	**-0.19**	**<.001**
SPQ-b	**456.78**	**642.89**	**22194.00**	**-6.003**	**-0.20**	**<.001**

A pairwise comparison was also performed to draw comparison between the PD and DD groups. The PD group scored significantly higher than the DD group on the cognitive perceptual subscale (see Tables 6 & 9). The effect size is within the boundaries of what is widely regarded as medium, accounting for 11.56% of total variance (Cohen, 1988). However, the two groups did not significantly differ in scores on the interpersonal and disorganised subscale or the SPQ-b total score. However, the SPQ-b total did have a small effect size accounting for 1.96% of total variance.

Table 9
Pairwise comparisons of cannabis users with reported diagnoses of depression and psychotic disorder on assessments of schizotypy

	DD Mean rank	PD Mean rank	U	Z	Effect size *r*	*p*-value
Cognitive-perceptual	**57.34**	**84.11**	**1218.50**	**-3.885**	**-0.34**	**<.001**
Interpersonal	66.25	68.32	1976.50	-0.300	-0.03	.764
Disorganised	67.44	66.23	2003.00	-0.176	-0.02	.861
SPQ-b	62.81	74.42	1684.00	-1.671	-0.14	.095

Comparison was also drawn between the CSCU and PD groups. As would be expected (see Section 1.2.2), the PD group scored significantly higher than the CSCU group on the cognitive-perceptual, interpersonal and disorganised subscales, and the total score (see Tables 6 & 10). However, only a small effect size was observed with only 4%, 3.61%, 1.96%, and 4.84% of total variance explained respectively (Cohen, 1988).

Table 10
Pairwise comparisons of cannabis users from a community sample and cannabis users with reported psychotic disorder on assessments of schizotypy

	CSCU Mean rank	PD Mean rank	U	Z	Effect size *r*	*p*-value
Cognitive-perceptual	**442.69**	**675.82**	**10064.50**	**-6.056**	**0.20**	**<.001**
Interpersonal	**443.13**	**667.89**	**10445.50**	**-5.832**	**0.19**	**<.001**
Disorganised	**446.36**	**609.98**	**13225.00**	**-4.281**	**0.14**	**<.001**
SPQ-b	**441.59**	**695.56**	**9117.00**	**-6.536**	**0.22**	**<.001**

2.3.5 Cannabis use, Diagnosis and Cannabis Experiences

Analysis contained within this section contributes to one of the primary aims of this chapter: To assess the presence of a differential sensitivity to the psychotomimetic effects of cannabis in those with psychotic illness. A Kruskal-Wallis test was performed to assess differences between the CSCU, DD, and PD groups on the three CEQ scales. The three groups significantly differed in their scores on the aversive scale (H (2) = 14.17, p < .001), and the appetitive scale (H (3) = 14.06, p = .001). However, the groups did not significantly differ on the intoxicated scale (H (3) = 4.62, p = .101).

Table 11
Measures of central tendency on the CEQ by participant groups

		Group CSCU	DD	PD
Aversive	Mean (SD)	14.77 (14.02)	11.44 (11.22)	22.15 (17.52)
	Median	11.00	10.00	17.00
Appetitive	Mean (SD)	16.88 (9.93)	20.85 (8.46)	16.92 (11.68)
	Median	17.00	21.00	12.50
Intoxicated	Mean (SD)	17.00 (8.82)	14.87 (7.52)	16.85 (8.70)
	Median	16.00	14.00	16.00

The groups were tested for group differences, by means of a linear effect (see Section 2.3.4) between the CSCU, DD, and PD groups in that respective order. A significant trend in the data was not noted in the median score of either the aversive scale (J = 61213.00, z = 0.62, r = 0.02, p =.532), or intoxicated scale (J = 53908.50, z = -1.75, r = -0.06, p .079). In the assessment of the statistical assumptions (Section 2.3.1 pp.118-121) the appetitive scale indicated a non-linear effect, thus this variable will not be assessed for a linear effect between groups.

Tests of difference in Cannabis Experiences between cannabis users diagnosed with depression and those diagnosed with a psychotic disorder

Pairwise comparisons were performed utilising the non-parametric equivalent of an independent t-test; the Mann-Whitney test. The three groups of cannabis using respondents will be assessed for differences in their aversive, appetitive, and intoxicated cannabis experiences. The three scales will be tested simultaneously consequently a Bonferroni correction for multiple tests is applied, at p< .017.

The CSCU group were tested for pairwise differences with the DD groups (see Tables 11 & 12). The participants did not significantly differ in their aversive experiences, nor their intoxicated experiences after a Bonferroni correction. However, the two groups did differ in their appetitive cannabis experiences with the DD group having significantly more pleasurable cannabis experiences than their counterparts in the community sample. Albeit, with only a small effect size accounting for only 1.44% of the total variance.

Table 12
Pairwise comparisons of a community sample of cannabis users and cannabis users with reported depression on assessments of cannabis induced experiences

	CSCU Mean rank	DD Mean rank	U	Z	Effect size *r*	*p*-value
Aversive	478.66	421.26	32152.50	-1.849	-0.06	.064
Appetitive	**463.14**	**578.42**	**27674.00**	**-3.713**	**-0.12**	**<.001**
Intoxicated	479.48	412.88	31439.50	-2.145	-0.07	.032

The community sample of cannabis users (CSCU) were also compared to the group of participants who had reported a diagnosis of a psychotic disorder (PD)

(see Tables 11 & 13). The PD group had significantly more aversive cannabis experiences than the community sample. However, the effect size was small, accounting for only 1% of the variance in the data. The two groups did not significantly differ in their appetitive or intoxicated cannabis induced experiences.

Table 13
Pairwise comparisons of a community sample of cannabis users and cannabis users with reported psychotic disorder on assessments of cannabis induced experiences

	CSCU Mean rank	PD Mean rank	U	Z	Effect size *r*	*p*-value
Aversive	**448.55**	**570.78**	**15106.50**	**-3.142**	**-0.10**	**.002**
Appetitive	455.81	440.50	19968.00	-0.393	-0.01	.694
Intoxicated	455.56	445.04	20186.00	-0.270	-0.01	.787

The DD group were tested for pairwise differences with the PD group (see Tables 11 & 14). The PD group had significantly more aversive cannabis experiences than the DD group. The associated effect size falls within the parameters of what is deemed a medium effect size (Cohen, 1988), accounting for 10.24% of variance in the data. The converse was found in the Appetitive scale with the DD group reporting significantly more appetitive cannabis experiences in comparison to the PD group. However, with only a small effect size accounting for 4.41% of the total variance (Cohen, 1988). The two groups did not significantly differ in their intoxicated experiences associated with cannabis (see Table 14).

Table 14
Pairwise comparisons of cannabis users with reported depression and cannabis users with reported psychotic disorder on assessments of cannabis induced experiences

	DD Mean rank	PD Mean rank	U	Z	Effect size *r*	*p*-value
Aversive	**57.60**	**83.65**	**1241.00**	**-3.746**	**-0.32**	**<.001**
Appetitive	**73.12**	**56.17**	**1520.00**	**-2.438**	**0.21**	**.015**
Intoxicated	64.14	72.06	1797.00	-1.140	-0.10	.254

2.3.6 Covariates (predictors) of psychotic mental illness

Assessing the CEQ scales as predictors of mental illness

Analysis contained within this section and Sections 2.3.7 and 2.3.8 contribute to one of the primary aims of this chapter: To assess the utility of assessments of cannabis induced experience and schizotypal trait as predictors of psychotic illness in cannabis using populations. The data was assessed via a multinomial logistic regression model, utilising a forced entry method. The three independent groups of cannabis users (CSCU, DD, and PD) were considered as an outcome variable, with the aversive and intoxicated scales as the predictor variables. This model will be referred to as 'the base model'. The groups were assessed initially with the CSCU as the baseline category and then DD as the reference category to produce three separate comparisons CSCU vs PD, DD vs PD, and also incidentally CSCU vs DD. Therefore, the model was computed in regards to PD vs reference category (CSCU or DD). This manner of running the regression model allows for the respective odds ratios to reflect an increase in the odds of membership to the PD group, i.e. a psychotic outcome.

The model fitted to the data (aversive and intoxicated scales as predictors, see Table 15) was significantly better at predicting the data than the intercept, χ^2 (4) = 22.451, $p < .001$. Goodness of fit was assessed with both the Pearson (χ^2 (1218) = 1221.20, $p = .47$) and Deviance (χ^2 (1218) = 670.664, $p = 1.00$) method and both assessments suggest a good fit of the model respectively. Cox and Snell's R^2 indicates the model explains only 2.2% of the response data and Nagerlkerke's R^2 indicates that the model explains 3.6% of the data. Thus, the associated pseudo R^2 values indicate that the model may not be an accurate means of assessing diagnosis.

Neither the aversive or intoxicated scales were significant predictors of membership to the CSCU in comparison to the DD group, i.e. these scales could not differentiate between a community sample of respondents and those diagnosed with depression (see Table 15). However, both the aversive ($b = 0.42$, Wald χ^2 (1) = 17.06, O.R.1.04, 95% CI 1.02 to 1.07, $p< .001$) and intoxicated ($b = -0.45$, Wald χ^2 (1) = 4.93, O.R.0.96, 95% CI 0.92 to 0.995, $p = .026$) scales were

significant predictors of whether the participant was in the CSCU or PD group. Thus indicating that cannabis induced phenomenology may be utilised to predict psychotic illness. With each unit increase on the aversive scale the odds of being in the PD group increased by 4.3%, whereas the same increase in the intoxicated scale decreased the odds of being in the PD group by 4.4%. The DD group was also assessed along with the PD group as outcome variables. The intoxicated scale did not significantly predict a diagnosis of depression or psychotic disorder. However, the aversive scale was a significant predictor of diagnosis (*b* = 0.06, Wald χ^2 (1) = 14.24, O.R.1.06, 95% CI 1.03 to 1.09, $p < .001$) indicating that these groups may be differentiated on these experiences. Each unit increase on the aversive scale increased the odds of having a diagnosis of psychosis by 5.8%.

Table 15

A multinomial forced entry regression model predicting group membership as a function of aversive and intoxicated cannabis experiences

		Beta	(SE)	OR	P	95% CI of O.R.	
						Lower	Upper
CSCU Vs DD	**Intercept**	**-1.855**	**0.235**		**<.001**		
	Aversive	-0.014	0.011	0.986	.233	0.964	1.009
	Intoxicated	-0.018	0.016	0.982	.278	0.951	1.014
CSCU Vs PD	**Intercept**	**-2.890**	**0.321**		**<.001**		
	Aversive	**0.042**	**0.010**	**1.043**	**<.001**	**1.023**	**1.065**
	Intoxicated	**-0.045**	**0.020**	**0.956**	**.026**	**0.918**	**0.995**
DD Vs PD	**Intercept**	**-1.035**	**0.384**		**.007**		
	Aversive	**0.056**	**0.015**	**1.058**	**<.001**	**1.027**	**1.089**
	Intoxicated	-0.270	0.025	0.973	.279	0.926	1.022

The SPQ-b subscales and the CEQ scales as predictors of psychotic illness and depression

The results presented in Section 2.3.4 indicate that the three SPQ-b subscales may not equally contribute to predicting a diagnosis of a psychotic disorder and by considering the SPQ-b total score as opposed to the subscales may result in loss of precision. For example in pairwise comparison the cognitive perceptual subscale was significantly higher in the PD group in comparison to the DD group (U = 1218.50, z = -3.89, p < .001, r = -0.34), however the groups did not differ in the SPQ-b total score (U = 1684.00, z = -1.671, p = .095, r = -0.14) (see Table 9). Consequently, in the assessment of the SPQ-b as a predictor in a regression model the subscales will be considered independently (see Table 16). The cognitive-perceptual, interpersonal, and disorganised SPQ-b subscales were assessed along with the aversive and intoxicated scales in a forced entry multinomial regression. This model will be referred to as 'Base + SPQ'. The aversive and intoxicated CEQ scales and the SPQ-b subscales were significantly better at predicting the data than the intercept (χ^2 (10) = 138.527, p < .001). Both the Pearson (χ^2 (1974) = 1821.210, p = .994) and Deviance (χ^2 (1974) = 817.802, p =1.00) methods suggest a good fit of the model. Cox and Snell's R^2 indicates the model explains 13.0% of the response data and Nagerlkerke's R^2 indicates that the model explains 21.1% of the data.

In comparing the CSCU and DD groups aversive cannabis experiences were significant predictors of group membership (b = -0.04, Wald χ^2 (1) = 8.49, O.R. 0.96, 95% CI 0.93 to 0.99, p< .004). Each unit increase on the aversive scale predicted a decrease of 3.8% in the odds of being a member of the DD group. The intoxicated scale did not significantly predict group membership. However, both the interpersonal (b = 0.33, Wald χ^2 (1) = 30.00, O.R.1.39, 95% CI 1.23 to 1.56, p < .001) and disorganised (b=0.30, Wald χ^2 (1) = 13.75, O.R.1.35, 95% CI 1.15 to 1.58, p < .001) SPQ-b subscales significantly predicted a diagnosis of depression. A unit increase on the interpersonal and disorganised subscales predicted a 38.5% and 34.8% increase in the odds of a diagnosis of depression.

In comparison of the CSCU and PD groups aversive cannabis experiences did not significantly predict group membership. However, the intoxicated scale did

significantly predict a psychotic diagnosis (*b* = -0.06, Wald χ^2 (1) = 6.76, O.R.0.95, 95% CI 0.91 to 0.99, *p* = .009). A unit increase on the intoxicated scale predicted a decrease of 5.4% on the odds of a diagnosis of a psychotic disorder. The two groups were also significantly predicted by the cognitive-perceptual subscale (*b* = 0.29, Wald χ^2 (1) = 10.44, O.R.1.34, 95% CI 1.12 to 1.59, *p* = .001) and interpersonal subscale (*b* = 0.25, Wald χ^2 (1) = 10.45, O.R.1.28, 95% CI 1.10 to 1.49, *p* = .001). Each unit increase on the cognitive-perceptual and interpersonal subscales predicted an increase in the odds of a diagnosis of psychosis by 33.5% and 28.1% respectively. However, the disorganised subscale was not a significant predictor.

In comparison of the DD and PD groups the aversive scale was a significant predictor of group membership (*b* = 0.06, Wald χ^2 (1) = 11.70, O.R.1.06, 95% CI 1.03 to 1.10, *p*< .001). Each unit increase on the aversive scale predicted a 6% increase in the odds of a psychotic diagnosis, in comparison to one of depression. The intoxicated scale however, was not a significant predictor. Two of the SPQ-b subscales were significant predictors of the outcome variable; the cognitive-perceptual subscale (*b* = 0.36, Wald χ^2 (1) = 10.94, O.R.1.43, 95% CI 1.16 to 1.77, *p* <.001) and the disorganised subscale (*b* = -0.30, Wald χ^2 (1) = 5.67, O.R.0.74, 95% CI 0.58 to 0.95, *p* = .017). Each unit increase on the cognitive-perceptual subscale predicted an increase of 42.9% in the odds of being in the PD group. Conversely each unit increase in the disorganised total predicted a decrease of 26.0% in the odds of a psychotic diagnosis. Given that the SPQ-b is a measure of schizotypy, a trait highly linked with schizophrenia, this is an unexpected finding.

The data contained within this section supports the notion of assessing the three SPQ-b subscales independently. In comparison of the CSCU and PD group the cognitive perceptual and interpersonal subscales were significant positive predictors of psychotic illness, but the disorganised subscale was not. In comparison with the DD and PD groups the cognitive perceptual subscale was a significant positive predictor of psychotic illness, but the disorganised subscale was a significant negative predictor.

Table 16

A multinomial forced entry regression model predicting group membership as a function of aversive and intoxicated cannabis experiences and schizotypal trait

		Beta	(SE)	Odds Ratio	P	95% CI of O.R. Lower	Upper
CSCU Vs DD	**Intercept**	**-3.179**	**0.327**		**<.001**		
	Aversive	**-0.038**	**0.013**	**0.962**	**.004**	**.938**	**.988**
	Intoxicated	-0.026	0.017	0.974	.127	.942	1.007
	Cognitive-Perceptual	-0.068	0.070	0.935	.335	.814	1.072
	Interpersonal	**0.326**	**0.059**	**1.385**	**<.001**	**1.233**	**1.556**
	Disorganised	**0.299**	**0.081**	**1.348**	**<.001**	**1.151**	**1.579**
CSCU Vs PD	**Intercept**	**-4.228**	**0.444**		**<.001**		
	Aversive	0.019	0.012	1.020	.105	0.996	1.044
	Intoxicated	**-0.055**	**0.021**	**0.946**	**.009**	**0.908**	**0.986**
	Cognitive-Perceptual	**0.289**	**0.089**	**1.335**	**.001**	**1.120**	**1.591**
	Interpersonal	**0.247**	**0.077**	**1.281**	**.001**	**1.102**	**1.488**
	Disorganised	-0.002	0.105	0.998	.984	0.812	1.226
DD Vs PD	**Intercept**	**-1.048**	**0.533**		**.049**		
	Aversive	**0.058**	**0.017**	**1.060**	**.001**	**1.025**	**1.095**
	Intoxicated	-0.029	0.026	0.971	.255	0.924	1.021
	Cognitive-Perceptual	**0.357**	**0.108**	**1.429**	**.001**	**1.156**	**1.765**
	Interpersonal	-0.078	0.092	0.925	.397	0.771	1.108
	Disorganised	**-0.301**	**0.126**	**0.740**	**.017**	**0.578**	**0.948**

2.3.7 Interactions between schizotypal trait and aversive cannabis experiences as predictors of psychotic illness

In Section 2.3.6 there is data presented indicating that the cognitive-perceptual subscale of the SPQ-b may be proficient in distinguishing those participants diagnosed with a psychotic disorder, from a healthy population and from those diagnosed with depression. The analyses contained in Section 2.3.6 indicate that the aversive scale is a significant predictor of psychotic mental illness, when compared to the DD group. This section seeks to ascertain if liability to cognitive-perceptual deficit may interact with aversive cannabis experiences to act as a significant predictor of psychotic mental illness (see Table 17).

The aversive scale and cognitive-perceptual scale are initially centred around the mean value for the total of the three groups of participants. These variables are then multiplied to create the interaction term. The SPQ-b subscales, the aversive and intoxicated CEQ scales and the interaction term between the cognitive-perceptual scale and the aversive scale were entered into a multinomial regression in a forced entry fashion. This model is referred to as 'Base + SPQ + X', where X denotes the interaction term. The model fitted was significantly better at predicting the data than the intercept, χ^2 (12) = 143.840, p < .001. The Pearson (χ^2 (1972) = 1905.99, p = .85) and Deviance (χ^2 (1972) = 812.49, p = 1.00) assessments suggest a good fit of the model. Cox and Snell's R^2 indicates the model explains 13.5% of the response data and Nagerlkerke's R^2 indicates that the model explains 21.8% of the data. Thus, suggesting that this model is the most accurate means of assessing group membership discussed so far. Nonetheless, the likelihood ratio test indicates that the interaction term may not in itself be significantly improving the model (-2LL = 817.80, χ^2 (2) = 5.31, p = .070).

In comparison with the community sample of cannabis users (CSCU) and those diagnosed with depression (DD), group membership was significantly predicted by aversive cannabis experiences (b = -0.39, Wald χ^2 (1) = 7.07, O.R.0.96, 95% CI 0.94 to 0.99, p = .008). Each unit increase on the aversive scale reduced the odds of a diagnosis of depression by 3.8%. The intoxicated scale was not a significant predictor of group membership. However, both the interpersonal (b = 0.33, Wald χ^2 (1) = 29.896, O.R.1.39, 95% CI 1.23 to 1.56, p < .001) and disorganised (b = 0.30, Wald χ^2 (1) = 13.93, O.R.1.35, 95% CI 1.15 to 1.58, p < .001) SPQ-b subscales were significant predictors of the groups. Each unit increase on the interpersonal and disorganised subscale accounted for an increase of 38.5%, and 35.1% (respectively) in odds of a diagnosis of depression.

In comparison of the community sample of cannabis users (CSCU) and those diagnosed with a psychotic illness (PD), diagnosis was significantly predicted by both aversive and intoxicated experiences (respectively, b = 0.37, Wald χ^2 (1) = 8.09, O.R.1.04, 95% CI 1.01 to 1.07, p = .004, b = -0.54, Wald χ^2 (1) = 6.97, O.R. 0.95, 95% CI 0.91 to 0.99, p = .017). Each unit increase in the aversive scale predicted an increase of 3.8% in the diagnosis of a psychotic illness, whereas the

same increase in the intoxicated scale predicted a 5.3% decrease. Both the cognitive perceptual and interpersonal subscales were significant predictors of group membership (respectively, b = 0.35, Wald χ^2 (1) = 13.86, O.R. 1.43, 95% CI 1.18 to 1.72, p <.001, b = 0.24, Wald χ^2 (1) = 10.22, O.R. 1.27, 95% CI 1.10 to 1.48, p = .001). Each unit increase in the cognitive-perceptual and interpersonal subscale predicted a respective increase 42.5% and 27.3% in the odds of a diagnosis of psychosis. There was also a significant, albeit negative interaction between the cognitive perceptual and aversive scales (b = -0.01, Wald χ^2 (1) = 5.19, O.R.0.99, 95% CI 0.98 to 0.99, p = .023). This indicates that a unit increase in the interaction term served to decrease the odds of a diagnosis of psychosis by 0.9%. This unexpected finding will be discussed in Section 2.4.2.

In comparison of the group of participants diagnosed with depression and those diagnosed with a psychotic disorder aversive cannabis experiences were a significant predictor of diagnosis (b = 0.08, Wald χ^2 (1) = 16.02, O.R.1.08, 95% CI 1.04 to 1.12, p <.001). Each unit increase on the aversive scale predicted a 7.9% increase in the odds of having a psychotic diagnosis. The intoxicated and interpersonal scales were not significant predictors, neither was the interaction variable. However, the cognitive-perceptual and disorganised subscales were significant predictors of diagnosis (respectively, b =0.42, Wald χ^2 (1) = 13.60, O.R.1.51, 95% CI 1.22 to 1.89, p <.001, b = -0.30, Wald χ^2 (1) = 5.76, O.R.0.74, 95% CI 0.58 to 0.95, p = .016). Each unit increase of the cognitive-perceptual scale predicted an increase of 51.4% in the diagnosis of a psychotic illness, whereas the same increase in the disorganised subscale predicted a 25.9% decrease.

Table 17

A multinomial forced entry regression model predicting group membership as a function of aversive and intoxicated cannabis experiences, schizotypal trait, and an interaction between the cognitive perceptual and aversive scales

		Beta	(SE)	Odds Ratio	P	95% CI of O.R.	
						Lower	Upper
CSCU Vs DD	**Intercept**	**-3.188**	**0.329**		**<.001**		
	Aversive	**-0.39**	**0.015**	**0.962**	**.008**	**0.935**	**0.990**
	Intoxicated	-0.026	0.017	0.974	.124	0.942	1.007
	Cognitive-Perceptual	-0.061	0.072	1.385	.396	0.817	1.083
	Interpersonal	**0.325**	**0.060**	**0.941**	**<.001**	**1.232**	**1.556**
	Disorganised	**0.301**	**0.081**	**1.351**	**<.001**	**1.154**	**1.583**
	Cog-Per * Aversive	0.000	0.005	1.000	.937	0.990	1.009
CSCU Vs PD	**Intercept**	**-4.681**	**0.526**		**<.001**		
	Aversive	**0.037**	**0.013**	**1.038**	**.004**	**1.012**	**1.065**
	Intoxicated	**-0.054**	**0.021**	**0.947**	**.008**	**0.909**	**0.986**
	Cognitive-Perceptual	**0.354**	**0.095**	**1.425**	**<.001**	**1.183**	**1.715**
	Interpersonal	**0.241**	**0.075**	**1.273**	**.001**	**1.098**	**1.476**
	Disorganised	0.001	0.103	1.001	.991	0.817	1.226
	Cog-Per * Aversive	-0.009	0.004	0.991	.023	0.983	0.999
DD Vs PD	**Intercept**	**-1.493**	**0.603**		**.013**		
	Aversive	**0.076**	**0.019**	**1.079**	**<.001**	**1.040**	**1.120**
	Intoxicated	-0.028	0.025	0.972	.263	0.925	1.021
	Cognitive-Perceptual	**0.415**	**0.113**	**1.514**	**<.001**	**1.215**	**1.888**
	Interpersonal	-0.084	0.092	0.919	.359	0.768	1.100
	Disorganised	**-0.300**	**0.125**	**0.741**	**.016**	**0.580**	**0.947**
	Cog-Per * Aversive	-0.009	0.006	0.991	.128	0.979	1.003

Cog-Per * Aversive = cognitive-perceptual and aversive scales interaction term

2.3.8 Covariates of psychotic mental illness whilst controlling for incidence of unreported or undiagnosed mental illness in the community sample

As discussed previously (Section 2.2.2), the participants in the community samples (CSCU and CSCN) were not presented with the opportunity to report any past or present mental illness. Thus, within this group it is feasible that some respondents may possess a diagnosis of a mental illness. Moreover, respondents in this cohort may possess an undiagnosed mental illness. Cohen et al., (2011) in their recent investigation differentiated their respondents according to percentile score on the SPQ-b (revised version). Participants scoring above the 95th percentile were deemed to be presenting prominent schizotypal features. Cohen and colleagues state their selection of participants at this percentile is…

> Informed by a) Meehl's theories of schizotypy (Meehl, 1962), b) taxometric studies suggesting a 10% population incidence of schizotypy (Lenzenweger and Korfine,1992), and c) findings that over half of individuals in the top 10% of SPQ scorers met criteria for a schizophrenia-spectrum disorder (Raine, 1991)(p.549).

In this section a similar criteria will be applied to identify unreported or undiagnosed mental illness (see Table 18). All participants (CSCN, CSCU, DD, and PD) were considered as one group (N = 1300), each of these participants scores on the SPQ-b were assigned a percentile. Participants in the CSCU group scoring at or above the 95th percentile, a score of 17 or more, were excluded from analyses. To this end 42 participants were excluded from the CSCU group (thus n = 819).

The model described in the previous Section (2.3.7) accounted for the most amount of variance in the data, thus, this model was re-computed with the remaining participants. The model included the SPQ-b subscales, the aversive and intoxicated CEQ scales and the interaction term between the cognitive-perceptual scale and the aversive scale. These variables were entered into the model in a forced entry fashion. The variable describing the interaction term was not found to have an effect on the model with the likelihood ratio test indicating no significant effect (*-2LL* = 769.479, χ^2 (2) =1.950, *p* = .377). Hence, the model was

re-computed with the interaction term omitted. This model is referred to as Base + SPQ ^{adjusted}

The model fitted was significantly better at predicting the data than the intercept (χ^2 (10) = 174.501, p < .001). Both the Pearson (χ^2 (1866) = 1872.05, p = .46) and Deviance (χ^2 (1866) =769.48, p = 1.00) assessments suggest a good fit of the model. Cox and Snell's R^2 indicates the model explains 16.7% of the response data and Nagerlkerke's R^2 indicates that the model explains 26.6% of the data. Thus, suggesting that this model explains the most amount of variance in the data than any other presented, however, this is based on fewer participants, thus less data.

In comparison of the community sample of cannabis users (CSCU) and those diagnosed with depression (DD), group membership was significantly predicted by aversive cannabis experiences (b = -0.32, Wald χ^2 (1) = 5.76, O.R.0.97, 95% CI 0.94 to 0.99, p=.016). Each unit increase on the aversive scale reduced the odds of a diagnosis of depression by 3.2%. The intoxicated scale was not a significant predictor of group membership. However, both the interpersonal and disorganised SPQ-b subscales were significant predictors, respectively, b = 0.36, Wald χ^2 (1) = 36.312, O.R.1.43, 95% CI 1.27 to 1.61, p <.001 and, b = 0.34, Wald χ^2 (1) = 18.28, O.R.1.41, 95% CI 1.21 to 1.65, p < .001. Each unit increase on the interpersonal and disorganised subscale accounted for an increase of 43.0%, and 41.0% (respectively) in odds of a diagnosis of depression.

In comparison of the community sample of cannabis users (CSCU) and those diagnosed with a psychotic illness (PD), diagnosis was significantly predicted by both aversive and intoxicated experiences (respectively, b = 0.30, Wald χ^2 (1) = 5.85, O.R.1.03, 95% CI 1.01 to 1.06, p=.016, b = -0.59, Wald χ^2 (1) = 7.12, O.R. 0.94, 95% CI 0.90 to 0.98, p = .008). Each unit increase in the aversive scale predicted an increase of 3.1% in the diagnosis of a psychotic illness, whereas the same increase in the intoxicated scale predicted a 5.7% decrease. Both the cognitive perceptual and interpersonal subscales were significant predictors of group membership (respectively, b = 0.36, Wald χ^2 (1) = 16.00, O.R. 1.44, 95% CI 1.20 to 1.72, p < .001, b = 0.30, Wald χ^2 (1) = 16.02, O.R. 1.35, 95% CI 1.17 to

1.57, $p < .001$). Each unit increase in the cognitive-perceptual and interpersonal subscale predicted a respective increase 43.6% and 35.3% in the odds of a diagnosis of psychosis.

In comparison of the group of participants diagnosed with depression and those diagnosed with a psychotic disorder aversive cannabis experiences were a significant predictor of diagnosis ($b = 0.06$, Wald χ^2 (1) = 13.15, O.R.1.07, 95% CI 1.03 to 1.10, $p < .001$). Each unit increase on the aversive scale predicted a 6.5% increase in the odds of having a psychotic diagnosis. The intoxicated and interpersonal scales were not significant predictors. However, the cognitive-perceptual and disorganised subscales were significant predictors of diagnosis (respectively, $b = 0.37$, Wald χ^2 (1) = 11.93, O.R.1.45, 95% CI 1.17 to 1.79, $p = .001$, $b = -0.26$, Wald χ^2 (1) = 4.32, O.R.0.77, 95% CI 0.61 to 0.99, $p = .038$). Each unit increase of the cognitive-perceptual scale predicted an increase of 44.8% in the diagnosis of a psychotic illness, whereas the same increase in the disorganised subscale predicted a 23.6% decrease.

Table 18

A multinomial forced entry regression model predicting group membership as a function of aversive and intoxicated cannabis experiences, schizotypal trait whilst controlling for unreported mental illness

		Beta	(SE)	Odds Ratio	P	95% CI of O.R.	
						Lower	Upper
CSCU Vs DD	**Intercept**	**-3.562**	**0.355**		**<.001**		
	Aversive	**-0.032**	**0.013**	**0.968**	**.016**	**0.943**	**0.994**
	Intoxicated	-0.025	0.018	0.975	.155	0.942	1.009
	Cognitive-Perceptual	-0.008	0.071	0.992	.909	0.863	1.140
	Interpersonal	**0.358**	**0.059**	**1.430**	**<.001**	**1.273**	**1.606**
	Disorganised	**0.344**	**0.080**	**1.410**	**<.001**	**1.205**	**1.651**
CSCU Vs PD	**Intercept**	**-4.922**	**0.508**		**<.001**		
	Aversive	**0.030**	**0.013**	**1.031**	**.016**	**1.006**	**1.056**
	Intoxicated	**-0.059**	**0.022**	**0.943**	**.008**	**0.903**	**0.984**
	Cognitive-Perceptual	**0.362**	**0.090**	**1.436**	**<.001**	**1.203**	**1.715**
	Interpersonal	**0.302**	**0.076**	**1.353**	**<.001**	**1.167**	**1.569**
	Disorganised	0.088	0.104	1.092	.396	0.891	1.338
DD Vs PD	**Intercept**	**-1.360**	**0.596**		**.023**		
	Aversive	**0.063**	**0.017**	**1.065**	**<.001**	**1.029**	**1.101**
	Intoxicated	-0.034	0.026	0.967	.194	0.918	1.017
	Cognitive-Perceptual	**0.370**	**0.107**	**1.448**	**.001**	**1.174**	**1.786**
	Interpersonal	-0.055	0.090	0.946	.541	0.793	1.129
	Disorganised	**-0.256**	**0.123**	**0.774**	**.038**	**0.609**	**0.985**

2.4 Discussion

2.4.1 Main findings

Significant group differences in schizotypal trait were found between; a community sample of cannabis naïve participants (CSCN); a community sample of cannabis users (CSCU); cannabis users who had a self-reported diagnosis of depression (DD); and cannabis users with a self-reported psychotic disorder (PD). This finding was also demonstrated in a trend difference in that respective order, ranging from lowest to highest. In a pairwise comparison it was seen that the CSCU group scored significantly higher than the CSCN group on the disorganised subscale of the SPQ-b, but the two groups did not differ in the interpersonal or disorganised subscale. The DD group scored significantly higher than the CSCU group on the interpersonal and disorganised subscales of the SPQ-b, and also on the measures total score. In comparison of the PD and DD groups, the PD group only scored significantly higher on the cognitive-perceptual subscale. Despite the theoretical aetiological overlap between schizotypal personality and psychotic (schizophrenia spectrum) mental illness (see Raine & Lencz, 1995).Nonetheless, as would be expected the PD group scored significantly higher than the CSCU group on all three SPQ-b subscales. Taken together, these results show that cannabis use in the absence of mental illness is associated with high levels of reported schizotypal trait, within the domain of disorganised deficit. Self-reported depression and psychosis are associated with higher levels of interpersonal and disorganised schizotypal traits, in addition to increases in cognitive-perceptual deficits in those reporting psychosis. These analyses serve to fulfil the first aim of this chapter: To assess variance in schizotypal trait related to cannabis use and reported mental illness.

The CEQ score of the cannabis using participants (CSCU, DD and PD) were also compared between groups. These analyses serve to fulfil the second aim of this chapter: To assess the presence of a differential sensitivity to the psychotomimetic effects of cannabis in those with psychotic illness. There were significant group differences on the aversive and appetitive scales, but not on the intoxicated one. In pairwise comparisons the DD group had significantly more appetitive cannabis experiences than the CSCU group, but they differ not on the other CEQ scales.

The PD group scored significantly higher than the CSCU group on the aversive scale, but the two groups did not differ on the appetitive or intoxicated CEQ scales. The PD group scored significantly higher on the aversive scale, and significantly lower than the DD group on the appetitive scale. However, the two groups did not differ in their scores on the intoxicated scale.

The third aim of this chapter is fulfilled by the use of regression models: to assess the utility of cannabis induced experience and schizotypal trait as predictors of psychotic illness in cannabis using populations. To this end, scores on the aversive scale were found to significantly and positively predict membership of the PD group from the CSCU group or the DD group. The intoxicated scale was also a significant, but negative predictor of the PD group from the CSCU group. Taken together, these results indicate that psychotic illness is associated with more aversive, and possibly fewer intoxicated, effects of using cannabis. When considering scores on the SPQb and the CEQ together, a number of regression models were able to predict group membership (CSCU, DD or PD). The model which accounted for the most amount of variance from the entirety of the data set included; the CEQ aversive and intoxicated scales; the three SPQ-b subscales; and an interaction term from the CEQ aversive scale and the SPQ-b cognitive-perceptual scale (Base + SPQ + X, Section 2.3.7).

2.4.2 Implications and comparison with other research

Comparing schizotypal trait in a community sample of cannabis users and non-cannabis users

Previous research has compared the schizotypal traits of cannabis users with non-users. It has been frequently documented that non-users have a lower schizotypal trait than cannabis users. Several investigations have utilised the SPQ-b to define and measure schizotypal trait. Bailey and Swallow (2004) compared cannabis users and non-users, they found a significant difference in all three SPQ-b subscales (and total score). Cohen et al. (2011), noted that frequent cannabis users were more likely to score highly on both the disorganised subscale, and the equivalent of the cognitive-perceptual subscale. Esterberg et al., (2009) also

demonstrated a significant relationship between indices of cannabis use and the disorganised and cognitive-perceptual subscales.

The current investigation has provided further evidence in support of these findings with a community sample of cannabis users scoring significantly higher on the disorganised subscale than a community sample of non-cannabis users. However, unlike some other investigations, there was no significant difference in scores on the cognitive-perceptual subscale or the interpersonal subscale. The rationale for this is at present unknown.

Schizotypy and self-reported depression

Although not one of the main research questions in this investigation, the DD group scored significantly higher than the CSCU group on the interpersonal, disorganised, and cognitive perceptual subscales. However, the differences in the cognitive-perceptual subscale did not remain significant after correcting for multiple comparisons. Lewandowski et al., (2006) demonstrated a significant association between both positive and negative schizotypy and depressive symptomatology. The DD group scored significantly higher than the cannabis naïve group (CSCN) on the cognitive-perceptual subscale. This may indicate that that the lack of a significant difference between the CSCU group and DD group on the cognitive-perceptual subscale may have been the result of either cannabis use[1] or the adoption of a too conservative a p-value threshold.

The group differences on the SPQ-b are consistent with findings showing that depressive symptoms are a positive correlate of schizotypy in both positive and negative dimensions (Fonseca-Pedrero, Paino, Lemos-Giráldez & Muñiz, 2011; Lewandowski et al., 2006; Vollema & Postma, 2002). The findings regarding the relationship between schizotypy and depressive symptomatology have often been framed within the context of schizophrenia research. Due to high incidence of depressive symptoms in patients diagnosed with schizophrenia, the relationship between schizotypy and depression has been taken as confirmatory evidence of schizotypy as a predictor of schizophrenia (Lewandowski et al., 2006).

[1] This does not necessarily suggest a causal association see section 1.6 for discussion.

Specificity of the SPQ-b

If the SPQ-b is considered to be an assessment for vulnerability to *only* schizophrenia spectrum disorders, from the current investigation one may conclude that a diagnosis of depression in cannabis users may reflect a greater liability for psychosis than the community sample. However, in a prospective cohort study Breetvelt et al. (2010) found that 'non-clinical psychotic symptoms' were often associated with other psychiatric symptoms, and they also share common socio-demographic risk factors. Although schizophrenia and depressive symptoms are often co-morbid, the latter is frequently a consequence of the dysphoric mood associated with the former (APA, 2013a, p.102). Thus, given the gamut of symptoms elicited in schizophrenia spectrum disorders a more plausible conclusion to draw from the data is that the SPQ-b is adept at highlighting these symptoms, even if they originate from different mental illnesses with (presumably) distinct aetiological and pharmacological processes.

Further evidence suggesting the SPQ-b cannot differentiate between psychotic liability and a broader range of psychiatric liability can be derived from the comparison of the DD and PD groups. The PD group scored significantly higher than the DD group on the cognitive-perceptual subscale. The two groups however, did not differ in their interpersonal or disorganised deficits, or the SPQ-b total score. Thus, suggesting that these groups could be differentiated on the basis of their scores on the cognitive-perceptual subscale, but not the other two subscales. This indicates that the cognitive-perceptual subscale may be the most proficient of the three SPQ-b subscales for the assessment of psychotic liability. However, the other two subscales do not demonstrate evidence of specificity, the ability to distinguish true incidence of psychosis proneness from false.

The relationship between the SPQ-b and self-reported depression seen in this study may seem unremarkable considering the SPQ-b is not a clinical assessment tool for schizophrenia spectrum disorders, but rather a brief measure of psychosis proneness. Thus, one may expect that it would not be sensitive enough to differentiate between various clinical groups, on all subscales under consideration. As discussed previously, it has been frequently reported that cannabis users display a higher schizotypal personality profile than their non-cannabis using

counterparts. This could feasibly represent a reflection of the increased risk of psychosis associated with cannabis use (Arseneault et al., 2007). Nonetheless, other psychiatric symptoms also correlate with schizotypy (Breetvelt al., 2010). Thus, a cannabis user with distinct psychiatric symptoms (or proneness) may present a schizotypal profile indistinguishable from those highly psychosis prone or even those with a psychotic illness, as demonstrated on the interpersonal and disorganised subscales. This could plausibly result in large incidence of false positives in assessments of psychosis proneness in cannabis users. Thus, the SPQ-b may not be an appropriate tool for assessing psychotic vulnerability in a cannabis using population.

Differential cannabis sensitivity in participants with a self-reported psychotic disorder

In pairwise comparisons the PD group had significantly more aversive cannabis experiences than the CSCU group and the DD group. Unlike the interpersonal and disorganised subscales of the SPQ-b, there was no significant difference between the DD and CSCU groups on the aversive scale. This indicates that the aversive scale is not simply reflecting the iatrogenic or substantive differences between those afflicted with a mental illness and those not. The notion of the aversive scale as a predictor of psychotic illness was further supported in the regression model containing just the CEQ scales (Base model), in comparison to both the CSCU and DD groups. However, the intoxicated scale of the CEQ was a significant negative predictor of the PD group in comparison to the CSCU group.

A differential sensitivity to the psychotomimetic effects of cannabis as a consequence of psychotic vulnerability has been demonstrated by previous investigations (GROUP, 2011; Henquet et al., 2010; Mason et al., 2009 see Section 2.1). This investigation has contributed to this growing area of research and demonstrated a differential sensitivity to cannabis in participants with reported psychotic disorder. This finding supports the assertions of Eisenberg (2010) which propose that genetic vulnerability to psychotic disorder may be evident in sensitivity to cannabis.

Interestingly, the data indicates that the CSCU group has more intoxicated cannabis experiences than the PD group. There are several plausible reasons why this finding may have occurred. The PD group may consistently experience high levels of the experiences listed in the scale as a consequence of their mental illness e.g. “Feeling that your thinking has been slowed down”. Thus, the effect of cannabis may produce a small amount of variance within the group on the scale. Evidence for such a notion may be derived from the groups not displaying homogeneity of variance. An alternative explanation is that the PD group has a substantive difference (possibly in their endocannabinoid system) which accounts for group differences in their intoxicated cannabis experiences, however, there is at present little data supporting this notion.

Assessing predictors of psychosis

Another regression model was computed considering the SPQ-b subscales and the CEQ aversive and intoxicated scales (Base + SPQ). Within this model the aversive scale became a non-significant predictor of the PD and CSCU groups. The construct assessed by the aversive scale is redundant when the SPQ-b subscales are considered, when comparing the PD and CSCU groups. This suggests that perhaps one or all of the SPQ-b subscales may be assessing a similar construct to the aversive scale (e.g. vulnerability). It is difficult to assess which subscale may be accounting for the same variance as the aversive scale, due to the aversive scale reflecting a breadth of psychotic symptomatology including experiences which are typically associated with positive (e.g. “threatened by an unknown force”), negative (e.g. “sad”), and disorganised psychotic-like experience (e.g. “disturbed in your thinking”). Moreover, the aversive scale also contains experiences which are not typically considered as (attenuated) primary psychotic symptomatology i.e. feeling “angry” and “anxious for no reason”.

Intriguingly, the disorganised SPQ-b subscale was not a significant covariate of the PD group in comparison to the CSCU group. This may indicate that the disorganised subscale is considering the same underlying construct as the interpersonal and/or the cognitive-perceptual subscales. This might suggest that

the disorganised subscale is considering secondary (attenuated) symptoms, or that the expression of a broad range of attenuated symptoms may have a common aetiology. Indeed disorganised symptoms are considered to fall within the remit of 'positive' symptomatology along with positive psychotic symptoms (APA, 2000, p. 299), which are reflected in the cognitive-perceptual subscale. However, whether the disorganised and psychotic positive constructs represent independent dimensions is still a matter of debate (APA, 2000, p. 299).

Furthermore, the disorganised subscale was a significant negative predictor of the PD group in comparison to the DD group. This finding was not anticipated, as logic would suggest that participants with a self-reported psychotic disorder should score higher on an assessment of psychosis proneness than other groups of respondents. This suggests that this subscale as an assessment of psychosis proneness lacks validity within cannabis using populations. The interpersonal subscale of the SPQ-b was not a significant predictor of the PD in comparison to the DD group. Thus, from the SPQ-b, only the cognitive-perceptual subscale was capable of differentiating between both; the PD and DD groups; and the PD and CSCU groups.

Controlling for unreported/undiagnosed mental illness and the interaction between the cognitive-perceptual subscale and the aversive scale

An interaction term was developed which considered the two predictors which appeared adept at distinguishing the PD group from both the DD and CSCU groups; the cognitive perceptual subscale and the aversive scale. This interaction term was added to a model including the SPQ-b subscales and the aversive and intoxicated CEQ scales (base + SPQ + X). Although the interaction variable did not significantly improve the model (p = .070) it was retained. Unlike the previous model (base + SPQ) without the interaction term this model indicated that the aversive scale was a significant positive predictor of the PD group compared to the CSCU group. However, the interaction term itself was a significant negative predictor of the PD group in comparison to the CSCU group. This could indicate that the predisposition assessed by the cognitive-perceptual subscale may interact with aversive cannabis experiences (or their underlying construct) to decrease the

propensity to psychotic reaction. However, there is no known rationale for why such an interaction may occur.

Perhaps an explanation for the significant effect of the interaction term (in Section 2.3.7) lies in the analysis which has attempted to control for undiagnosed or unreported mental illness in the CSCU group (Section 2.3.8, Base + SPQ ^{adjusted}). The interaction term did not significantly improve the model, however, the p-value is much larger than the previous mode (p = .377). Moreover, in this model the interaction term was not a significant covariate of group membership. Thus, Base + SPQ ^{adjusted} was re-computed with the interaction term excluded, this model displayed the same significant covariates as the model containing the interaction term (Section 2.3.7 Base + SPQ + X). This included the aversive cannabis experiences as a significant positive predictor of the PD group in comparison to the CSCU. The aversive scale was not a significant covariate of the model assessing all of the same variables, but without the adjustment for unreported/undiagnosed mental illness or interaction term (Section 2.3.6 Base + SPQ). This could possibly indicate that the negative relationship between the PD group and the interaction term (Section 2.3.7 Base + SPQ + X) could feasibly be identifying unreported/undiagnosed mental illness.

Schizotypy is a known correlate of a raft of different mental disorders, including anxiety (Rey, Jouvent, & Dubal, 2009), bi-polar mood disorder (Rybakowski & Kolonowska, 2011), autism (Dinsdale, Hurd, Wakabayashi, Elliot, & Crespi, 2013), and attention deficit hyperactive disorder (Keshavan, Sujata, Mehra, Montrose, & Sweeney, 2002). If the aversive scale is *only* elevated in individuals with schizophrenia spectrum disorders then individuals with other mental illnesses may develop a negative interaction term. The interaction term is generated by centering the participants around the group mean on the two variables and then multiplying the resultant scores. Thus, such a scenario may develop where an individual with an unreported diagnosis of depression for example may score above the mean on assessments of schizotypy (the cognitive-perceptual subscale), but below the mean on the aversive scale. This would in turn generate a negative value for the interaction term.

Self-reported depression and appetitive cannabis experiences

Although this was not the main purpose of this investigation, one of the findings elucidated suggests a differential effect of cannabis on people with a diagnosis of depression. Participants in the DD group reported significantly more appetitive cannabis experiences than the CSCU group and the PD group. Moreover, aversive cannabis experiences were a significant negative correlate of the DD group in comparison to both the PD and CSCU groups. It is unlikely that the DD group had lower psychotic liability than the CSCU group as evinced by the former scoring significantly higher than the latter on two of the SPQ-b subscales. This may indicate a true differential effect i.e. the DD group derived more pleasure from cannabis than the CSCU group and had fewer aversive effects. Alternatively, this may plausibly reflect within group differences i.e. the DD group felt more pleasure than they would typically experience, which was a larger increase than the CSCU group. Intra-group reliability on one of the CEQ scales is assessed in Section 4.3.3. However, inter-group reliability between the CSCU and DD group has not been assessed. Nonetheless, the significant difference in the appetitive scale indicates that the DD group could possibly be experiencing some beneficial effect on mood from cannabis.

A review indicates that there is a relationship between the endocannabinoid system and depression in animal models (Serra & Fratta, 2007). However, the data pertaining to whether cannabis may have an anti-depressant effect is conflicting. Nonetheless, cannabinoids have treated the symptoms of depression in two case studies (Blass, 2008). At present there is insufficient data to conclude an antidepressant effect, “there appear to have been no formal clinical trials of cannabinoids in depression” (Ashton & Moore, 2011 p.255). Nonetheless, the current investigation provides supporting evidence of a relationship between cannabinoids and depression, which could suggest an antidepressant effect of cannabis.

2.4.3 Strengths and Limitations

Web-based research has been frequently used with illicit substance users (Miller & Sønderlund, 2010). It is thought that web based research may serve to elicit a more diverse sample than traditional methods (Gosling, Vazire, Srivastava, & John, 2004). A recent review concluded that one of the strengths of the web based research reviewed "was their ability to reach hard-to-reach samples (or 'hidden populations') of illicit drug users" (Miller & Sønderlund, 2010, p.1562). In addition to the challenges of recruiting illicit drug users, this investigation required the recruitment of persons with either psychotic or depressive illness, which considerably reduces the population of eligible participants. Moreover, it was thought that the use of web-based research may improve confidentiality for respondents (Miller & Sønderlund, 2010, p.1557). Despite the advantages of internet research there are limitations. Internet based research affords the investigators little control over the environment in which the measures are completed, no control can be applied to extraneous variables (e.g. temperature, light, sound). Furthermore, with the development in mobile technology, the participant would not have necessarily been constrained to responding from a P.C. (see Section 3.2.1). Although, it is anticipated that the vast majority will not have responded from a mobile phone as the questionnaires aesthetics were not designed for display on a small device. Nonetheless, although these issues might have increased overall level of 'noise' (error term/residual) in the data, it is unlikely that they would have resulted in systematic, confounding, differences in the responses given by each group. Therefore, if anything, the effect sizes seen here might be underestimates of what may be attained under more controlled conditions.

Two of the principal limitations of this investigation were that drug use and mental health history were not independently verified. This could not be performed due to the use of online research, the recruitment of an anonymous international sample, limited resources, and ethical complications (e.g. obtaining NHS ethical approval, along with its international equivalents). The consequence of not independently verifying drug use may have resulted in participants being miscategorised as a cannabis user or cannabis naïve. The misallocation of respondents would likely result in a reduction of statistical power. Nonetheless, statistical differences

between the cannabis using groups and the non- cannabis groups were still noted despite the potential reduction of statistical power. As before, this means that the effect sizes may be underestimates of the true value. Moreover, anonymous internet research is thought to decrease social desirability and social anxiety, and thus feasibly increase accuracy of measurement (Johnson, 1999; though see Lelkes, Krosnick, Marx, Judd, & Park, 2012 for an alternative view). The anonymity afforded to participants in this study may have made it easier for them to make accurate honest responses to the items.

The problem of misreporting of diagnoses may also result in the misallocation of respondents to groups, in all likelihood, reducing group differences. One way in which accuracy of group allocation can be assessed is to compare the participants reported diagnosis with their reported medication. In the PD group, 44 participants (91.6%) stated (by either using the name of the medication or brand) an antipsychotic that they had previously taken. In the DD group 76 participants (86.4%) reported by name an antidepressant that they had previously taken. Moreover, in several instances where participants could not state the name of the drug they reported the class (i.e. SSRI) or type of drug (i.e. antipsychotic). This does not unequivocally mean that participants were or were not misallocated, given that detailed information about medication is freely available and easily accessible. However, it does provide reassurance that instances of misallocation are likely to be infrequent.

The limitation of misallocation also extends to the community sample groups (CSCN and CSCU). The investigations that recruited these respondents did not specifically enquire about participants' past and current mental health. Although no specific efforts were made to recruit participants with mental illness, it would be expected that there would be a population rate prevalence of mental illness, which may be exaggerated in the community sample of cannabis users (e.g. Manrique-Garcia et al., 2011). Nonetheless, when an attempt was made to control for undiagnosed or unreported mental illness in the CSCU group the results produced were similar to when such a control was not employed (see Section 2.3.6). Furthermore, whilst the use of a 'cleaner' 'healthy' sample may have been preferable for hypothesis testing, using a large community sample reflects a

broader representation of the cannabis using population and thus, may be preferable for the generalisability of results. Moreover, the results are feasibly more conservative than the true difference between the groups, making the findings of this investigation appear even more compelling.

Another limitation of the investigation is associated with the measurement of phenomenology of cannabis. Cannabis is known to impair cognitive functioning (Pope, Gruber, Hudson, Huestis & Yurgelun-Todd, 2001) including memory (Ilan, Smith & Gevins, 2004). Thus, it is feasible that the recall of cannabis-induced phenomena may be influenced by level and duration of acute intoxication. Nonetheless, the validity of the CEQ is evinced by the significant positive relationship between subscales of aversive cannabis experiences and schizotypal personality which has been replicated in several cohorts (Barkus et al., 2006; Barkus & Lewis, 2008; Morris, Unpublished data; Stirling et al., 2008). Furthermore, the results of this investigation may be taken as further evidence as convergent and discriminant validity of the CEQ as an assessment of psychotic vulnerability in cannabis users. Thus, although recall may be altered by intoxication there is substantial evidence suggesting the CEQ is a valid assessment nonetheless.

2.4.4 Conclusion

Being a cannabis user appears to raise schizotypal traits within the disorganised subscale, but not the other SPQ-b scales under assessment. The cross-sectional nature of the study design means the mechanisms which underpin this association are at present poorly understood. However, they are tested to some extent in Chapter 3. Cannabis users with self-reported depression displayed schizotypal profiles indistinguishable from cannabis users with a self-reported psychotic illness on two of the SPQ-b subscales. This may indicate that measures of schizotypy are assessing general psychiatric vulnerability as opposed to only psychotic vulnerability. Assessments of schizotypy may be capable of assessing schizotypal thinking or schizotypal behaviour; the “schizophrenic phenotype” (Rado, 1960 p.87). However, the phenotype (the expression of certain traits) does not always provide inference of the aetiology of the schizotypal traits; the ‘schizotaxic’ liability.

One means by which psychosis proneness might be assessed is through measurement of differential sensitivity to cannabis (Eisenberg, 2010). This investigation has demonstrated that those with a self-reported psychotic illness displayed more aversive cannabis experiences than both a community sample and participants with self-reported depression. This indicates that aversive cannabis experiences might be a valid means of discriminating between groups of cannabis users. The data indicates that the differences in cannabis induced experiences may not just be displaying the characteristics of psychotic liability (irrespective of the aetiology of the disturbance), but plausibly the characteristics of schizotaxic vulnerability as well. Nonetheless, it must be acknowledged that aversive environmental factors may prime for both; aversive cannabis experiences; and increased psychotic vulnerability. This notion is tested to some extent in Section 4.3.4. Van Os et al., (2009) suggest that persistent psychotic experiences are as a consequence of genetic and environmental factors. Thus, it is feasible that the persistent psychotic like experiences assessed by the CEQ could also be reflective as such factors.

The current investigation also provided evidence suggesting that participants with self-reported depression have significantly more appetitive and fewer aversive cannabis experiences than a community sample. This may plausibly implicate cannabis as having an antidepressant effect. However, it is important to note that the cannabis induced experiences did not necessarily occur at the same time as the point of mood disturbance. Thus, instead of cannabis serving to elevate mood in this sample, an increase in appetitive experiences may be representative of a dysfunctional endocannabinoid system being related to mood disturbance. This could indicate that drugs which bind to the CB_1 receptors may be efficacious in the treatment of mood disorder. Nonetheless, whether a beneficial effect may be conferred by a CB_1 agonist or antagonist remains unclear. This highlights the need for further research in this domain, perhaps utilising momentary assessments of appetitive cannabis experiences in participants currently suffering with depression.

The literature reviewed in Section 1.6.4 infers that cannabis may have a causal effect on psychotic disorder. The literature reviewed in Section 1.7.4 provides

evidence of a possible interaction between cannabis and stress on psychotic disorder. To establish causality it is necessary to establish temporality and discuss plausible mechanisms. The next chapter will utilise experience sampling data to assess temporal priority between cannabis use and psychotic-like states. Furthermore, the next chapter will also examine the plausibility of a cannabis and stress interaction effect as a causal factor in psychotic-like states.

3. Cannabis use, stress, and schizotypal state: An experience sampling investigation

Brief overview

This chapter aims to test various (causal) models of association between cannabis and a schizotypal state. An additional aim is to assess the plausibility of cannabis and stress interacting to increase incidence of schizotypal states. These aims are achieved by examining the data from cannabis using participants.This study utilised a repeated measures experience sampling study design.

Contained herein is a brief introduction which contextualises this investigation (Section 3.1 pp. 161-65). Following the introduction there is a description of the methodology utilised in this investigation (Section 3.2 pp. 166-205). The results of this investigation are contained within Section 3.3 (pp. 206-238). Section 3.3.1 (pp. 207-213) describes the participant's characteristics. Section 3.3.2 (pp. 214-17) describes the process by which the experience sampling items were validated. Section 3.3.3 (pp. 217-226) examines factors which predict a schizotypal state. Section 3.3.4 (pp. 227-29) assesses stress as a mediating influence between cannabis and psychosis. Section 3.3.5 (pp. 230-34) considers factors which predict calm and stressed states. Section 3.3.6 (pp. 234-38) examines factors which predict the consumption of cannabis. Section 3.4 pp. (238-258) discusses the implications, limitations and conclusions that can be drawn from this research.

3.1 Introduction

As discussed in Section 1.6 (pp. 61-79) there is a link between cannabis use and schizophrenia. However, whether this is a causal relationship is still a matter of debate. One particular means by which investigations have sought to assess the relationship between cannabis and schizophrenia is through examination of the personality trait schizotypy. Nonetheless, this has also failed to demonstrate evidence of a causal relationship, partly due to the possibility of time variant, state-like aspects to schizotypy (see Section 1.8 pp. 96-98). A principal difficulty with establishing a causal relationship between cannabis and schizophrenia is that there is a paucity of information regarding the temporality of the variables (see Section 1.6.4). Various different study designs have been utilised to examine this relationship, including experimental laboratory design (e.g. D'Souza et al., 2004), longitudinal investigation (e.g. Manrique-Garcia et al., 2013) and cross sectional investigations (Mass et al., 2001). However, Khimy et al., (2009) highlighted that studies using ESM methodology may be capable of revealing the temporal sequence of this relationship.

Experience Sampling Methodology is a naturalistic sampling technique which utilises repeat measurements within a close temporal proximity, typically several times a day for a period of days or weeks. ESM has been used in both substance using (Messiah, Grondin & Encrenaz, 2011) and patient populations (Oorschot et al., 2012). In Kimhy, Durbin and Corcoran (2009) review, four investigations were identified which may elucidate the relationship between cannabis and psychotic disorder. Verdoux, Gindre, Sorbara, Tournier and Swendsen (2003) collected data five times a day for a period of seven days. Verdoux and colleagues found that in schizotypal participants, cannabis elicited more psychosis-like experiences than in participants scoring lowly on measure of schizotypy. Thus, indicating a differential sensitivity to cannabis in a naturalistic environment, Tournier, Sorbara, Gindre, Swendsen and Verdoux (2003) found no significant relationship between cannabis consumption and an anxious state. An anxious state did not predict cannabis use, and cannabis use did not predict an anxious state. This suggests that cannabis use is not dependent on the self-medication of anxiety. However, the presence of anxiety disorder symptoms as assessed by cross-sectional measure significantly predicted cannabis use throughout the ESM period, although this finding remained

restricted to symptoms from with the domain of agoraphobia. In another ESM investigation Henquet et al., (2009) found a significant interaction between psychotic vulnerability, the Val allele of the COMT gene, and cannabis use on the presentation of hallucinations. Thus, demonstrating that cannabis use holds temporal priority over hallucinatory experiences. However, this is restricted to psychologically and genetically vulnerable individuals. Van Winkel, Henquet et al., (2008) found that the COMT gene moderated the effect between cannabis and emotional reactivity to stress in the expression of psychotic experience in patients, but not controls. Unlike the findings of Henquet and colleagues (2009) the presence of the Met allele conferred a greater risk. These findings once again implicate a very complex genetic model (see Section1.2.3 pp. 37-48).

Henquet et al., (2010) conducted further research within this domain and found that cannabis use positively predicted and held temporal priority over positive affect in controls and patients with a psychotic disorder alike. Moreover, cannabis reduced negative affect in patients, but not the control group. This could plausibly indicate that cannabis may confer a beneficial affect on symptomatology from within this domain. Nonetheless, within the patient group, but not the controls cannabis induced psychotic like experience. This may be as a consequence of a Khantzian model of self-medication of the negative symptomatology (see Section 1.6.1 pp. 63-68), at the expense of exacerbation of positive symptomatology within the patient group. Kuepper et al., (2013) found that the presence of negative affect and positive psychotic symptomatology significantly elevated cravings for cannabis within both patients with a psychotic disorder and healthy controls. This further implicates a self-medication model. However, within the control group the association between craving and consumption was significantly larger than in the patient group. This could reflect differences in the group's access to cannabis, or suggest that within patients, rather than craving, cannabis use may be "under stronger guidance by other, unmeasured factors, such as fluctuating mental states"(p.7). When considered together the findings from previous ESM research are inconsistent, with cannabis seemingly maintaining (or exacerbating) some symptomatology, but conversely alleviating others. However, given the dearth of research in this area, further exploration is required.

In examination of plausible mechanisms by which cannabis may cause psychotic disorder there are inconsistencies in the data indicating a dopaminergic action of the drug (See section 1.7.1 pp. 80-84). In animal models, the interaction of cannabis and stress significantly elicited striatal DA release (Littleton & Maclean, 1975; Maclean & Littleton, 1977). However, non-stressed conditions did not produce such an effect. There is evidence in humans to suggest that both cannabis and stress interact, which may occur through a process of sensitisation or cross-sensitisation (see Sections 1.7.3 pp. 88-91 & 1.7.4 pp. 91-95). However, at present there is also a paucity of data to this effect.

Nonetheless, ESM research has also been utilised to elucidate the relationship between stress and psychotic symptomatology. Collip et al., (2011) found that the physiological stress response to adverse daily events was heightened in first degree relatives of patients with a psychotic disorder in comparison to controls. Moreover, within the sibling group psychotic experience was associated with physiological assessments of stress. The association between stress reactivity, psychotic vulnerability and psychotic symptoms have also been demonstrated in other cohorts (e.g. Lataster, Collip, Lardinois , van Os & Myin-Germeys 2010; Lataster et al., 2009). Further evidence for the effect of stress on psychotic symptoms can be derived from the ESM investigation of Lardinois, Lataster, Mengelers, van Os & Myin-Germeys (2011) who found a significant interaction between daily stress and childhood trauma on the intensity of psychotic experience. Moreover, Simons et al., (2009) have found that functional polymorphism within the COMT gene alters psychotic reactivity to stress within a healthy population. Simons and Colleagues found that Val carriers displayed greater paranoid symptoms in response to event stress, whereas Met carriers had greater paranoia associated with social-stress. Thus, stress has been consistently implicated in elevations in symptomatology. However, there is a need to explore which domains of symptomatology are elevated by stress, and if ‘calm’ states serve to attenuate such symptomatology.

3.1.1 Aims of this chapter

To date, the relationship between cannabis and stress on a psychotic outcome has not been well documented (see Section 1.7.4 pp. 91-95). Furthermore, the literature has demonstrated inconsistencies whilst attempting to establish the temporal sequence of cannabis and psychotic experience (see Section 1.6.1 pp. 63-68). This investigation seeks to address such deficiencies in the literature. Previous experience sampling investigations have elucidated information about the association between cannabis and psychotic symptoms, and stress and psychotic symptoms. This investigation aims to provide evidence related to; the relationship between cannabis and a schizotypal state; stress/calm and a schizotypal state; and the interaction between cannabis, stress and psychotic-like experience. Considering the repeated measures nature of this investigation it is possible to establish the temporal sequencing of the variables.

Chapter 3 has five primary aims:

1. To assess whether cannabis use is related to the presence of a schizotypal state.
2. To assess the evidence for temporal priority in the relationship between cannabis and psychotic experience in a naturalistic setting.
3. To assess the effect of a stressed and calm state on psychotic-like states utilising a cannabis challenge to facilitate a model of psychosis.
4. To assess factors which may influence the consumption of cannabis (self-medication).
5. To assess the plausibility of an interaction between cannabis and psychological stressors on psychotic (like) experience.

The first aim of this chapter is partially addressed by the consideration of scatterplots of the participant's scores on the SSQ (Figure 9). This aim is addressed in more depth in analyses contained within Section 3.3.3 (pp. 217-26), which assesses cannabis as a covariate of a schizotypal state. Analyses provided in Section 3.3.3 and 3.3.6, (pp. 234-38) address the second aim by investigating temporality between cannabis and psychotic-like states. Respectively, these sections assessed cannabis as a predictor of schizotypal state, and schizotypal state as a predictor of cannabis consumption.

Analyses contained within Section 3.3.3 serves to fulfil the third aim of this investigation. In this section stressed and calm states are assessed as predictors of psychotic-like states. Thus, assessing psychosocial stress and factors which mitigate such stress (calmness) as a contributory factor to psychotic experience, utilising a cannabis model of psychosis. Aim four is addressed by assessing variables which increase the O.R. of cannabis consumption (Section 3.3.6). This aim is also addressed in Section 3.3.5 (pp. 229-34) in which evidence is assessed for cannabis' ability to attenuate stressed states or induce calm states. These analyses are assessing aspects of the self-medication hypothesis.

Aim five of the investigation is attended to in Section 3.3.3 in which a cannabis stress interaction variable is assessed as a predictor of a psychotic-like state. The fifth aim of this investigation is also addressed in Section 3.3.4 (pp. 226-29). In this section participants that displayed the least and most stressed states throughout the investigation were assessed independently for an effect of cannabis consumption on psychotic-like states.

3.2 Methodology

3.2.1 Study Design

Overview of Experience Sampling Methodology (ESM)

This study utilised Experience Sampling Methodology (ESM), which is "the collection of self-report indices of behavior, [sic] cognition, or emotions in near real time in the daily lives of the participants" (Trull & Ebner-Priemer, 2009, p457). ESM enables the investigation of phenomena at a momentary level. In ESM investigations, participants typically receive multiple stimulus signals per day for several consecutive days (Csikszentmihalyi & Larson, 1992, p 46). Participants are (typically) signalled via an electronic device (signal-contingent) or temporal and social cues (interval-contingent), for example at meal times. However, action-contingent data entries are also used (e.g. after eating). Signal-contingent data entries are typically sent "…according to a random schedule" (Csikszentmihalyi & Larson, 1992, p.45). This random schedule is utilised to limit participant anticipation of a data entry, which would invalidate the notion of a momentary response. The additional advantage of the randomisation of signal times is that it is anticipated that it will elicit variability in psychological states which are contingent on environmental or temporal factors.

ESM is capable of circumventing some of the disadvantages of a cross-sectional study design. ESM is a repeated-measures 'micro-longitudinal' technique, which may enable the researcher "to demonstrate how variables are related to each other across time and environments, even when participants are not consciously aware of the association between variables" (Palmier-Claus, et al., 2011, p13). One of the most frequently stated benefits of ESM research over cross-sectional study design is the ability to research phenomena in an environment high in ecological validity. With regards to (certain) cross-sectional study design Csikizentmihalyi and Larson (1992) stated "the data are gathered in retrospect outside the context of the situation, thus permitting distortions and rationalizations to become important" (p44).

Non-ESM self-report measures typically rely on either a person making a generalised global assessment of themselves or, retrospective account. Therefore, they rely on subjective retrospective information which can be influenced by recall bias. Stone and Shiffman (2002) state that of the associated methodological constraints “the most vexing is the extensive memory distortion that pervades retrospective self-reports” (p.236). Moreover, non-ESM self-report measures (typically) require the participant to amalgamate any relevant phenomena experienced. Whereas ESM items typically refer to concurrent phenomena, they are set ‘in the moment’. Thus, ESM research is purportedly not marred “by the same motivational processes that affect standard self-reports (i.e., socially desirable responding or psychological defense)” (Christensen, Barrett, Bliss-Moreau, Lebo & Kaschub, 2003, p.55).

ESM in its current form has been in use since the mid 1970’s (Csikszentmihalyi, Larsson, & Prescott, 1977). In seminal research as well as contextual cues, various devices have been employed to signal the participant including pocket calculators (Csikszentmihalyi & Larson, 1992, p.45) pagers (Csikszentmihalyi et al., 1977) and wrist watches (Delle Fave & Massimini, 1992). In early ESM research despite an electronic device often being used to signal participants, these devices were not used to record the participants’ data. Instead the participant typically completed (paper) ‘hard copies’ of items in a booklet. However, there are some notable disadvantages to this method of capturing data.

ESM research can place a demand on participants beyond that which is typical of cross-sectional research. Consequently, during the course of an ESM investigation it is reasonable to expect participants will miss time points for item completion. Distinguishing between a valid entry and one that is not may be susceptible to errors of inclusion or exclusion with hard-copy data capture. ESM research is the momentary monitoring of phenomena, if participants do not initiate their data entries within a specific time window then this notion is violated; “their account is no longer considered to represent ambulant monitoring of their experiences” (Palmier-Claus et al.,2011, p18). Typically, with hard-copy signal-contingent data capture participant’s document the time at which they initiate their response and this is compared to the time at which the prompt was sent / received. However,

without the ability to objectively assess the time at which the data was submitted instances of prospective or retrospective data completion cannot be ruled out.

In an investigation into prospective and retrospective item completion Stone, Shiffman, Schwartz, Broderick and Hufford (2002) demonstrated that the participant's reported compliance of 90% for paper and pen data capture was substantially higher than the objectively measured compliance of 11%. However, it should be noted that in Stone and colleagues investigation response times were not randomised and thus the participant was aware of the time that they were *supposed* to have responded. In the same investigation the objectively measured compliance using electronic data capture was 94%.

Design of the current investigation

The current investigation consisted of three phases; a pre-ESM phase; the ESM phase; and a post-ESM phase. The ESM phase utilised electronic data capture, which enabled the electronic and objective time stamping of data. Thus, errors of inclusion of non-momentary data or exclusion of momentary data are mostly negated. The current investigation utilised remote data storage, all information submitted by the participants was stored in a location other than the device that submitted it. This prevented data loss in instances of device loss and damage.

An additional advantage of the use of remote data storage is it prevented the participant or anyone else from accessing the previously completed responses. This may have served to increase data validity by preventing participants adjusting their current response in lieu of their previous one. Furthermore, this would have served to assure participants that in the event of access to the device by persons other than themselves then there would be no breeches of confidentiality. Additionally, remote data storage also facilitated the 'real-time' monitoring of data.

However, there was one principal disadvantage to the sole use of remote data storage, as opposed to data stored on the device, or a combination of the two. Remote data storage requires a means of connecting the device to the data store. In the current investigation this relied on a mobile phone network and thus data

transfer may not be possible in certain (typically remote) geographic areas. As well as the possibility of data loss this also may have resulted in delayed data transfer. The data is time stamped at the data receiver as opposed to data sender, and thus it is possible that errors of exclusion for non-momentary response may have occurred. To circumvent this methodological issue, in the current study the time of *initiation* of response was recorded (in addition to cessation).

In the current investigation, the word 'prompt' is utilised in reference to the means by which participants are alerted to initiate a data entry. The word prompt is used, as opposed to signal, to disambiguate from reference to other uses of the word signal (e.g. in reference to what is also known as mobile phone reception strength). The current investigation also utilised a remote means of generating a prompt. This offered greater flexibility to altering the prompts (if necessary) throughout the course of the investigation. However, the principal disadvantage of this is in the instance when the device has little or no reception strength. In practice such a scenario would delay the prompt being received. This delay may result in the exclusion of true momentary responses (see Sections 3.2.1 & 3.2.2).

One means by which the limitation of reception strength has been circumvented is by utilising the time at which the device receives the prompt, as opposed to scheduled delivery time. This should serve to avoid some instances of erroneous exclusion of data. Nonetheless, this could still introduce a bias by a possible scenario in which an area that has low signal strength is also associated with a psychological state in the participant. This is an unavoidable consequence of the sole use of remote data storage. However, it should be noted that the purported coverage of reception strength sufficient for data transfer in the U.K. is 99%, on the phone network (Orange) used in this investigation (UKmobilecoverage.co.uk, n.d.). Thus, instances of such a bias being introduced are thought to be rare, if they have occurred at all.

Utilising the hardware and software outlined in Section 3.2.3 (materials) both equidistant interval-contingent and (pseudo)randomised signal-contingent prompts were sent to participants. On each of the fourteen days of the ESM phase participants were sent six signal-contingent prompts assessing; schizotypal state;

concurrent states of calm and stress; previous stressful and pleasurable events; and drug consumption.

As the focal point of the investigation is cannabis use, the randomisation of responses was pertinent. Cannabis consumption is a behaviour which for some will occur at specific set times and set places, of which the participant may or may not be consciously aware. For other participants their cannabis use will form no discernible pattern. In order to adopt a uniform methodology, whilst still prompting participant's at various temporal proximity to their cannabis use a (pseudo)-randomising procedure is most appropriate.

Nonetheless, for brevities sake only one interval-contingent data entry assessing aversive cannabis experiences was sent on each of the fourteen days. This data entry is scheduled at a pre-arranged time during the hour before the participants approximate bed time. At this point participants respond to a checklist of aversive cannabis experiences they may have experienced on that day. Although not strictly speaking an action-contingent measure, it does require the participant to have consumed cannabis at least once on that day.

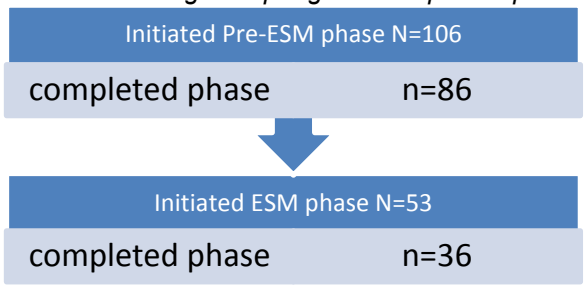
3.2.2 Participants

Inclusion and exclusion criteria

Inclusion and exclusion criteria were applied at each phase of the investigation, including the analyses. This procedure was adopted for several reasons firstly participants eligibility may fluctuate with time. Secondly, inclusion and exclusion criteria must not only be applied to the participants, but each individual resultant data entry.

Figure 2

Demonstrating the progress of participants through the investigation



From data derived from the pre-ESM phase, and an interview (typically via telephone) participants were assessed for their eligibility to continue to the ESM-phase. Participants were assessed against various inclusion criteria; a minimum of 18 years old; current cannabis use at a minimum frequency of twice a month; anticipated cannabis use (for the ESM-phase) of at least once a week; and an anticipated minimum of a 10 hour window, in which data may be entered, available each day for the majority of the ESM-phase. Various exclusion criteria were also applied at this stage. Participants were ineligible for the ESM-phase if they had; reported currently being a frequent user of recreational drugs other than cannabis, alcohol, caffeine and nicotine (>than once a month); a diagnoses of chronic mental illness (e.g. personality disorders); recent diagnosis of any mental illness (<3 years); or lifetime diagnosis of psychotic disorder (e.g. drug induced-psychosis); anticipated first and last cannabis use within a 24 hour period not typically more than 16 hours apart.

In the post-ESM phase the participant's data was assessed against various exclusion criteria. As described in Section 3.2.1 ESM is a momentary assessment, thus only data submitted within 30 minutes of a prompt were considered eligible for inclusion. This cut-off is one at which "researchers typically restrict response to" (Scollon, Kim-Prieto, & Diener, 2003, p.18). Scollon et al., (2003) describe the use of a 30 minute response window as an "arbitrary cut-off" (p.18). Nonetheless, for uniformity of data responses exceeding the response window were excluded from analyses. In addition participants responding to fewer than 30% of the signal-contingent items were excluded from the analysis, as they are thought to be less reliable (Henquet, et al., 2010; Wichers, et al., 2007). Furthermore, participants were excluded from analysis if they consumed recreational drugs other than

cannabis, caffeine, alcohol and nicotine throughout the ESM-phase. Throughout the ESM period the data were monitored and participants were informed if they were likely to be excluded from the analysis on the basis of the aforementioned criteria.

Recruitment

Opportunity Sampling was utilised via the distribution of study information (flyers) and brief presentations of study information. Study advertisements were distributed both in strategic locations and on an ad-hoc basis. The study advertisement sheet included a brief description of the investigation, the researcher's contact details, and a URL linked to the pre-ESM measures (See Appendix 22). Study advertisements were distributed by seven shops which purveyed drug use paraphernalia and 'legal highs'. Study advertisements were also distributed to undergraduate psychology students attending a compulsory lecture at Manchester Metropolitan University (MMU). This group were also advertised to in a virtual environment via a post on the university internal messaging board and notification system (Moodle). Advertisements were also distributed on an ad-hoc basis, to person's who expressed an interest in the research topic.

In addition to distributing advertisements to prospective participants, flyers were also distributed to participants who had initiated the ESM phase. Participants were requested to pass a flyer on to any person or persons over the age of 18, who they thought may be receptive to the idea of participating in the investigation. This method of advertisement distribution is one means by which participant snowballing was employed.

Participant snowballing was also employed in a virtual environment; this was primarily undertaken on the social networking websites Twitter and Facebook. Study advertisements were distributed via a purpose built Twitter account, these advertisements were then 're-tweeted' (forwarded on to other Twitter users) by various individuals and organisations. Facebook was employed to contact various organisers of groups or key figures in the online community. To this end study

advertisements were posted to virtual communities of people based in the appropriate geographic location which have subscribed to an interest group related to drug use. Advertisements were also distributed by various persons and organisations involved in the music industry. Participants were given the opportunity to complete the pre-ESM measures in either 'hard-copy' or online. Nonetheless, no 'hard-copy' responses were returned.

Demographic data

Participant demographic data is described in detail in Section 3.3.1 and in Tables 21 and 22, by drawing comparison between those who were included in the main analyses with those who were not. Briefly, the final sample comprised of 36 participants (male= 23), 21 of whom were employed, and 7 who were in education or training. The sample had a mean age of 27 years (SD 8.06), and started first using cannabis on at least a monthly basis at a mean age of 16 years (SD 2.60).

3.2.3 Materials: Technical Equipment

The current investigation utilised electronic prompt generation and data capture. To this end three different technologies (pieces of hardware) were utilised. A messaging distribution web based programme was employed to send prompts, in the form of Short Messaging Service (SMS) to participants. A smartphone was utilised as a means of receiving prompts and submitting data. A questionnaire hosting programme and server were utilised for the 'hosting' of the measures (displaying the measures in an online environment), and the storage of data.

Smartphone

This investigation utilised the Orange Stockholm (which is also known as the Huawei U8180), a user/troubleshooting guide tailored specifically to this smartphone was produced for participants and this is included in Appendix 23. This handset was chosen because at £49.99 (per handset) this represented the most economical smartphone that possessed a full web browser, and the

possibility of 3G and Wi-Fi data transfer. In addition this handset had a lower resale value than the value of the remunerations on offer.

Participants utilised the smartphone's full web browser to access and complete items in an online environment. For this, wireless data transfer was necessary. The function of 3G data transfer was a sought after feature because, at the time of conducting the investigation, it represented the fastest (widely available) means of transferring data from and to a mobile phone. However, the speed and reliability of the 3G network is typically not comparable with the preferable, but less widely available Wi-Fi networks. Hence, in the current investigation participant's had the option of connecting to a Wi-Fi network if one was available, or alternatively the phone would default to using the fastest mobile data transfer method available (e.g. 3G, EDGE, etc.).

For the purposes of this investigation several applications were installed on to the smartphone's Android (version 2.2.2) Operating System (OS); Angry Birds 2.2.0; App Lock 1.32; Maxthon Mobile Browser 2.6.9; and SMS to Text 1.3.1. The only function of Angry Birds 2.2.0, which is a popular game, was to attempt to get participant's to engage with using and carrying the device. The other applications provided a specific function in the data collection process.

Maxthon Mobile Browser

This enabled pages to be opened automatically in a 'private' browsing mode, unlike the browser which comes as standard on the OS. A private browser prevents the website storing information on the device such as cookies and temporary files, thus facilitating the preservation of confidentiality.

App Lock 1.32

This application was utilised to prevent participants from accessing some of the content on the smartphone. Participants were prevented from accessing applications that require data transfer (e.g. GPS services, Facebook etc.), to ensure that participants were not utilising the limited data allowance which was required to access the online measures.

SMS to Text 1.3.1

This application was used to export data from the smartphone after study completion. This application enabled an accurate assessment of when the participant received a prompt for data collection, as opposed to when the prompt was scheduled to be sent.

Messaging Distribution Facility

SMS messages were typically used to 'prompt' a data entry, but in some instances they were also used to make contact with participants if they were un-contactable via a phone call. They were distributed via Meercat communications SMS web portal. This system allowed for the scheduling of multiple SMS' to be sent to multiple recipients for any time point in the future.

These text messages served a dual purpose they prompted participants, and they contained an embedded (hyper)link to the relevant measure (See Figure 3). In this instance the link contained a Uniform Resource Locator (URL), which contained a web page with the relevant measures displayed. These embedded URLs act in much the same way as hyperlink would do on a desktop PC, by clicking it a browser and webpage with specific content opens up on the mobile display. Each URL linked to a unique data set for the storage of a specific participant's data on a specific measure. For each participant there were five separate URLs (webpages) each linking to five separate data sets. This pertains to the five different groups of measures or sequences of measures displayed throughout the investigation (see Section 3.2.6 and Table 19).

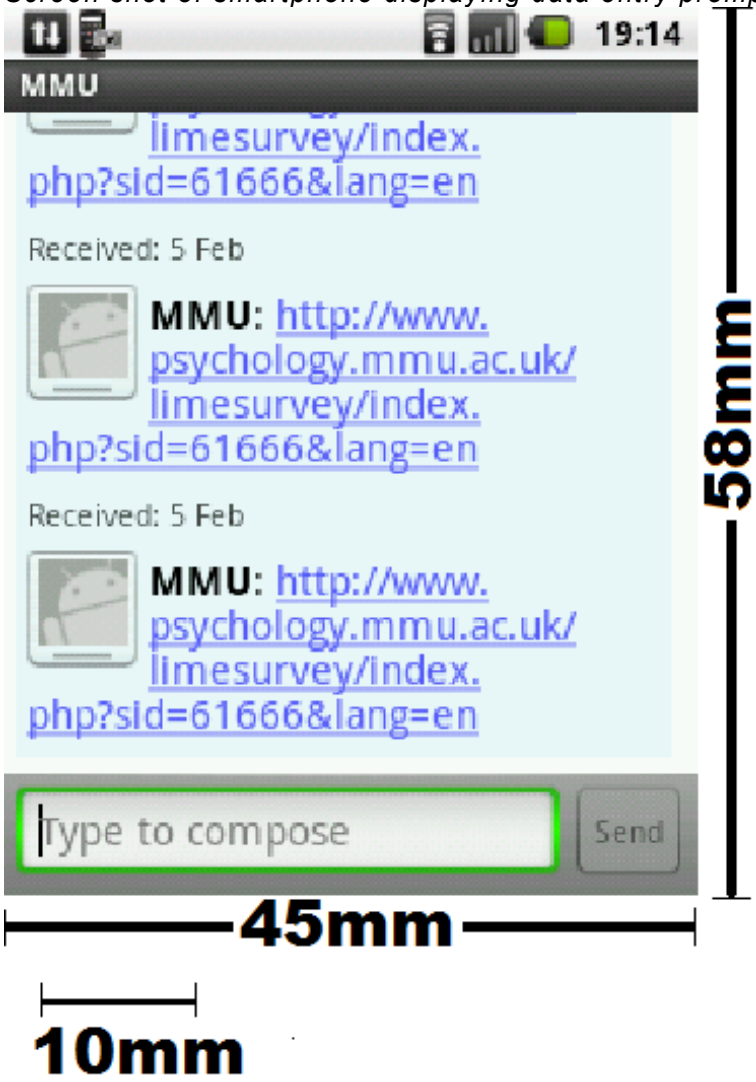
Questionnaire Hosting Facilities

LimeSurvey 1.87+ Build 8518 was installed on an 'in-house' server to facilitate the hosting (presentation in a virtual environment) of the respective measures. This was capable of presenting items in the various 'question types' necessary for this investigation e.g. Likert items (see Figure 4), and open ended text boxes (see Figure 5) etc. Participants were provided with a user guide tailored specifically to

completing the measures on LimeSurvey. LimeSurvey was also responsible for the secure storage and retrieval of data, in addition to the formulation of the hyperlink addresses.

Figure 3

Screen shot of smartphone displaying data entry prompts with embedded URL



Random time generator

The participant's interval-contingent prompts were assigned according to a random time generator this was created on Excel (J. Cavill, personal communication, February 3, 2012). This generator created six randomised time points between personalised wake and sleep times. There was a mean interval of 120.9 minutes (SD 60.68) between each response, and a minimum interval of 60

minutes. The sampling period encompassed between ten and sixteen hours out of any twenty-four hour period (See Section 3.2.2).

Figure 4

Screen shot of smartphone displaying SSQ items

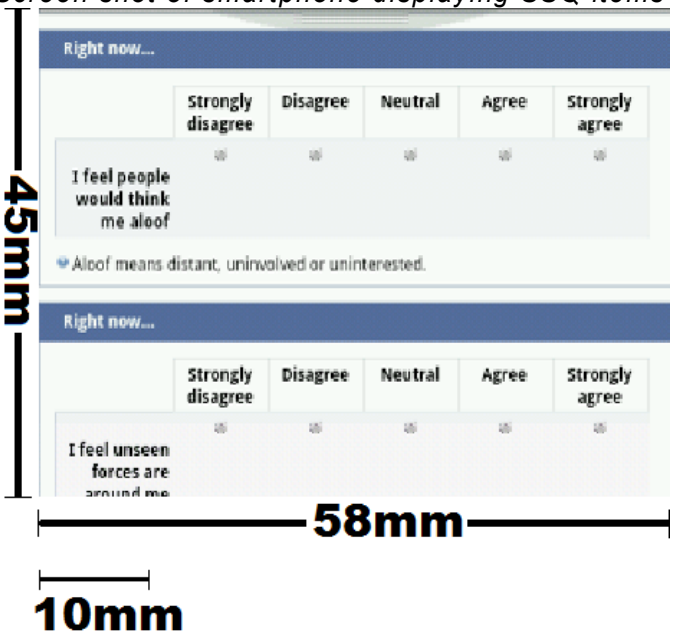


Figure 5

Screen shot of smartphone displaying text box data entry

3.2.4 Materials: Psychological Measures

Several measures were utilised at various time points throughout the investigation. These measures can be differentiated into; pre-ESM measures; concurrent ESM measures; retrospective ESM measures; post-ESM measures; and measures utilised in the testing of ESM items. Several of the measures utilised in this investigation were either adapted versions of pre-existing measures, or developed specifically for the purpose of this investigation. A procedure of testing these measures has been taken in parallel with the current investigation. The process of assessing validity and in some instances reliability of these items is described in Section 3.2.6, Section 3.3.2, and Appendix 29.

Pre- ESM measures

Cannabis Experiences Questionnaire

The CEQ is described in detail elsewhere in this thesis (see Section 2.2.3 and Appendix 1).

Schizotypal Personality Questionnaire- brief-Likert version (SPQ-b-L)

This measure is based on adapted versions of the Schizotypal Personality Questionnaire (SPQ, Raine, 1991); the Schizotypal Personality Questionnaire-brief (SPQ-b, Raine & Benishay, 1995); and the Schizotypal Personality Questionnaire- Likert version (SPQ-Lv, Wuthrich & Bates, 2005). The SPQ-b-L is substantially the same as the SPQ (the full version of the questionnaire described above). The principal difference is in the revised version instead of asking participants to respond dichotomously ('Yes' or 'No') responses are recorded on a five-point Likert scale. The Likert scale ranges from 'Strongly disagree' to 'Strongly agree'. It is anticipated that this will encourage disclosure from the participants (Wuthrich & Bates, 2005). Greater variability will allow for more gradations of schizotypy to be identified. Furthermore, a Likert version may be more sensitive to identifying "high scores missed by the standard version" (Wuthrich & Bates, 2005). For the development of the brief version of the SPQ Raine and Benishay (1995) selected the 22 (of 74) of the most reliable items from the measure. These 22 items disaggregated into three factors pertaining to cognitive-perceptual distortion (8 items), interpersonal distortion (8 items), and distortion of (dis)organisation (6

items). In the current investigation akin to the modification of the SPQ to form the SPQ-Lv, for brevity and variability of data, the most reliable 22 items from the original SPQ have been utilised with a 5 point Likert scale to form the SPQ-b-L.

Concurrent ESM measures

The signal-contingent measures were displayed on two pages, with concurrent phenomena displayed on the first and retrospective items on the second. Two concurrent measures were administered, between them assessing three constructs. DeVries (1992) recommends that "since thoughts at the time of the signal are the most difficult to catch, they are asked about first" (p.320). The first item participants are presented with is in regards to the time. The purpose of this item is to place the participant in the 'mind-set' of considering experiences and psychological states that are currently occurring. Not utilised in the current investigation but, another consequence of utilising this item could be as a measure of participant's accuracy/honesty of response.

Schizotypal States Questionnaire (SSQ) (Appendix 25)

As described in Section 1.2.2 the stability of schizotypy has been brought into question. As a consequence this investigation sought to take a measure of a 'schizotypal state'. The SSQ is an adapted version of the SPQ-b-Lv, with items amended for brevity and rubric altered to set the participant in the 'moment' (i.e. Right now I feel). For example, original SPQ-b item 'Are you sometimes sure that other people can tell what you are thinking?' has been altered to 'Right now I feel: Other people can read my mind'. Participants respond on a 5-point Likert scale, ranging from 'Strongly disagree' to 'Strongly agree'. This measure was adapted specifically for use in this investigation, the reliability and validity of this measure has been assessed in parallel with this investigation (Section 3.3.2).

Concurrent states questionnaire: Stress and Calm scales (Appendix 26)

Participant's concurrent states of stress and calm were assessed by a 6 and 5 item measure (respectively). Responses were recorded on a five-point Likert scale ranging from 'Not at all' to 'Very much so'. The scales contain short (one or two word) statements such as 'Chilled out' (Calm scale) and 'Anxious' (Stress scale), which are preceded by the rubric 'Right now I am feeling'. These items were

devised for the current study in discussion with John Stirling. The validity of these items have been discussed in Section 3.3.2, various means of scoring the scales have been assessed in Appendix 29.

Retrospective ESM items

The retrospective items were presented on a separate page after the concurrent ESM items. The first item played a role in setting the participant in the mind-set of considering retrospective events. This consisted of a text box with the open ended item 'The most noteworthy (good or bad) event that happened to me since the last beep [prompt] was…' (See Figure 5).

Event related items (Event Rating, ER; Stressful Events, SE; Pleasurable Events, PE)

Immediately after the text box an item was displayed requiring an evaluation of the most 'noteworthy' event. This item (Event Rating, ER) was scored on a 5 point Likert scale ranging from 'Very unpleasant' to 'Very pleasant' and consisted of the words 'and it was…'

Two other items were presented pertaining to previous events and these consisted of the consideration of 'How many nice/stressful events have (the participants) experienced since the last prompt'. The items were scored on a 5 point Likert scale ranging from 'none' to 'a lot' participants responded to 'Nice' and 'Stressful', which constitute items PE (Pleasurable Events), and SE (Stressful Events) respectively. These items were devised for the purposes of this investigation the validity of these items has been examined in Section 3.3.2.

Drug use items

After the items pertaining to 'events' participants responded to a dichotomous item requesting the participants to consider if they had '…used cannabis since the last (prompt)?' A positive ('Yes') response from the participant resulted in the presentation of three additional items pertaining to their cannabis use. Participants were asked to document 'What type of cannabis [they had consumed]?' Participants responded with one of the following options; 'Hash (cannabis resin/solid)'; 'Skunk (sinsemilla)'; 'Traditional herbal cannabis (bush)'; 'Cannabis

oil'; or 'Don't know'. Respondents also documented by which method of administration the drug was consumed either; 'Spliff/Joint- Tobacco cannabis mix'; 'Blunt, Bong or Pipe- Only cannabis'; 'Vaporiser'; or 'Eaten'. The final item in pertaining to cannabis consumption was in regards to how many units of the participant's standard dose had been consumed ('How many have you had?'). The advantage of the participant assessing their standard dose is that in the presence of vast numbers of uncontrolled and immeasurable variables (see Section 1.4) a measure of quantity can be made. However, the dose of cannabis consumed can only be considered within participants, in the absence of a standard unit common across the sample.

After the items pertaining to cannabis consumption participants were presented with four open text boxes, to document their consumption of drugs other than cannabis. There was a text box pertaining to the consumption of caffeine, tobacco, alcohol and any other drug, which participants were requested to respond in as much detail as possible. The consumption of one cigarette was considered as one unit, this was the only means by which nicotine was consumed. Caffeine and alcohol consumption were more challenging to quantify. The most commonly consumed caffeine substance in the sample was tea. Thus, one cup of tea formed the base unit (one cup of tea = one unit). Purcărea, Chiş, Vicaş, and Fodor (2008) suggest that "tea usually contains about half as much caffeine per serving as coffee" (p.966). However, it should be noted that there is a high degree of variability in the ranges of caffeine between tea products (Purcărea et al., 2008). Thus the second most commonly consumed form of caffeine, coffee, was considered as two units. Each caffeine containing carbonated drink (e.g. Coke) was coded as one unit, as these are thought comparable to one cup of tea. "When compared to previous studies, the caffeine concentration (per oz) in brewed teas tended to be lower than in specialty coffees and energy drinks, but similar or higher than carbonated sodas" (Chin, Merves, Goldberger, Sampson-Cone, & Cone 2008, p.704).

These 'carbonated sodas' were differentiated from 'energy drinks' in the current investigation. A standard measure (250ml) of a popular brand of energy drink (Redbull) contains 80mg of caffeine. This value is higher than the range of tea

caffeine volumes per serving documented by Chin, Merves, Goldberger, Sampson-Cone & Cone (2008) (14 to 61 mg). Furthermore, in an analysis of various drinks available on the market it was reported that the "caffeine content for the majority of energy drinks included in this study was higher than the maximum allowed limit for cola beverages" (McCusker, Goldberger, & Cone, 2006, p.114). Thus, each energy drink was coded as two units.

A different approach was taken to measuring the consumption of alcohol, due to the use of standard volumes of liquid and percentages of alcohol content, in addition to average data pertaining to those factors. Thus, in the instances where participants made reference to specific brand of alcohol beverage and/or specific volume, the units of alcohol (UK unit) consumed were calculated precisely. In instances when any of the specific information was absent or ambiguous average volumes and percentage of alcohol content were utilised (See Turner, 1990).

Cannabis Experiences Questionnaire-brief (CEQ-b)

The CEQ-b comprises of a checklist of cannabis induced experiences, this measure consisted of the aversive subscale of the CEQ, twenty items identified by the factor analysis conducted by Stirling (Unpublished data, see Section 2.2.3 and Appendix 1). This subscale consists of seventeen concurrent cannabis experiences (e.g. feeling fearful) and three after effect experiences (e.g. paranoid without reason). For the concurrent items participants responded to; 'Have you had the following experiences today whilst using cannabis?' For the after effect items participants responded to; 'Have you had the following experiences today AFTER the initial effects of cannabis?' Participant's responded to the CEQ-b on a 5-point Likert scale ranging from 'Not at all' to 'Very much so'. These items were answered once daily for the duration of the two week ESM period.

Post-ESM Measures

Quantitative Feedback Questionnaire (QFQ)

In the post ESM phase a quantitative feedback questionnaire devised by Palmier-Claus and Lewis (personal communication) was administered. The questionnaire consists of 26 items, 3 of which are related to time taken, e.g. 'How long did it take

you to complete each set of questions once you started?' These items are scored on a Likert scale (typically) ranging from 1 (within one minute) to 5 (5+ minutes). The other 23 items are related to the participant's experience (e.g. 'Did answering the questions take a lot of work?') these are scored on a 7-point Likert scale ranging from 'Not at all' to 'Very much so'. For brevities sake the data gleaned from this measure will not be considered within this thesis.

Measures utilised in the testing of ESM items

Psychotomimetic States Inventory (PSI)

The PSI (Mason, 2008), a measure of a schizotypal state, was administered for the purposes of establishing concurrent validity for the SSQ. The PSI is a 48-item self-report measure with rubric 'Please complete the following questions by circling the number that best describes your experience at the moment'. Participants respond to items such as 'at the moment: you think you are being talked about' on a 4-point Likert scale ranging from 'Not at all' to 'Strongly'. The 48 items disaggregated into 6 subscales pertaining to; delusional thinking (8 items); perceptual distortions (10 items); cognitive disorganisation (9 items); anhedonia (7 items); mania (6 items); and paranoia (8 items).

Weekly Stress Inventory (WSI)

To help establish concurrent validity with the ESM measures of stress (and stressful events) participants completed the WSI (Brantley et al., 2007). The WSI was completed twice throughout the course of the ESM period (at the end of the first week and again at the end of the second). The WSI is a 25 item measure which participants respond to on a 7-point Likert scale with items such as 'Lost or misplaced something (wallet, keys)'. The WSI generates scores on two scales; the 'Events' scale that documents the occurrence of stressful events; and the 'Impact' scale which assess the psychological impact of the aforementioned events.

3.2.5 Piloting

Piloting of measures

Prior to the initiation of this investigation the measures were piloted with ten cannabis using participants over a two week ESM investigation. Instead of using smartphones to record responses paper and pen methods were utilised. Prompts were sent in the form of text messages to participants' own mobile phone. This allowed for an assessment of the measures prior to the availability of the hardware. As a consequence of feedback from participants after the ESM phase it was deemed that the effort required was not too excessive for the population. However, the feedback gleaned from this endeavour proved invaluable in altering the presentation and scoring of some items. For brevity and clarity six dichotomous items pertaining to previous stressful events were changed to what are currently items PE, and SE.

To assist with the participants understanding the anchors of the SSQ were altered from 'hardly at all' to 'definitely', to their current notation of 'strongly disagree' to 'strongly agree'. The CEQ-b showed little variability in the data and thus a dichotomous ('Yes' or 'No') response was adapted to a five point Likert scale. The item used as a framing tool for ER previously referred to "The most important event…" however, several participants inferred that they did not complete the item because 'nothing important had happened to them'. Thus, this item was subsequently changed to "The most noteworthy event…" Several participants also reported difficulty remembering the meanings of the words aloof, vague, and elusive which are contained within SSQ items. As a consequence of this feedback in the current investigation these words were accompanied with a brief definition (See Figure 4).

To further increase the breadth of the information gained after the piloting phase an additional item was added pertaining to the preparation of cannabis consumed (e.g. sinsemilla, cannabis resin etc.). Furthermore, two additional options were added in the consideration of methods of administration of cannabis; eaten (orally consumed); and in a vapour form (vaporised cannabinoids).

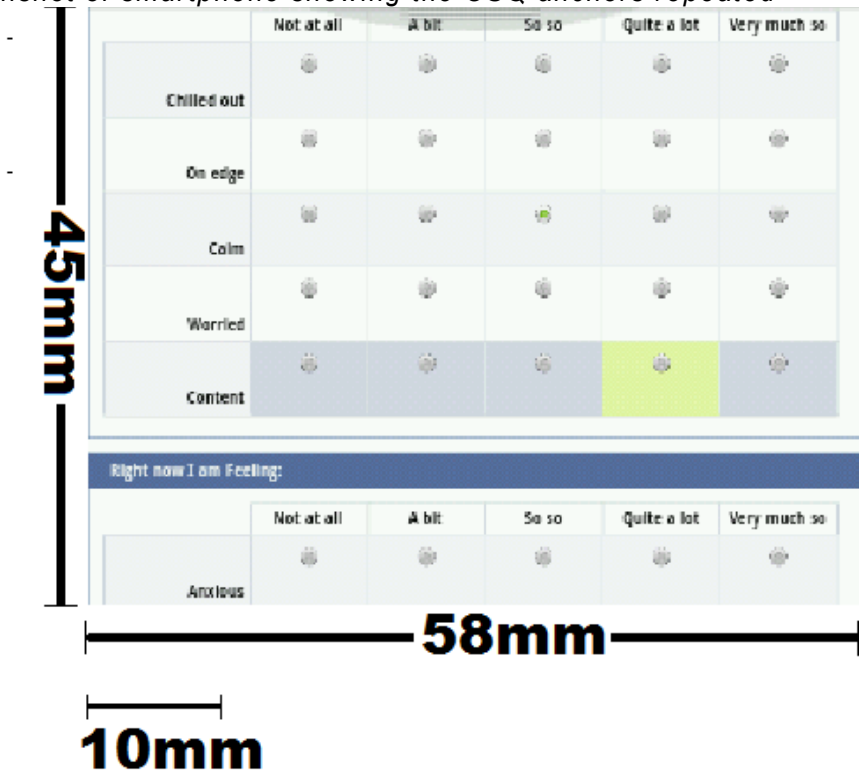
Piloting of technology

After the piloting of the measures five participants (three non-cannabis users, two cannabis users) assisted with the piloting of the technology. This pilot investigation was much the same as the current investigation. Feedback from the pilot helped to establish the topics included in the two 'how to guides' assisting with phone use (Appendix 23) and answering items (Appendix 24). Furthermore, many aesthetic aspects of the design were also adapted to facilitate ease of use. One example is the CSQ items were split into two tables so that the anchors could be seen at the same time as all of the items, reducing the need for scrolling up and down (see Figure 6). Moreover, the pilot study highlighted two errors (bugs) which were causing an unexpected reaction between the different technologies.

The pilot investigation utilised drop down menus in some instances e.g. for selecting a method of administration of cannabis. However, drop down menus from time to time caused a several second delay between button press and device action. On occasion drop down menus also caused the browser to crash. Irrespective of the errors associated with this question format participants also documented that they took longer to respond to than other types of question. As a consequence in the full investigation drop down menus were replaced with other question formats (e.g. tick boxes).

Figure 6

Screenshot of smartphone showing the CSQ anchors repeated



The main error that was highlighted by this piloting phase was one attributable to the use of cookies. At the end of answering a questionnaire an error occurred if the participant did not close the browser window before exiting the web browsing application. When starting up a new data submission the questionnaire hosting facility detects that the device already has a data entry 'session' in progress and does not allow another one to commence. As a result of this in the current investigation participants were advised to only have one data entry browser window open at a time. Furthermore, the Maxthon browser was added in private browse mode to ensure the automatic deletion of cookies at the end of each session.

3.2.6 Procedure

This investigation consisted of several distinct phases, the schedule of the pre-ESM phase and ESM phase measures are considered in Table 19.

Table 19

Data entry schedule throughout the duration of the investigation

Day	ESM diary	CEQ-b	PSI	WSI	CEQ and SPQ-b-L
T -1					1
T 0	1		1		
T 1	6	1			
T 2	6	1			
T 3	6	1			
T 4	6	1	1		
T 5	6	1			
T 6	6	1			
T 7	6	1		1	
T 8	6	1			
T 9	6	1			
T 10	6	1			
T 11	6	1			
T 12	6	1			
T 13	6	1			
T 14	6	1		1	

Pre-ESM phase

The pre-ESM phase (T-1) consisted of the completion of the CEQ and the SPQ-b-L in addition to several other items to assess eligibility for participation in the ESM phase. Participants left contact details in the form of email, phone number or postal address and a name or pseudonym. Participants were given the opportunity to respond electronically (via the research group's website) or alternatively to respond via 'hard copy' (none did so). Participants logged on to the website where they could read information relating to the background of the research in addition to a participant information sheet (PIS, see Appendix 27) and consent form (Appendix 28). Due to the medium of electronic participation, participants affirmed consent through clicking a button as opposed to a signature.

Once the measures had been completed, at a future time point, the researcher contacted the participants by telephone or email. During this exchange the

respondent was provided with further information about the ESM phase of the investigation and an assessment was made of the participants' eligibility for it (see Section 3.2.2). If the participant was receptive and eligible, a meeting (briefing session) was arranged. These briefing sessions were at a time most convenient to the participant (in some instances this was late into the evening) and a location of the participant's choosing, this was typically on one of the MMU university campuses or in the participant's own home.

At a time prior to the meeting it is necessary for the researcher to prepare the equipment for use. A new 'Pay as you go' Subscriber Identity Module (SIM) card was installed, which assigns the card a new (unused) phone number. This phone number was then added to the messaging distribution facility database and a link (SMS message), with the relevant measures for the briefing session, was forwarded to the smartphone. The researchers contact details were then stored in the device for the participants' use. The day prior to the meeting £10 worth of credit was added to the device. This served several functions, under the promotion offered by the network provider it allowed the smartphone to utilise up to 100 megabytes (MB) of data usage (web traffic) within a 30 day period (in addition to 400 SMS messages). This was more than sufficient for the data usage necessary for completion of the study (which was estimated at 11.7MB).

The second purpose of the phone credit was it provided the participant with a means of contacting the researcher without incurring any costs. The 400 SMS messages and £10 of phoning credit was well above what would be required to contact the researcher, and thus participants were encouraged to utilise the phone for their personal purposes if they so wished. The rationale for this was it was anticipated that by utilising the device more there would be an increased chance that the smartphone would be in close proximity to the participant when a prompt was received. This also served the purpose of (feasibly) increasing the participants' familiarity and engagement with the smartphone.

At the briefing session (T0) participants were provided with a background to the research and the purposes of the study. Participants were provided with a 'hard copy' of the PIS and were asked to carefully read through it and ask the

researcher any questions they may have. Participants were presented with a consent form and if they were agreeable they affirmed their consent by signing, a pseudonym was once again permitted. Then the researcher and participant in conjunction completed the briefing document.

This document was utilised for two purposes; to capture demographic information not considered by the other measures; and to provide a portrait of the participant's anticipated schedule and cannabis use over the coming ESM period. The items collecting demographic data were pertaining to employment status and age at which the participant first became a (at least once) monthly cannabis user. The items pertaining to the participants schedule facilitated the construction of parameters by which the (pseudo)-randomised prompts could be scheduled within (e.g. What time do you anticipate you will wake up on each of the study days?) Utilising the information gleaned participants were once again assessed against the inclusion and exclusion criteria (Section 3.2.2 pp. 170-72).

The researcher then conducted a brief training session describing how to use the smartphone's functions (e.g. how to log in to a Wi-Fi network, mute the phone etc.), here participants were given a how to/trouble shooting phone guide (Appendix 23). The demonstration then progressed to describe how to use the phone to answer the questionnaire. The participants were then given a second 'how to guide' pertaining to accessing (and answering) the measures hosted on the internet (Appendix 24). The participants then read through the items that were due to be administered six times a day, i.e. the signal-contingent measures (SSQ, CSQ, Event Related items, drug consumption items). Participants were given the opportunity to ask any questions about the items they were due to answer. Once any queries were satisfied participants proceeded to initiate their first unsupervised data entry.

In addition to testing the main aims of this investigation, the validity and in some instances reliability of some of the signal-contingent measures were also assessed. Thus to assess the concurrent validity of the SSQ at T0 participants also completed another state measure, assessing psychotomimetic experience (PSI) in close temporal proximity (<3 minutes). Both these measures were

completed by all participants who started the ESM phase. However, participants could opt to submit an extra data submission at a later time point.

The SSQ and PSI were administered in a randomised counterbalanced crossover study design to eliminate the possibility of an order effect. Dependent on which condition the participants were assigned to, this consisted of completing the signal-contingent measures prior to the PSI or vice-versa. Participants were once again provided with the opportunity to ask any questions. After this data entry, participants were presented with the interval contingent measures (CEQ-b) and the researcher responded to any questions about the items. Once any questions were answered this was the end of the briefing session. The next day the ESM phase of the study commenced (T1). With the exception of one participant who, due to unforeseen circumstances, started two days after the briefing session.

After the briefing session, but before the commencement of the ESM phase utilising the information provided; random times were generated for the schedule of the interval contingent 'prompts'. Utilising this information SMS text messages were scheduled to be sent via the message distribution facility for all prompts due on T1 to T4 (inclusive).

In comparison, to some other ESM investigations, a less stringent parameter was applied in regards to the participant's potential hours of response, with others ensuring the participants hours of response are uniform (e.g. Husky, Mazure, Carroll, Barry, & Petry 2008; Kimhy et al., 2006 etc.). However, given the population under investigation there is sufficient rationale for adapting this arbitrary parameter. Thus, an approach more responsive to individual need was adopted.

In the current investigation participants were able to assign their own hours of response, and these hours of response could vary from day to day (e.g. to allow for a longer resting period at the weekends). Participants were also able to suggest times when it would be inappropriate for them to respond (e.g. whilst performing in a sporting event). However, few did with most preferring to utilise the option to mute the 'prompt' generating device. Despite the need to be sensitive to

the participant's schedules, parameters were still assigned to ensure some uniformity between respondents (see Section 3.2.2).

ESM phase

The participant then entered the ESM phase of the investigation (T1). On every day of the ESM phase of the investigation the participant is sent a link to the signal-contingent measures six times per day, in addition to one to the (interval-contingent) CEQ-b at around their anticipated bedtime. On the fourth study day (T4) participants were presented with the option of entering a second PSI completion, to assist with an assessment of test-retest reliability. Participants were presented with this opportunity at each of the six interval-contingent prompts they received on T4. Participants were informed that the second completion of the PSI was not mandatory and did not impact on their minimum data requirements, this questionnaire could be dismissed by the press of one button (Figure 7).

Throughout the course of the ESM-phase the data was frequently monitored utilising the questionnaire hosting facilities. Typically prior to the fourth day of the 'ESM phase' the researcher contacted the participant to enquire with regards to the appropriateness of the schedule. Additionally, in lieu of the participant's data submitted (or not submitted) up to that time point the researcher when necessary provided additional guidance or support and reminded the participant of their right to withdraw. If the participant wished to proceed the remaining 'prompts' (T5 – T14) were scheduled on the message distribution facility.

Figure 7

Screen shot of smartphone displaying item requesting a PSI completion

To assist with assessing the concurrent validity of the SSQ scales, and the event related items (ER, SE and PE), participants performed a weekly assessment of stress, the WSI. On the seventh (T7) and fourteenth (T14) day's participants were presented with the WSI, the completion of which was optional. On each of those days participants were presented with two SMS messages containing a link to the WSI, these were not sent within forty-five minutes of another prompt or within three hours of each other.

Typically between three to five days since the last contact, the researcher contacted the participants again (typically T7 or T8). However, daily monitoring of the data was undertaken and thus in instances where there was a large proportion of missing data the participants were contacted sooner. Participants were contacted once more, prior to the cessation of the ESM phase (typically T12 – 14). After the end of the ESM phase of the investigation another meeting (de-briefing) was arranged with the participant.

Post-ESM phase

At the de-briefing the smartphone (and charger) were collected back from the participant, remunerations and study advertisements (to facilitate snowball recruitment) were distributed and both oral and written feedback from the

participant was sought. Oral feedback was sought according to four broad domains related to; the device and technology; items presented in the study; the methodology; and the demands placed on the participant. Written feedback was acquired in the form of the quantitative feedback questionnaire.

The SMS messages sent from the messaging distribution facility that are stored on the smartphone are exported off the device. Then any of the participant's personal data is removed from the smartphone, and the SIM card associated with the device disposed of. The participant's data is downloaded from the questionnaire hosting facility and the databases are reset ready for another participant's data.

3.2.7 Ethical consideration

Risks and possible harm

The procedure was granted approval by the MMU Research Ethics Committee. This investigation represented no tangible risk to respondents. However, as participants completed items pertaining to psychotic-like symptoms and *their* own drug use there is a possibility of causing some degree of distress in certain sensitive individuals. To minimise this, participants were reminded throughout the investigation of their right not to answer any items which they found distressing. Participants were also informed of their right to withdraw their data at any time point during and up to two weeks after the completion of the ESM phase.

The research group's website contained a list of information groups and support services aimed at addiction, drug use and mental health for the use of any participant experiencing distress. This information was also included on the 'hard-copy' of the participant information sheet distributed out at T 0.

A more likely consequence of this methodology is that some of the participants found the investigation intrusive, particularly whilst trying to conduct other activities. To minimise the occurrence of intrusion participants were informed on how to mute the smartphone, or switch it off. However, participants were reminded not to respond to the device at any time that it may be dangerous to do so, for example whilst driving. Although not decreasing the inconvenience of the intrusive

methodology participants were remunerated for their efforts in the form of a £20 shopping voucher.

In addition to the intrusion per se of being frequently 'prompted' the completion of multiple data entries can be time consuming. Unfortunately, this is an unavoidable aspect of the methodology, in the current investigation several piloting phases were utilised to expedite item completion. These developments were typically in the form of adaptations to the visual display of items and the manner which data is input into said items. Furthermore, when appropriate (i.e. SSQ) items have been truncated to allow for the quickest possible response time.

Confidentiality

Due to the sensitive area of research (illegal drug use) confidentiality was paramount in this investigation. Therefore, several steps were taken to ensure confidentiality. In the pre-ESM phase only necessary contact details were collected and this could be in whichever medium the participant wishes to be contacted via. If contact *is* made by phone the participant *is always* asked whether it is an appropriate time to have a confidential conversation. Furthermore, participants were given the option to use a pseudonym throughout the investigation (many of whom exercised this option) thus, although not permitting full 'anonymity' (as the study requires a face to face meeting) this does serve to decrease the possibility of breaches of confidentiality. Nonetheless, further steps were taken to ensure confidentiality. In instances where the participant briefing session was undertaken on a university campus at no point was their name or the area of research (i.e. illegal drug use) reported on any of the relevant documents for booking a room or facilitating a visitor access on to campus.

Participants were able to request not to receive 'prompts' to be delivered at certain times. In an attempt to minimise intrusion into the participant's lives and also reassure them that they will not be contacted at times when they anticipate they will be in proximity to persons who are unaware of their drug use. Furthermore, the device had no (visible) identifying marks as one associated with research and is a model commercially available and commonly purchased. In the information stored

on the device itself no reference is made to cannabis or drug use, thus even in the instance of access by persons other than the participant this would not result in a breach of confidentiality or data protection.

Through the use of a private browsing mode to access the measures no data is ever stored from the internet on to the smartphone this includes cookies, memory cache data etc. Thus as long as the participant does not have an active session running (i.e. is not currently completing the measures) it is impossible to access any study data from the smartphone. In the instance of an active session only the data due to be submitted is accessible. All study data (including the pre-ESM measures) was stored on the questionnaire hosting facility prior to exportation to data analysis software. Only the primary investigator had access to the account on which the data was stored.

Data was sent from the smartphone to an 'in-house' server, for the advantages of the use of an in-house server please see Section 2.2.6. Only the named researchers had access to data stored on the server. Once this data was downloaded it was stored on a password-protected computer (in a locked office) that only the researchers had access to. No personal identifiers were stored with the data to ensure confidentiality, and individuals were, instead, identified by a unique identifier number.

3.2.8 Analysing multilevel data

Procedures adopted in the current study

ESM presents a unique set of challenges when analysing the resultant data. 'ESM data has a hierarchical structure in which repeated observations are nested within subjects' (Kimhy et al., 2006, p224). Due to this structure (see Figure 8) typical 'uni-level' tests of association, such as multiple regressions and logistic regressions, cannot be applied. Every participant enters multiple repeated observations these cannot be viewed as independent, as the observations associated within each respondent will in all likelihood have a greater similarity, than observations between respondents. Moreover, the observations submitted

within a participant on a specific day will in all likelihood have a greater similarity to other observations submitted on that day, in comparison to observations from other days within that participant. Consequently, multilevel modelling (MLM) is typically performed which takes into consideration the structure of the data i.e. the non-independence of observations (e.g. Henquet et al., 2010; Myin-Germeys, Delespaul, & Van Os, 2005; Tournier, et al., 2003; Verdoux et al., 2003 etc.). Data was analysed using STATA 12.1 (StataCorp). For analyses with binary outcome variables the Xtmelogit routine was performed. Whilst testing continuous dependent variables the Xtmixed command was utilised.

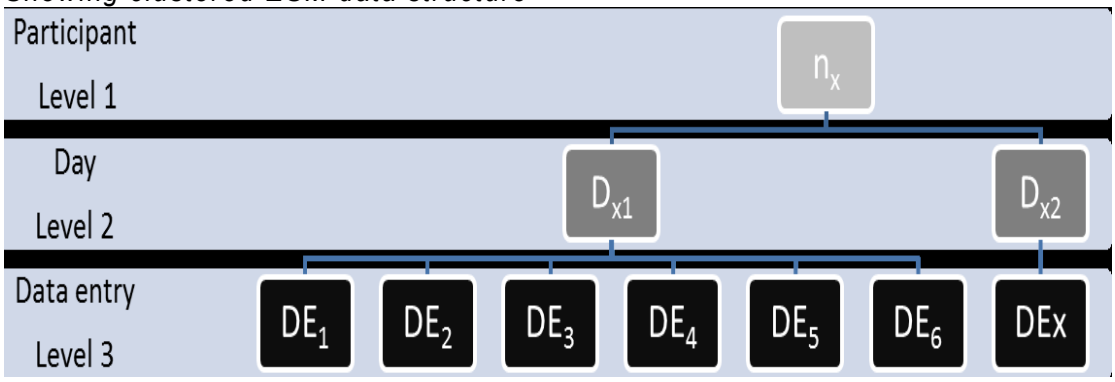
The majority of multi-level analysis described in this thesis utilise a three level model; where data entries (level 3) are nested within days (level 2); and days are nested within participants (level 1) (see Figure 8). The modelling of the data structure in this manner should account for the non-independence between the observations. This three level structure models the relationship between multiple responses generated by one individual and the relationship between responses in any one given day. Thus, the model should be adjusted for individual differences between participants, and differences within participants between the events behaviours and states of mind associated with a particular day. To rephrase the third level of the model is addressing the assumption that there are 'good days' and 'bad days' and adjusting for this accordingly. The three level model has the participants at the top level of the hierarchy (level 1), and individual data entries at the lowest level (level 3) (see Figure 8). However, it is worthwhile noting that in some texts (e.g. Snijders and Bosker, 2012) the level notation is reversed with units at the micro-level (in Figure 8 Data entry level) being described as "level-one units" (p.8).

However, in this thesis there are three exceptions to a three level data structure; the validation described with regards to the WSI (Section 3.3.2); and the analyses including the CEQb as an outcome variable (Section 4.3.1). These measures were administered on a weekly and daily basis (respectively) consequently there is no variability in the level three unit, making a three level analysis inappropriate. Analyses with these measures utilised a two level data structure where weeks/days (level 2) are nested within participants (level 1). The third exception

occurs in the instance when the third model fails to account for variance within the data i.e. the third data level does not alter responses. In such instances (i.e. Section 3.3.6) a two level model will be adopted with days constituting the lowest level unit within the model.

Figure 8

Showing clustered ESM data structure



It is convention in ESM research to centre 'continuous' predictor variables around a meaningful value, this procedure is typically adopted for ease of interpretation of the output and to give the relevant scores a mean, or true value of 0 (Bolger and Laurenceau, 2013 pp37-9). In most analyses in this investigation the grand mean (mean of all participants' scores) is the most appropriate value to centre to. However, there is an exception, the variable 'quantity of cannabis consumed'. As cannabis is the focal point of this investigation cannabis consumption per se is considered in most models displayed herein. To establish the presence of a 'dose dependent effect' a measure of quantity of cannabis consumed must be considered. Measuring cannabis consumption is very challenging (see Section 1.4).

The procedures adopted in this study to measure cannabis consumption generate values which represent a proxy as opposed to literal measure of cannabinoid absorption. Participants were requested to estimate their standard dose (e.g. one "spliff") and record each time this amount was consumed. Thus, quantity of cannabis consumption is relative to each participant and therefore not comparable between participants. Consequently, an adjustment must be made to the value at which quantity of cannabis consumed is centred around. The most appropriate

value to centre to is the participant's own mean. Thus, the value contained within the predictor variable will represent fluctuations within participant's overtime.

In order to generate a variable representing within participant effects initially a variable was created centred to the grand mean (the mean of all participants' scores). Following the procedure outlined by Bolger and Laurenceau (2013) this variable was then split "into two (orthogonal) components: a between-subjects means component….and a within-subject deviations from those means components." Thus, allowing for observation of the within participants effect of cannabis consumption. These newly created variables representing between and within participant effects cannot be considered within the same model as cannabis consumption per se. The data regarding consumption per se and quantity of consumption are highly related. In some instances these items may contain the same value, which is pertaining to the same event a consumption of (solely) one cannabis unit since the last data entry. If the aforementioned were considered within the same model this may result in collinearity. Thus, cannabis consumption and quantity of consumption will be considered independently from one another within separate models. However, this also applies to variables which require the presence of cannabis consumption within the model, i.e. the variable pertaining to the interaction between cannabis and stress (CXS).

Cannabis consumption is a binary variable, whether cannabis is consumed or not. By multiplying a binary variable by a continuous variable it is possible to generate a variable that represents the interaction between its two composite parts. In this instance cannabis consumption is multiplied by CSQ Stress (centred) thus generating a variable that consists of scores on the CSQ Stress scale (only) when combined with cannabis use (per se). Thus when the interaction of stress and no cannabis consumption is considered a value of zero is assigned. By centering CSQ Stress around the mean value this ensures that the data set contains negative values, and thus the zero value does not influence the point of intercept. This technique of creating an interaction variable is described in Bolger and Laurenceau (2013, chapter 5), for use in a moderation analysis. If the newly created variable (cannabis x stress, CXS) is considered as a predictor in the same model as both cannabis consumption and CSQ Stress then the effect of the

interaction variable can be considered as independent of its composite parts. Hence, the rationale for not including the CXS variable in analyses utilising the variable pertaining to quantity of cannabis consumed. Unlike, the procedure described by Bolger and Laurenceau (2013) CXS is considered an explanatory variable in all levels of the analysis (both within and between participants). In the current investigation, CXS may be considered to reflect the effect of stress (on the predictor variable) when cannabis has been consumed in the moments since the last valid data entry.

Variables which are hypothesised to contribute to the outcome variable are considered simultaneously within the same model, with the exception of possible instances of colinearity. Whilst using a multilevel hierarchical linear regression all explanatory variables within the model should be able to establish the effects of each variable on the outcome independently from one another. Thus, the inclusion of certain variables (i.e. alcohol consumption) although not pertaining to a specific hypothesis will control for the activity or behaviour and should in theory reduce the size of the residual. As Snijders and Bosker (2012) state

> Some variable, say X_q, may be omitted from the fixed part of the model. Part or all of this variable will then be represented by the residuals in the random part. If the fixed part includes some variables that are correlated with X_q, then the effects of the variables included will take up some of the effect of the variable omitted (p.157).

However, in the current study stable (or relatively stable) between participant differences, do not need to be controlled for (e.g. age) as these between participant differences are inherently modelled within the data structure (level 1, participant level).

However, the same approach cannot be adopted for the analysis utilising a binary outcome variable, whether cannabis has been used or not. If items not directly pertaining to hypotheses are included in the analysis utilising a binary outcome variable then this may result in miss-estimation of the other predictor variables.

> Now suppose that a multilevel logistic or probit model has been estimated, and the fixed effect of some level-one [level three in the current study, the data entry level] variable X_{r+1} is added to the model. One might think that this would lead to a decrease in the level-one residual variance σ^2_R. However, this is impossible as this residual variance is fixed, so that instead the estimates of the other regression coefficients will tend to become larger in absolute value and the intercept variance (and slope variances, if any) will also tend to become larger (Snijders and Bosker, 2012, p309).

Thus, when utilising the xtmelogit routine a different strategy to analysing the data will have to be adopted. Initially all the relevant predictor variables will be considered within one model. The model will then be recomputed with any predictor variables identified as not achieving significance (at the 0.05 level) dropped from the analyses. Thus, this should help prevent mis-estimated odds ratios (O.R.) as a result of "[increasing] the random intercept variance and the effects of uncorrelated level [three] variables" (Snijders and Bosker, 2012, p321).

Mis-estimation as a result of adding effects of level three variables is a methodological constraint that is common to all analyses that utilise regression and a binary outcome variable. One methodological disadvantage that is typically associated with most (micro) longitudinal data collection techniques such as ESM is the problem of missing data. The frequency of missing data elicited from ESM type research typically prohibits the use of other statistical procedures (than MLM) of modelling data structure such as that which can be applied with ANOVA and the related statistical procedures.

In the current study missing data typically occurred in the form of missing the entirety of the items associated with a signal contingent prompt, referred to as unit missingness or non-response. This has been described as a "ubiquitous problem" with participants often displaying "intermittent missingness" (Rabe-Hesketh and Skrondal, 2012, p 278). Fortunately, utilising maximum likelihood estimation in instances where data is 'Missing At Random' (MAR) this ensures "that consistency…is retained for correctly specified models" and has the added advantage over "old-fashioned approaches to longitudinal data, such as MANOVA,

where subjects with any missing responses or covariates are discarded altogether…Using all available data does not waste information and is less susceptible to bias." (Rabe-Hesketh and Skrondal, 2012, p 278). Thus, MLM is preferable to ANOVA related statistical procedures. However, utilising such an approach may introduce bias when data is not MAR, unfortunately such instances are difficult to identify.

There were instances of missing values within data entries (item missingness), however, these were less frequent than non-response. Furthermore, item missingness did not appear to occur in any consistent patterns (See Table 20). In an attempt to glean information about variables which may predicate non-compliance with the methodology or item reactivity participants that were included, and those that were not, were examined together for item missingness.

Table 20

Summary of missing data points of ESM data collected for both participants included and those not included in the main analyses

Measure (number of items)	Number of items with missing values (%)	Responses without item missingness* (%)	Most frequent pattern of missingness* (%)	Minimum number of values in a row prior to prorating
SSQ (22)	16 (73)	90	<1	15
CSQ Stress (6)	6(100)	96	<1	4
CSQ Calm (5)	5 (100)	96	<1	3
Event Rating (1)	n/a	90	10	n/a
Stressful Events (1)	n/a	95	5	n/a
Pleasurable Events (1)	n/a	94	6	n/a

*Percentage of the items with missing values

In instances of item missingness when these items contributed to a scale, a procedure of prorating was adopted. Thus, imputation was undertaken for the SSQ total, CSQ stress scale, and CSQ Calm scale. Prior to imputation participants must have attained a minimum number of values (see Table 20.). If these requirements were met a procedure of prorating from the mean score of the data was adopted. In the context of ESM research prorating using the grand mean (the mean of all responses for all participants on item *x*) or even participant mean (the mean of all responses on item *x* for the *i*th participant) is not appropriate as this is contrary to

the notion of a hierarchical data structure. If the grand mean or participant mean were the most appropriate value to prorate from this would invalidate the necessity for a multilevel analysis, as this would be based on the assumption that the mean of all participants data (grand mean), or all data from a given participant is the most related value. In the context of the assessment of variables which fluctuate from moment to moment, the most related data is that which is collected from the same person within the same time period. Consequently, the mean of data collected at the same time point was utilised. For instance if one item was missing from day one, data entry one on the SSQ scale, the mean of all items from the same scale within the same data entry were pro-rated to the missing value.

In this chapter (and Chapter 4) there are several figures displaying the fluctuation of variables over time. In all cases an inspection of all participants' scores has been undertaken, however, given the volume of data it is impractical to display it here in its entirety. Instead, a subset of participants will be selected on the basis of their mean score over the ESM period, and their data for day number one (T1) will be displayed, this was a similar procedure to that adopted by Bolger & Laurenceau (2013). Participants scoring the highest within the 5^{th}, 25^{th}, 50^{th}, 75^{th}, and 95^{th} percentile of the measures under assessment will be displayed graphically. However, the plotting of time in a figure and the utilisation of time as a variable or concept may introduce bias if caution is not applied.

Methodological challenges of non-equidistant data entries

Contained within this chapter there are several figures representing the fluctuation of the relevant ESM measures over time. It is suggested that one of the pre-requisites for the utility of multi-level modelling is variability in the data (Snijder and Bosker, 2012, p153). Utilising a scatterplot it is possible to display variables according to time. In the instance where non-equidistant data inputs are utilised the creation of such a scatterplot may result in miss-estimation if each data input is considered as a unit of time. There are several advantages of non-equidistant prompts (see Section 3.2.1), however, one disadvantage is time is a proxy (rather like ranked data) as opposed to a true continuous variable. As a consequence of the limitations of utilising ranked data, for the scatterplots contained in this chapter

time will be considered on a scale of the number of minutes since that day's first data entry, rather than i_{th} data entry of that day.

The limitations of ranked data do not only present a challenge when plotting responses, but may also result in miss-estimation of the statistical model. One means in which it is possible to circumvent this methodological limitation is to record the time at which participants submit their data and utilise this variable as the measure of time.

Several analyses contained in this section have utilised items referring to the time period "since the last (data entry)". Furthermore, variables which are time adjusted to refer to a previous as opposed to current data entry (a lagged variable) have been utilised. There are two types of time lagged variables utilised in this thesis, one which refers to the previous data entry (within the same day) this is denoted by the (post) superscript time – number of data entries ($^{t-x}$), for example CSQ Calm $^{t-1}$. The other type of lagged variable utilised herein is one which has had a day (24 hour) time lag applied which is denoted by the (post) subscript Time – (number of days) e.g. CEQ-b_{T-1}. By lagging data entries the effect of previous response and action on concurrent response can be measured, for example it is possible to predict the effect of a schizotypal state on future cannabis consumption.

Non-equidistant time points do not just present methodological challenges for accurately plotting time, they can also introduce bias into analyses with both lagged and retrospective items. The use of these retrospective items is advantageous for recording both infrequent and enduring events such as cannabis consumption and its subsequent period of intoxication. Despite the utility of such items when utilised simultaneously as non-equidistant data entries they present a methodological challenge. One means by which this challenge can be addressed is to include the effect of time within the statistical model to be tested.

Bolger and Laurenceau (2013) recommended "the influence of time should always be taken into account in your statistical model. That is time should be an explicit factor, or predictor, in any model of interest" (p27). The amount of minutes that have passed since the last data entry will be considered as a predictor in all

models that utilise retrospective or time-lagged items, within tables this variable is referred to as Time. This should help to negate the effect of the linear relationship between some of the predictor variables and time (e.g. amount of cannabis consumed since last entry and time since last entry). Consequently, it would be anticipated that all coefficients (betas) cited are in consideration of when the time difference is at a constant of zero. Thus, an attempt has been made to control for non-equidistant data entries. The efficacy of this adjustment (for the retrospective items) can be further increased by only including data points which have a completed response at the previous data entry. This will ensure that the time period in which the participant refers to does not span over two days or a non-predetermined proportion of one day. It is important to note that other more sophisticated methods of accounting for non-equidistant entries have been reported such as the "spatial power error structure approach", however, this method can currently only be administered on one platform (SAS) (Bolger and Laurenceau, 2013, p93).

A cautionary note on causality and terminology

Throughout this chapter reference is made to some commonly held theories, such as the 'Self-Medication hypothesis', the use of which is merely to signpost the relevant analyses to the reader. In the current study analyses have been conducted which will allow inferences to be made regarding said hypotheses, and the results obtained herein (in some instances) provide corroborating evidence. Nonetheless, all results must be considered in lieu of the literature discussed in the first chapter and the discussion contained within Section 3.4 and in no instances should be considered unequivocal support of said hypotheses.

At the core of all MLM is a regression type analyses. As a consequence the terminology typically associated with regression analyses, specifically the phrase "predict", is used throughout this thesis. However, the use of this terminology should not be mistaken to be an attribution of a causal inference. Establishing causality is very challenging (see Section 1.6) instances where causality can be inferred are typically reserved for studies that utilise an experimental design with manipulation of the dependent variables. The current study meets no such

requirement, as the relationships between the variables are being observed as opposed to directly (or indirectly) manipulated. Thus, the nature of the relationship between the 'cause' and the 'effect' is not established.

However, one of the advantages of ESM research, as opposed to cross-sectional study design, is it does satisfy one of the key principles that is a pre-requisite for causal inference; temporal priority (see Section 1.6.4). By establishing the sequence of the occurrence of the variables one can observe the effect of an independent variable on a dependent variable at a future time point. Nonetheless, although temporal priority may be established on one scale there are likely several relevant scales of time which may influence factors. The current study does not establish temporal priority at micro- or macro- levels of the scale of time under-investigation. For example, the current investigation does not measure second to second variability or, differences year on year.

Furthermore, temporal priority is not the only consideration in establishing causality and once it is established there still may exist multiple plausible explanations for the association between the two variables. The possibility of a third (unmeasured) factor accounting for an association between a predictor and an outcome variable typically cannot be eliminated. Neither, can in some instances the possibility of a synergistic (self-maintaining) relationship between predictor and outcome.

3.3 Results

The results comprise of several components the first of which sets out to describe the studies participant's and their resultant data (Section 3.3.1 pp. 207 -13), in this section comparison is drawn between participants who were included in the final analysis with those who are not. Section 3.3.2 (pp. 214-17) describes briefly some of the analyses undertaken as means of validating the measures utilised in this investigation. The process of validation is described in more detail in Appendix 29. Section 3.2.8 (pp. 195-205) discusses the statistical procedures adopted in performing MLM. The main analyses are contained in sections 3.3.3 to 3.3.6 (pp. 217-34).

Section 3.3.3 relates to covariates of a schizotypal state, which will expand on the discussion pertaining to cannabis' propensity to induce 'psychosis proneness'. Furthermore, in this section there are also results pertaining to a stress cannabis interaction effect. Section 3.3.4 further explores the notion of a cannabis stress interaction for the most and least stressed participants in the sample. Section 3.3.5 examines factors that co-vary with states of stress and calm which will further elucidate the relationship these variables have with schizotypal states. Analysis contained within this section will allow for inferences to be made about cannabis' purported anxiolytic effect. Section 3.3.6 assesses covariates of cannabis use, in this section the plausibility of the purported 'self-medication' of distressing symptoms related to psychotic disturbance is assessed.

3.3.1 Participant characteristics

The current study consisted of two phases; the pre-ESM phase in which participants were required to complete a screening questionnaire online to assess their eligibility for participation; and the ESM phase. One hundred and six participants began the pre-ESM measures, of those 86 participants completed the questionnaires. A total of 53 Participants (36 males) with a mean age of 27 years (SD 7.57) commenced the ESM phase of the study (for a description of inclusion and exclusion criteria see Section 3.2.2). After inclusion/exclusion criteria were applied, 36 participants (23 males) were considered in the final analysis.

Research utilising Experience Sampling Methodology (ESM) typically follow guidelines to enhance the validity of the data. As is the procedure adopted by other researchers, the current study requires participants to have entered a minimum of 30% of the signal-contingent items, participants recording fewer than this figure are thought to be less reliable and thus excluded (Henquet et al., 2010; Wichers et al., 2007). Eleven participants recorded fewer than 25 valid signal-contingent entries (30% of 84 opportunities for data entry) and consequently were not included in the main analysis. Furthermore, participants in the current study were required to have responded to the signal contingent prompts within a 30 minute window to be considered valid, as any time period longer than this may no longer be considered a 'momentary' response (Scollon et al., 2003). Any responses outside of these 30 minutes were excluded from the analyses. The interval/action-contingent items (CEQ-b) were not subject to a minimum of 30% completion, however, all participants completed at least 3 of the 14 opportunities to record data.

As the primary substance under investigation in this study is cannabis, participants were excluded if they had consumed any intoxicating substances other than cannabis, alcohol, nicotine and, caffeine at any point during the ESM phase. The frequency of alcohol, nicotine and caffeine consumption was sufficient in that it could be included, and thus controlled for as independent variables within the statistical models. Furthermore, "most joints contain tobacco" (EMCDDA, 2012, p119). That is to say that the majority of cannabis uses observed in this

investigation, and more broadly within the population; is the simultaneous use of cannabis and tobacco. Thus, to ensure the investigation is as naturalistic as possible tobacco use was permitted, as was caffeine and alcohol.

However, the use of other psychoactive substances resulted in exclusion from the analyses. This will ensure that these chemicals do not act as potential confounding factors during the analyses. The instances of consumption of other psychoactive substances were too infrequent, and not measured precisely enough to accurately adjust for their effects within the analyses (i.e. include them within the statistical model). For example, a participant consuming a unidentifiable white powder described to them as a specific substance could be surreptitiously ingesting a number of different licit and illicit psychoactive chemical constituents (Kavanagh et al., 2010; Parrott, 2004).

The rationale for excluding all (as opposed to a proportion of) data belonging to such participants is that it is difficult, if not impossible, to judge the period of intoxication or psychological disturbance induced. On this basis five participants were excluded, two for use of MDMA, one for use of amphetamine, one for use of "Magic mushrooms" and another for use of a combination of MDMA and cocaine. One other participant documented MDMA use however, they had submitted sufficient data (see above) prior to the event and consequently data up until that time point (day 8 [T 8]) was included in the main analyses. Another participant was also excluded from the main analyses as they had recently started a course of medication commonly prescribed to treat mental illness (fluoxetine). As there was not enough available data regarding the interaction between cannabinoids and SSRIs, this participant's data cannot be considered comparable with the rest of the sample.

There are several methods by which comparison could be drawn between the participants included in the final sample and those not included. Comparison could be made between those participants included and those that completed the screening phase, but did not initiate the ESM phase. Alternatively comparison could be drawn with a (more) general population of cannabis users by utilising the dataset described in Chapter 2. However, comparison will be drawn between

participants that completed the ESM phase and those that initiated, but did not complete the ESM phase. The decision to draw comparison between these two groups is based on cannabis' purported propensity to elicit an 'amotivational syndrome', which is still a relevant area of research today (Barnwell, Earleywine, and Wilcox, 2006). Due to the demanding nature of the current study utilising a methodology which is not commonly applied to this population (see Kimhy et al., 2009), it was important to ascertain if heavy cannabis use was a factor determining inclusion in the current study. If inclusion was partially determined by a 'ceiling effect' of intoxication or chronicity of use (i.e. those that were heaviest or longest standing users being less likely to complete the study) then this would bias the sample and reduce the generalisability of the findings from the study. However, it is important to note that if amotivation is a factor influencing participation, then this may reduce the likelihood that some members of the population will volunteer to initiate the pre-ESM phase.

Consequently, participants who had initiated the ESM phase, but were not included in the main analyses were compared to those included. The characteristics of the participants are shown in Table 21 and Table 22. From Table 21 it can be seen that the participants did not significantly differ by gender ($\chi 2$ (1) = 0.84, p = .36). Nor did the two groups of participants differ by age. Participants were allocated into three groups, currently employed, in education or training, and Not in Education Employment or Training (NEET). Participants that were included did not significantly differ in employment status from those who were not included ($\chi 2$ (2) = 0.92, p = .16).

Table 21
Socio-demographic data and cannabis use information sorted by participants who were included in the main analyses and those who were not

Variable		Excluded (%)	Included (%)	Total (%)
Gender	Female	4 (23.5)	13 (36.1)	17 (32.1)
	Male	13 (76.5)	23 (63.8)	36 (67.9)
Employment status	Student	4 (23.5)	7 (19.4)	11 (20.8)
	Employed	9 (52.9)	21 (58.3)	30 (56.6)
	NEET	4 (23.5)	8 (22.2)	12 (22.6)
Preparation	Hash	1 (5.9)	3 (8.3)	4 (7.6)
	Sinsemilla	14 (82.4)	31 (86.1)	45 (84.9)
	Traditional herbal cannabis	2 (11.8)	2 (5.6)	4 (7.6)
	Cannabis oil	0	0	0
	Don't know	0	0	0
Social context	On their own	0	0	0
	Socially	4 (23.5)	4 (11.1)	8 (15.1)
	Both	13 (76.5)	32 (88.9)	45 (84.9)

A Levene (1960) test was conducted to assess homogeneity of variance of age and cannabis exposure as assessed prior to the ESM phase of the research. Neither age, expenditure, number of uses in lifetime, frequency of use, age of first use, nor age the participant first became a monthly cannabis user were shown to have unequal variances. Due to the number of variables that would have to be controlled and measured (e.g. ratios of the >80 cannabinoids, mass, method of administration etc. see Section 1.4) it is very difficult to accurately assess consumption. One means in which consumption can be assessed is by taking a measure of several indices of factors related to consumption. To this end, a measure of consumption was constituted derived from values for expenditure, frequency of use and number of times used, these scores were derived from the data of both those included and not included in the main analyses. This method of measuring consumption has been shown to have validity as evinced by self-reported *current* ketamine users producing significantly higher mean scores in comparison to *former* users (Stirling et al., 2012). All scores on theses indices were converted into a percentile, to ensure that the data is normally distributed and not influenced by any outlying data points. These percentiles were then converted to a Z-score to provide 'standardised' scores, before the indices outlined previous were combined providing a measure of 'consumption'.

Independent samples t-tests were conducted to ascertain if there was a significant difference between the variables outlined above for those that were included, and those who were not included in the main analysis. There was no significant

difference in self-reports of expenditure, number of lifetime uses, current frequency of use, or consumption. Participants did differ significantly according to self-reports of age of first use (p = 0.02) and there was a trend difference (p = 0.06) in the age at which the two groups reported becoming monthly users. These findings indicate that participants in the group not included were significantly more likely to initiate cannabis use at a younger age and the trend difference indicates that they were also more likely to become 'monthly' cannabis users earlier than those included in the final analyses.

There is likely to be a very strong relationship between age at which cannabis use was initiated and age at which use at least once monthly was common place. Thus, given that the t-tests performed were both two tailed, and the arbitrary 0.05 p value has been applied if the two findings are considered unilaterally this could result in a type 2 error, incorrectly accepting the null hypothesis. The effect size for age of cannabis initiation (d = 0.66) and the effect size of age of monthly cannabis use (d = 0.54) both exceed Cohen's (1998) convention for a medium effect size. Given the lack of independence between the variables and the infeasibility of using a repeated measures design to collect such data the two effect sizes cannot be combined. Nonetheless, when considered simultaneously there could be said to be an effect of age with participants that were not included initiating cannabis use younger and becoming regular users sooner than their counterparts. Unfortunately, there is not enough available data to estimate what the impact of this group difference is, this may or may not be influential in creating a sampling bias. However, it is important to note that the other indices of cannabis consumption did not differ, at even trend significance, between the two groups.

Included and excluded participants were tested for difference on other aspects of their cannabis use (see Table 21). Participants were asked to document the social context of their cannabis use, if they typically consumed cannabis either on their own; socially; or both on their own and socially. Participants that were included and those that were excluded did not significantly differ in social context of cannabis use ($\chi 2$ (2) = 1.39, p = .24). Nor, did participants significantly differ in the typical preparation of cannabis they consumed ($\chi 2$ (4) =0.70, p = .70). Assertions that sinsemilla is the most commonly used preparation in the U.K. (see Section

1.4) are borne out in the data with the vast majority of participants (84.91 %) reporting that it was their most frequently used cannabis preparation.

The majority of the 36 participants (23 males) included in the main analyses were employed (see Table 21). They had a mean age of 28 (SD 8.001, minimum 18) and the participants typical cannabis use information is described in Table 22. Out of the possible total of 3024 (84 per participant) of the signal contingent-prompts they completed 1487 data entries, a minimum of 25 each, with a mean of 41.31 entries each and a median of 37. The included participants recorded some 175 entries that fell outside of the 30 minute time envelope an average of 4.86 per participant. In the moments preceding each data entry this group made there were, 734 reports of cannabis use, a mean of 20.39 per participant over the 14-day period. Out of the 722 reports on methods of administration, 84.21% of cannabis uses documented were combined with tobacco and smoked, and 15.79% was the use (through combustion) of solely cannabis. There were no documented uses of a vaporiser as a method of administration, neither was oral consumption of cannabis reported. Reports of some 1590 units of cannabis were documented in the investigation, which is a mean of 2.20 units per (cannabis using) observation. Of the interval-contingent measure (CEQ-b), which was also cannabis use dependent, the included participants completed 299 out of a possible 504 completing a mean of 8.31 entries each.

Table 22

Measures of central tendency, equality of variance and t- tests of differences in age and cannabis use information drawing comparison between those included and those not included in the main analyses

	Levene's F value (DF)	*p.* of *F*-value	Participants included in the main analysis						Participants not included in the main analysis						*t*-value (DF)	*p.* of *t*-value
			Mean (SD)	Within percentile			Range		Mean (SD)	Within percentile			Range			
				25th	50th	75th	Min	Max		25th	50th	75th	Min	Max		
Age (years)	0.180 (1, 51)	.67	27 (8.06)	23	25	30	20	61	25 (6.60)	21	24	25	18	42	1.042 (51)	.30
Expenditure (£ per week)	1.516 (1, 50)	.22	>30 <50	>20 <30	>30 <40	>50 <60	>10 <20	>80	>20 <40	>20 <30	>20 <30	>50 <60	<2.5	>80	0.676 (50)	.50
No. of lifetime uses	2.765 (1, 48)	.10	20922 (32794)	1500	5785	18000	100	100000	13229 (24639)#	2500	6000	10000	18	100000	0.833 (48)#	.41
Current frequency of use	0.784 (1, 51)	.38	>once a week < every day	>once a week	Every day	Every day	Twice a month	Every day	> once a week < everyday	Every day	Every day	Every day	Once a week	Every day	0.518 (51)	.61
Age of first use (years)	0.102 (1, 50)	.75	**15 (2.12)**	**14**	**15**	**16**	**11**	**20**	**13 (2.10)**	**11.5**	**14**	**15**	**10**	**17**	**2.349 (50)**	**.023**
Age of monthly use (years)	0.007 (1, 51)	.93	16 (2.60)	14.5	16.5	18	13	22	15 (2.46)	13	16	17	11	18	1.945 (51)	.057
Consumption	0.060 (1, 47)	.81	0.176 (1.98)	-1.043	0.621	1.537	-5.072	3.419	-0.210 (2.28) ~	-0.864	0.133	1.576	-5.544	3.046	-0.605 (48) ~	.59

#One anomalous value excluded; z-score = 6.91, within the 99.99th percentile.
~ 95% confidence interval includes 0

3.3.2 Validating the ESM measures

Participants were encouraged to complete the validation measures (WSI and a re-test of the PSI). For analyses utilising the PSI, the data from those that had been included and those that had not, were considered in this analysis. The PSI was administered in a cross-sectional study design, and thus has been utilised with uni-level statistical procedures. Therefore, for analyses utilising this measure the same rigorous inclusion and exclusion criterion utilised for MLM is not adopted. Any participant considered eligible to commence the ESM phase of the investigation was also considered eligible for participation in the validation process. The first administration of the PSI was prior to the ESM-phase (T0, See Table 19) thus, all data collected at this phase was considered eligible for inclusion in this investigation (N=53).

Validating measures of a schizotypal state

Participants were assessed for schizotypal state utilising an adapted version of the SPQ-b (see Section 2.2.3). Prior to this investigation the validity and reliability of such an adapted version of the SPQ-b had not been assessed. Prior to the commencement of the ESM phase all participants completed the SSQ and the PSI. A Pearson's r was computed to assess the relationship between the total score on the SSQ and the total score on the PSI. There was a strong positive correlation between the two variables ($r = 0.63$, $n = 51$, $p < .001$), furthermore the majority of the subscales displayed a significant positive correlation between each other (for correlation matrix see Appendix 29). The SSQ was also assessed for internal reliability displaying good internal reliability (22 items; $\alpha = 0.91$). Upon inspection of the subscales the Cronbach's alpha for the eight item Cognitive subscale ($\alpha = 0.79$), the six item disorganised subscale ($\alpha = 0.76$), and the eight item interpersonal subscale ($\alpha = 0.88$) were all acceptable (Nunnally,1978). Whilst performing Cronbach's alpha tests of the SSQ and subscales in no instance would item elimination have served to elevate alpha.

On the fourth day of the study participants were requested to complete the PSI for a second time. Once more, the SSQ total displayed a strong positive relationship

with the PSI total (r = 0.82, n = 37, p < .001) and a similar relationship was found between the subscales (See Appendix 29). The results displayed within this section provide supporting evidence for convergent validity, test-retest reliability and internal reliability of the SSQ and its subscales.

Validating momentary measures of stress and calmness

In addition to testing the reliability and validity of the SSQ items it was also necessary to examine the measures of feelings of stress and feelings of calm. The WSI provides scores on two scales, an events scale to ascertain the number of stressful incidents, and an impact scale to assess the consequence of these events. It was anticipated that a measure of stress and one of calm would display convergent validity with the impact and event scale. In order to assess the adequacy of the measures at predicting the amount of stress a participant reports in one week of the ESM investigation, participants were tested to establish to what extent the measures under assessment co-vary with scores on the WSI.

The CSQ consists of eleven items pertaining to concurrent feelings of stress, and concurrent feelings of calmness. The two constructs are considered as independent, i.e. feeling calm and feeling stress do not exist along a continuum and all combinations of high and low scores could potentially co-occur. For further information as to why this approach was adopted see Appendix 29. Therefore, the CSQ was considered as consisting of two independent scales, six items assessing stress and five items assessing calmness referred to as CSQ Stress and CSQ Calm respectively.

This analysis was performed in-line with the procedures outlined in section 3.2.8. Of the participants (N=29) who completed the WSI, seventeen of them completed both the first and second week, consequently the WSI was completed forty-six times. There was no significant association between either CSQ Calm or CSQ Stress with the WSI Event scale (see Appendix 29). There was also no significant association between CSQ Calm and the WSI Impact, however, CSQ Stress did significantly co-vary with the scale (b = 0.21, 95% CI 0.07 to 0.35, p = .004).

The analysis conducted in this section provides evidence of the CSQ Stress' ability to identify concurrent stress, as evinced by its covariance with weeks in which stressors have had a large impact on the participant's perception of stress. This finding demonstrates convergent validity thus substantiating the utility of the CSQ Stress scale for assessing concurrent stress throughout this investigation. Furthermore, the findings outlined above demonstrate evidence of the independence of concurrent experiences of calmness and concurrent experiences of stress, further vindicating the approach to scoring the relevant measures (see Appendix 29 for further information).

Validating event related items

In addition to utilising the WSI to assist with the validation of the CSQ, the WSI was also used in the consideration of the validity of items associated with stressful and pleasurable events. Three independent retrospective items ('Since the last data entry..'); one requesting the participant to rate their most important event (Event Rating, ER); another requesting participants report the number of pleasurable events (PE) that have happened; and a third enquiring as to the number of stressful events (SE). ER, SE and PE were not significant covariates of the WSI event scale (see Appendix 29), nor, did they significantly co-vary with scores on the WSI Impact scale.

As a means of making inferences about the validity of the aforementioned items participants were assessed for convergent response between the ESM measures. It would be anticipated that the (stressful/pleasurable) evaluation of events would predict scores on measures of concurrent stress and concurrent calm. Consequently, ER, SE, and PE were tested for covariance with the CSQ scales (outcome variable). Concurrent measures of stress and calm were simultaneously administered with retrospective measures of stressful and pleasurable events, thus it is feasible to use data from within one data entry to observe the relationship between the aforementioned variables. Additionally, time was considered as a covariant within the model (see Section 3.2.8).

ER, PE, and SE, were tested as predictors of CSQ Stress and CSQ Calm (Appendix 29). Both ER (*b* = -0.42, 95% CI -0.59 to -0.24, *p* < .001) and SE (*b* = 2.03, 95% CI 1.78 to 2.27, *p* < .001) were significant covariates of the CSQ Stress scale. A one unit increase in ER resulted in a decrease of 0.42 units of the CSQ stress and a unit increase in SE resulted in a 2.03 unit increase in the outcome variable. PE did not significantly increase scores in the CSQ Stress. However, all explanatory variables assessed, with the exception of time, were significant covariates of scores on CSQ Calm. In assessment of CSQ Calm as the outcome variable; a one unit increase in ER resulted in an increase of 0.67 units (*b* = 0.67, 95% CI 0.44 to 0.90, *p* < .001); a unit increase in SE resulted in a 1.78 unit decrease (*b* = -1.78, 95% CI -2.10 to -1.46, *p* < .001); and a unit increase in PE equated to an increase of 0.73 (*b* = 0.73, 95% CI 0.47 to 1.00, *p* < .001). These results provide evidence of convergent validity between measures of concurrent stressed and calm states, and previous stressful and pleasurable events, as well as an evaluation of the most important event.

3.3.3 Covariates of a Schizotypal State

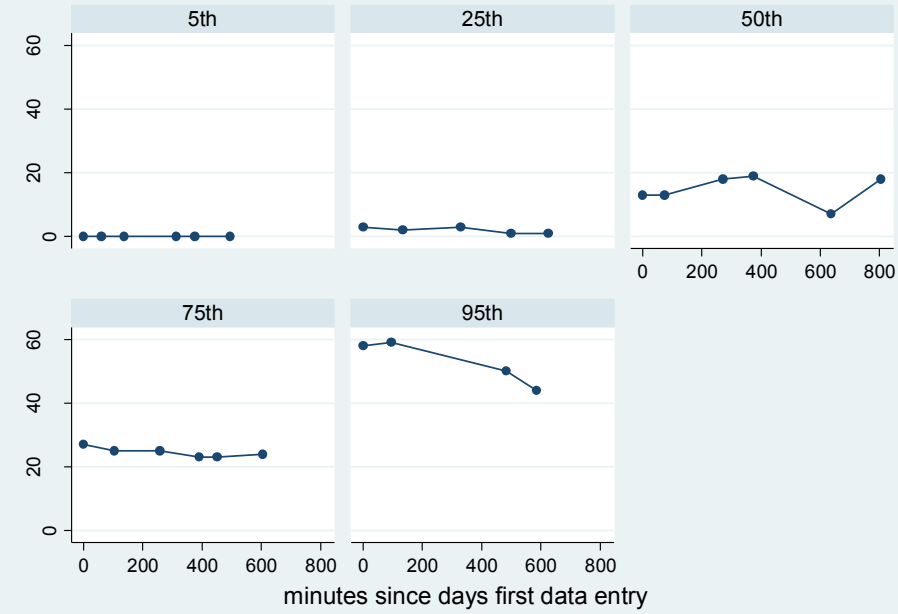
The first aim of this chapter is partially fulfilled by the examination of scatterplots of scores on the SSQ. The aim sought to establish whether schizotypy has state like components that are altered by cannabis intoxication. Further evidence contributing to this aim is displayed later on in this section (in addition to Section 3.3.4 pp. 227-29). The second aim of this chapter is also partially fulfilled by analyses considered in this section (3.3.3). The second aim of this investigation was to assess temporal priority in the relationship between cannabis and psychotic experience in a naturalistic setting. This aim is also addressed in Section 3.3.6 (pp. 234-38), in which predictors of cannabis use are assessed. The third aim of this chapter sought to assess the effect of a stressed and calm state on psychotic-like states utilising a cannabis challenge to facilitate a model of psychosis. Aim five of this chapter is also addressed in this section, in addition to the next section (3.3.4). This aim sought to assess the plausibility of an interaction between cannabis and psychological stressors on psychotic (like) experience.

Fluctuations in schizotypy over time

In order to illustrate trends using data from individual participants, five were selected on the basis of their mean score on the SSQ over the ESM-phase, at the 5th, 25th, 50th, 75th and, 95th percentile. These participant's scores on the first day of the study were plotted in a graph (see Figure 9) it was anticipated that the SSQ would show little moment to moment variability, due to the fact that the SSQ is an adapted version of a measure of a trait. Nonetheless, there was variability both within and between participants.

Figure 9

Scatterplots of a subset of participants displaying the variability of a schizotypal state over time



Covariates of the Schizotypal States Questionnaire (SSQ)

The analyses considered within this subsection are subsumed in Table 23. It has been hypothesised that stress may be a developmental antecedent of psychotic disorder (see section 1.2.3), to test this notion it was sought to establish what, if any, relationship exists between schizotypal state and concurrent perceptions of stress and feelings of calm. Concurrent stress as assessed by the CSQ Stress was a significant covariate of scores on the SSQ (*b* = 0.54, 95% CI 0.35 to 0.73, *p* < .001), each unit increase on CSQ stress resulted in an increase of 0.54 on the

SSQ total, indicating that states of stress significantly co-vary with schizotypal states. However, no significant relationship was observed between the CSQ Calm and the SSQ total (*b* = -0.06, 95% CI -0.20 to 0.080*, p* = .41). This indicates that concurrent feelings of calm do not serve to have an antagonistic relationship with stress, thus vindicating the approach taken to stress-calm dichotomy. No significant effect was found of ER, SE, nor PE indicating that the perception of previous stressful or pleasurable events does not influence a schizotypal state. This finding does not concur with that of Docherty et al. (2009) which suggests that the occurrence of potentially stressful life events predicted increases in psychotic symptoms in patients with a diagnosis of schizophrenia. However, the time frame under consideration in Docherty and colleagues investigation is not comparable to that of the current investigation.

Within the same statistical model the effect of cannabis consumption on a schizotypal state was observed. Cannabis consumption *per se* (*b* = 1.04, 95% CI 0.34 to 1.74, *p* = .004) was found to have a highly significant effect, with cannabis consumption since the previous data entry predicting a 1.04 unit increase on the SSQ total. The model simultaneously considered caffeine, tobacco and alcohol, thus the effect of cannabis on SSQ can be considered to be independent of these variables, none of which were significant covariates of the SSQ. The notion of an interaction effect can be tested by utilising the CXS variable which, considers both stress and cannabis consumption. The CXS variable was a significant covariate of the SSQ total (*b* = 0.33, 95% CI 0.17 to 0.49, *p* < .001). This indicates a significant interaction effect of cannabis and stress on schizotypal state, independent of the main effects of the variables.

The other variable considered within this model was (time) minutes since last data entry, which was found to be statistically significant (*b* = -0.006, 95% CI -.010 to -.0007, *p* = .026). Each unit (minute) increase from the mean score, predicted a decrease of 0.006 on the SSQ total. To rephrase, the further apart data entries were the greater likelihood of a decrease in SSQ total. This finding could be as a result of reactivity to the methodology, the task of having to answer questions with regards to schizotypy too frequently in fact could be independently influencing scores on schizotypy.

Table 23
Parameter estimates for multilevel model of schizotypal state (SSQ total) as a function of states of stress, states of calm, stressful events, pleasurable events, cannabis consumption per se and a cannabis-stress interaction

Fixed effect (intercept, slopes)	Estimate	(SE)	Z	P	95% CI	
					Lower	Upper
Intercept	**14.278**	**1.836**	**7.78**	**<.001**	**10.680**	**17.876**
CSQ Stress	**0.536**	**0.097**	**5.53**	**<.001**	**0.346**	**0.726**
CSQ Calm	-0.058	0.070	-0.82	.412	-0.196	0.080
Event Rating (ER)	-0.127	0.207	-0.61	.539	-0.534	0.279
Stressful Events (SE)	-0.011	0.328	-0.03	.974	-0.654	0.632
Pleasurable Events (PE)	0.342	0.245	1.40	.163	-0.138	0.821
Cannabis Consumed	**1.039**	**0.358**	**2.90**	**.004**	**.337**	**1.741**
Cannabis X Stress	**0.330**	**0.081**	**4.05**	**<.001**	**0.170**	**0.489**
Caffeine	0.096	0.183	0.53	.597	-0.261	-0.454
Tobacco	-0.259	0.227	-1.14	.255	-0.704	0.187
Alcohol	0.322	0.208	1.55	.122	-0.086	0.730
Time	**-0.006**	**0.002**	**-2.23**	**.026**	**-0.010**	**-0.0007**

Random effects ([co-]variances)		Estimate	(SE)	ICC (%)	95% CI	
					Lower	Upper
Level 1	Intercept	118.733	28.749	83.955	73.870	190.843
Level 2	Intercept	10.706	1.497	7.570	8.139	14.082
	Residual	11.986	0.793		10.528	13.646

The current investigation also sought to test if the relative quantity of cannabis consumed rather than cannabis consumption per se was a significant covariate of the SSQ Total. A separate model was generated to consider the effect of quantity of cannabis consumed to avoid any occurrence of collinearity. As the variable CXS requires the consideration of cannabis consumption within the same model, CXS was also omitted. For brevity (and to avoid repetition) the results of this model are not included in the main body of this thesis and are instead displayed in Appendix 30. A dose dependent relationship was observed within participants (b = 0.44 95% CI 0.125 to 0.754, p = .006), for every unit of cannabis consumed there was an increase of 0.44 on the SSQ total. This indicates that cannabis appears to have a dose dependent relationship with schizotypy, the more cannabis consumed the more likely a participant was to have an elevated schizotypal state.

Covariates of the SSQ subscales

The relationship between the aforementioned predictor variables and the SSQ can be further explored through the examination of the sub scales of the SSQ. The SSQ is based on the SPQ which consists of 3 subscales pertaining to 'distortions' within the realms of cognitive-perceptual (8 items), interpersonal (8 items), and disorganisation (6 items). The model described above (Table 23) was re-computed with the SSQ subscales considered as the out-come variables. The cognitive-perceptual subscale is displayed in Table 24, the disorganised subscale is in Table 25 and the interpersonal subscale is in Table 26.

In further examination of the SSQ Cognitive perceptual subscale it was found that CSQ Stress was a significant covariate, with each unit increase on the predictor variable accounting for a rise of 0.22 in the outcome variable (b = 0.22 95% CI 0.16 to 0.28, p < .001). Neither, CSQ Calm, ER nor SE produced a significant effect on SSQ Cognitive Perceptual scale. However, PE did have a significant relationship with the SSQ subscale (b = 0.21 95% CI 0.05 to 0.36, p = .009), with each unit increase on PE accounting for an increase of 0.21 on the subscale. This is in the opposite direction to that hypothesised; the rationale behind this finding is not clear. One feasible explanation is that the participants are considering a variable which appears highly related to the SSQ as a pleasurable event; cannabis use. Neither, caffeine, tobacco, alcohol, nor interestingly cannabis consumption per se had a significant effect on the cognitive perceptual subscale. Thus, no evidence has been found of cannabis eliciting psychotic-like states within this domain. Despite the significant effect of CSQ stress on subsequent SSQ cognitive perceptual scores, no such relationship was found between a cannabis stress interaction and the SSQ subscale. Furthermore, no evidence of a within participant dose dependent effect was found (b = 0.04 95% CI -0.06 to 0.143, p = .41). The lack of influence of cannabis consumption, cannabis dose, and cannabis stress interaction, on the cognitive perceptual scale in light of the findings in Chapter 2 might indicate that cannabis does not induce the schizotypal features most predictive of psychotic vulnerability.

Table 24
Parameter estimates for multilevel model of cognitive perceptual distortions (outcome) as a function of states of stress, states of calm, stressful events, pleasurable events, cannabis consumption per se and a cannabis-stress interaction

Fixed effect (intercept, slopes)	Estimate	(SE)	Z	P	95% CI	
					Lower	Upper
Intercept	**4.033**	**0.705**	**5.72**	**<.001**	**2.651**	**5.414**
CSQ Stress	**0.216**	**0.031**	**6.97**	**<.001**	**0.155**	**0.277**
CSQ Calm	0.033	0.023	1.45	.148	-0.012	0.077
Event Rating (ER)	-0.005	0.067	-0.07	.940	-0.137	0.127
Stressful Events (SE)	-0.011	0.106	-0.10	.919	-0.218	0.197
Pleasurable Events (PE)	**0.208**	**0.079**	**2.62**	**.009**	**0.052**	**0.363**
Cannabis Consumed	0.055	0.117	0.47	.639	-0.174	0.283
Cannabis X Stress	0.021	0.027	0.81	.420	-0.031	0.073
Caffeine	-0.015	0.059	-0.26	.797	-0.132	0.101
Tobacco	-0.066	0.074	-0.90	.369	-0.211	0.078
Alcohol	0.011	0.067	0.16	.874	-0.122	0.143
Time	-0.0009	0.0008	-1.11	.269	-0.002	0.0007

Random effects ([co-]variances)		Estimate	(SE)	ICC (%)	95% CI	
					Lower	Upper
Level 1	Intercept	17.42	4.229	88.963	11.028	28.221
Level 2	Intercept	0.880	0.132	4.438	0.656	1.180
	Residual	1.309	0.085		1.152	1.486

The SSQ subscale pertaining to interpersonal distortion was also tested with the aforementioned predictor variables. The CSQ Stress variable was a significant covariate of the interpersonal scale of the SSQ (b = 0.20 95% CI 0.09 to 0.30, p < .001), each unit increase on the CSQ scale predicted an increase of 0.20 on the interpersonal distortion subscale. CSQ Calm was also a significant covariate on the SSQ interpersonal subscale (b = -0.09 95% CI -0.16 to -0.11, p = .024), each unit increase on the Calm scale predicted a decrease of 0.09 on the interpersonal subscale.

None of the other predictor variables were significant covariates of the interpersonal subscale, with the exception of the variables pertaining to cannabis use. Cannabis consumption per se was a significant covariate (b = 0.59 95% CI 0.20 to 0.98, p = .003), cannabis use predicted an increase of 0.59 in the SSQ interpersonal scale. The variable accounting for a cannabis stress interaction was

also a significant covariate of the SSQ interpersonal subscale (*b* = 0.18 95% CI 0.09 to 0.27, *p* < .001), each unit increase on the CXS predicted an increase of 0.18 on the outcome. These findings indicate that interpersonal distortions appear to be influenced by both stress and cannabis consumption independently, and an interaction between stress and cannabis. In an alternative model considering quantity of cannabis consumption a dose dependent effect was established (*b* = 0.24 95% CI 0.07 to 0.42, *p* = .006), with each unit of cannabis predicting a 0.25 increase on the SSQ subscale (see Appendix 31).

Table 25
Parameter estimates for multilevel model of interpersonal distortions (outcome) as a function of states of stress, states of calm, stressful events, pleasurable events, cannabis consumption per se and a cannabis-stress interaction

Fixed effect (intercept, slopes)	Estimate	(SE)	Z	P	95% CI	
					Lower	Upper
Intercept	**6.067**	**0.764**	**7.94**	**<.001**	**4.569**	**7.565**
CSQ Stress	**0.196**	**0.053**	**3.71**	**<.001**	**0.092**	**0.300**
CSQ Calm	**-0.087**	**0.039**	**-2.26**	**.024**	**-0.163**	**-0.011**
Event Rating (ER)	0.029	0.114	0.25	.803	-0.196	0.254
Stressful Events (SE)	0.007	0.180	0.04	.971	-0.347	0.360
Pleasurable Events (PE)	-0.170	0.134	-1.26	.207	-0.433	0.094
Cannabis Consumed	**0.587**	**0.198**	**2.96**	**.003**	**0.198**	**0.975**
Cannabis X Stress	**0.177**	**0.045**	**3.92**	**<.001**	**0.088**	**0.265**
Caffeine	0.052	0.101	0.51	.607	-0.146	0.250
Tobacco	-0.142	0.125	-1.13	.257	-0.388	0.104
Alcohol	0.112	0.115	0.97	.330	-0.114	0.338
Time	-0.002	0.001	-1.41	.157	-0.005	0.0008

Random effects ([co-]variances)		Estimate	(SE)	ICC (%)	95% CI	
					Lower	Upper
Level 1	Intercept	20.291	5.001	75.505	12.518	32.893
Level 2	Intercept	2.836	0.432	10.511	2.103	3.823
	Residual	3.747	0.250		3.287	4.272

The predictor variables utilised in the previous analyses were tested with the SSQ disorganised subscale as an outcome. CSQ Stress was a significant covariate of the disorganised subscale (*b* = 0.14 95% CI 0.07 to 0.20, *p* < .001). Each unit increase on CSQ Stress scale predicted a 0.14 increase on the disorganised subscale. Item ER was found to be a significant covariates of the SSQ disorganised subscale (*b* = -0.15 95% CI -0.29 to -0.004 *p* = .045). Similarly, PE

was also found to be a significant covariate of SSQ disorganised scale (*b* = 0.30 95% CI 0.13 to 0.46, *p* = .001). A unit increase on ER predicted a 0.15 decrease on the SSQ disorganisation subscale. The more unpleasant the most significant event was the more likely a participant is to have a decrease in the SSQ subscale. However, a one unit increase in PE predicted a significant 0.33 increase in the disorganisation subscale, this was not anticipated. As discussed previously this could be as a consequence of the participant considering cannabis consumption or activities surrounding cannabis consumption (e.g. socialising) as pleasurable.

Alcohol consumption was also a significant covariate of the SSQ disorganisation scale (*b* = 0.20 95% CI 0.06 to 0.35, *p* = .006), each unit accounting for an increase of 0.20 in the outcome variable. Alcohol consumption has been shown to be an antecedent of psychotic episode (APA, 2013a, p.502), and is known to elicit psychotic symptoms during withdrawal (APA, 2013a, p.499). The effect of alcohol within the statistical model is considered independent of cannabis, however, given that the sample were all cannabis users the possibility of an interaction between cannabis and alcohol at a neuropharmacological level cannot be excluded. Thus, it is difficult to extrapolate these findings to non-cannabis using populations. Nonetheless, other investigations have also noted a relationship between alcohol consumption and elevations in schizotypal trait (Esterberg et al., 2009). The number of minutes that had elapsed since the last data entry was also found to be a significant covariate of the SSQ disorganised subscale (*b* = -0.003 95% CI -0.004 to -0.001, *p* = .002). Each minute (unit) increase above the mean predicted a reduction of 0.002 on the subscale. This finding indicates that as the study requires a greater intensity (data entries x time) of response this corresponds to an elevation of scores on the disorganisation scale of the SSQ.

Cannabis consumption per se was also a significant covariate of the disorganisation subscale (*b* = 0.41 95% CI 0.16 to 0.66, *p* = .001), with the independent variable predicting a 0.41 unit increase in scores on the SSQ disorganisation subscale (see Section 3.4 for further discussion). A significant effect of a cannabis and stress interaction was also observed (*b* = 0.12 95% CI 0.07 to 0.18, *p* < .001), with each increase of a unit on the CSQ stress scale when combined with cannabis use per se predicting an increase of 0.12 in the

disorganisation subscale. In an alternative model quantity of cannabis consumed was a significant covariate of the disorganised subscale (within participants) (*b* = 0.16 95% CI 0.04 to 0.27, *p* = .006), each unit of cannabis consumed predicted an increase of 0.16 on the outcome variable (see Appendix 32).

Table 26
Parameter estimates for multilevel model of distortions of disorganisation (outcome) as a function of states of stress, states of calm, stressful events, pleasurable events, cannabis consumption per se and a cannabis-stress interaction

Fixed effect (intercept, slopes)	Estimate	(SE)	Z	P	95% CI	
					Lower	Upper
Intercept	**4.164**	**0.562**	**7.40**	**<.001**	**3.061**	**5.266**
CSQ Stress	**0.137**	**0.034**	**4.06**	**<.001**	**0.071**	**0.203**
CSQ Calm	-0.008	0.025	-0.30	.761	-0.056	0.041
Event Rating (ER)	**-0.147**	**0.073**	**-2.01**	**.045**	**-0.291**	**-0.004**
Stressful Events (SE)	-0.012	0.115	-0.11	.916	-0.238	0.214
Pleasurable Events (PE)	**0.295**	**0.086**	**3.43**	**.001**	**0.127**	**0.464**
Cannabis Consumed	**0.410**	**0.127**	**3.24**	**.001**	**0.162**	**0.659**
Cannabis X Stress	**0.122**	**0.029**	**4.25**	**<.001**	**0.066**	**0.179**
Caffeine	0.062	0.065	0.96	.338	-0.065	0.188
Tobacco	-0.047	0.080	-0.58	.559	-0.204	0.110
Alcohol	**0.202**	**0.074**	**2.75**	**.006**	**0.058**	**0.346**
Time	**-0.003**	**0.0009**	**-3.16**	**.002**	**-0.005**	**-0.001**

Random effects ([co-]variances)		Estimate	(SE)	ICC (%)	95% CI	
					Lower	Upper
Level 1	Intercept	11.096	2.696	80.823	6.891	17.864
Level 2	Intercept	1.089	0.178	7.931	0.790	1.501
	Residual	1.544	0.105		1.351	1.764

In this section a stressed state was a significant positive covariate of a schizotypal state and the three subscales. Furthermore, the CSQ Calm was a significant negative covariate of the interpersonal subscale of the SSQ. However, the CSQ Calm did not significantly predict scores on the SSQ total score, the cognitive-perceptual subscale and the disorganised subscale. This indicates that stress serves to elevate schizotypal states within several domains, however states of calm can only attenuate this effect within a restricted area of psychotic experience. There is also evidence herein suggesting the consumption of cannabis serves to predict scores on measures of a schizotypal state, indicating that cannabis

consumption holds temporal priority and thus could ‘cause’ a schizotypal state. Cannabis consumption per se was a covariate of the SSQ total, SSQ interpersonal subscale, and the SSQ disorganised subscale. The quantity of cannabis consumed within participants was also a covariate of the same SSQ subscales, indicating a dose dependent effect.

The quantity of caffeine, tobacco and alcohol consumed does not have a significant effect on scores on the SSQ total nor subscales, with the exception being alcohol’s ability to predict scores on the disorganised subscale. SE was not a significant covariate of the SSQ or its subscales, whilst ER was capable of predicting scores on the interpersonal subscale in a negative fashion (as ER increases scores on the subscale decrease). However, the small beta value and p-value may indicate only a slight association between the variables. Unexpectedly, PE had a positive relationship with the disorganised subscale and interpersonal subscale. The rationale for the nature of this relationship is at present unclear, but could plausibly reflect an association between cannabis and pleasurable experiences. An effect of (time) proximity of data entries has also been noted in this section, the closer data entries were together predicted an elevation in the disorganised subscale, which produced a significant effect on the SSQ total score. It is hypothesised that the relationship between schizotypy and time may be as a result of reactivity to the methodology, this notion will be discussed further in Section 3.4.

Moreover, in this section there is evidence of a cannabis stress interaction term being a significant positive covariate of a schizotypal state, thus indicating that these factors may interact in the presentation and maintenance of transient experience. Whilst stress and cannabis consumption per se are controlled for the interaction variable CXS significantly predict scores on the SSQ total, SSQ interpersonal subscale and SSQ disorganised subscale. The notion of a stress interaction moderating the relationship between cannabis and psychotic-like experience will be further tested in the next section.

3.3.4 Assessing stress as a mediator of the relationship between cannabis and schizotypal states

Aim five of this chapter is addressed within this section (as well as Section 3.3.3). This aim sought to assess the plausibility of an interaction between cannabis and psychological stressors on psychotic (like) experience. To further elucidate the relationship between a schizotypal state and stress the sample was split into tertiles (three quantiles) each containing 12 participants (see Table 27). Participants were split according to their mean score (participant mean) on the CSQ Stress scale over the duration of the study, for the purposes of the analysis comparison will be drawn between the upper and lower tertile. Consequently, the two groups can be said to consist of individuals who have had the highest mean stressed states in comparison to those that have had the lowest, respectively. Thus, herein analyses are performed to establish whether cannabis consumption significantly co-varies with scores on the SSQ total and its subscales in both of the groups.

In the lower tertile CSQ Stress did not significantly co-vary with scores on the SSQ total, whereas the upper tertile did (b = 0.81 95% CI 0.47 to 1.15, p < .001) with each unit increase in the independent variable predicting an increase of 0.86 on the SSQ total. This finding may indicate that there is a threshold of concurrent stress which must be attained prior to an effect on schizotypal state. However, given that participants were differentiated on the basis of their CSQ Stress mean score, it is feasible that the non-significant finding may be due to a small effect size and reduced statistical power rather than no relationship between the variables. The CSQ Calm scale was not a significant covariate of a schizotypal state in either tertile, neither were the items ER, SE and PE.

The interaction between stress and cannabis can be explored through the comparison of the two tertiles on the ability of cannabis consumption (per se) to predict scores on the SSQ. In the lower tertile group there was not a significant effect of cannabis on SSQ Total. The same was not found in the upper tertile group cannabis consumption in the moments prior to a data entry was a significant covariate of the SSQ Total (b = 2.81 95% CI 1.01 to 4.61, p = .002). For the upper tertile consuming cannabis in the moments prior to a data entry predicted an

increase of 2.8 on SSQ total score, whereas in the lower tertile cannabis use not a significant covariate. This finding indicates that cannabis consumption predicts a schizotypal state in the participants' who experienced the highest states of stress, but not those who experienced the lowest.

In section (3.3.3) the results presented demonstrate a significant positive relationship between the cannabis stress interaction variable and the SSQ interpersonal subscale, disorganised subscale and total score. This indicates that in the current study a proportion of disturbance within the domains of the aforementioned subscales may be attributable to an interaction effect between cannabis and stress. This section sought to explore this relationship further. Thus, contained with this section is convergent data indicating; participants that had higher states of stress during the ESM period appeared to be affected by the (psychologically) deleterious effects of cannabis; whereas those who experienced the lowest states of stress did not appear to be affected by cannabis. Therefore the data indicates further support for a cannabis stress interaction contributing to a psychotic state. Thus, herein is data suggesting a stress interaction 'moderating' the relationship between cannabis and psychotic-like experience. These findings will be discussed in further detail in Section 3.4.

Table 27
Parameter estimates for multilevel model of a schizotypal state (SSQ total, outcome) as a function of states of stress, states of calm, stressful events, pleasurable events, cannabis consumption per se and a cannabis-stress interaction, for the participants that have had the lowest and highest stressed states

Fixed effect (intercept, slopes)	Tertile	Estimate	(SE)	Z	P	95% CI	
						Lower	Upper
Intercept	**L**	**8.065**	**1.850**	**4.36**	**<.001**	**4.439**	**11.690**
	U	**19.976**	**3.836**	**5.21**	**<.001**	**12.458**	**27.494**
CSQ Stress	L	0.283	0.207	1.36	.173	-0.124	0.689
	U	**0.812**	**0.174**	**4.66**	**<.001**	**0.470**	**1.153**
CSQ Calm	L	0.006	0.086	0.07	.948	-0.162	0.174
	U	0.115	0.170	0.67	.501	-0.219	0.448
Event Rating (ER)	L	0.095	0.204	0.47	.640	-0.304	0.494
	U	0.136	0.523	0.26	.795	-0.890	1.161
Stressful Events (SE)	L	-0.253	0.398	-0.64	.525	-1.034	0.527
	U	-0.249	0.703	-0.35	.723	-1.626	1.128
Pleasurable Events (PE)	L	0.311	0.273	1.14	.254	-0.223	0.846
	U	0.291	0.617	0.47	.637	-0.917	1.500
Cannabis consumed	L	0.518	0.352	1.47	.141	-0.171	1.208
	U	**2.813**	**0.918**	**3.06**	**.002**	**1.014**	**4.613**
Caffeine	L	0.025	0.178	0.14	.888	-0.323	0.373
	U	0.373	0.503	0.74	.458	-0.612	1.359
Tobacco	L	0.019	0.284	0.07	.946	-0.537	0.576
	U	-0.622	0.514	-1.21	.226	-1.629	0.385
Alcohol	L	-0.260	0.193	-1.35	.178	-0.639	0.119
	U	0.723	0.538	1.34	.179	-0.332	1.778
Time	L	-0.0001	0.003	-0.06	.953	-0.005	0.005
	U	-0.014	0.008	-1.87	.061	-0.294	0.0007

Random effects ([co-]variances)		Tertile	Estimate	(SE)	ICC (%)	95% CI	
						Lower	Upper
Level 1	Intercept	Lower	41.128	16.531	80.516	18.707	90.421
		Upper	169.007	71.391	79.848	73.849	386.779
Level 2	Intercept	Lower	5.173	1.026	10.127	3.507	7.630
		Upper	18.858	5.063	8.910	11.143	31.917
	Residual	Lower	4.780	0.461		3.956	5.775
		Upper	23.796	2.982		18.614	30.419

L= Lower U= Upper

3.3.5 Covariates of concurrent states of stress and calm

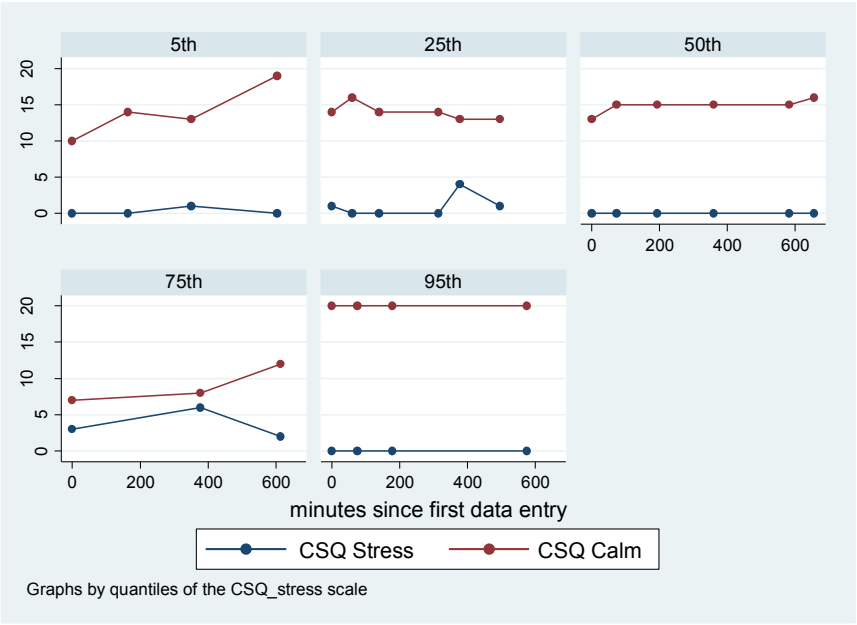
This section serves to address the fourth aim of this chapter; to assess factors which may influence the consumption of cannabis. Given cannabis' purported anxiolytic effect, stressed and calm states could plausibly be determinates of cannabis consumption. Nonetheless, this aim is considered in greater depth in Section 3.3.6 in which factors that predict cannabis consumption are considered.

Fluctuations in states of stress and calm over time

In order to illustrate trends using data from individual participants, five participants were selected on the basis of their mean score on the CSQ Stress scale over the ESM-phase, at the 5th, 25th, 50th, 75th and, 95th percentile. These five participant's data on the CSQ scales (stress and calm) for day one are displayed in Figure 10. An advantage of plotting participant's scores on the various measures is that it is possible to observe the relationship between two variables over a period of time, such as that displayed in Figure 10. The relevant scatterplots broadly show, that when CSQ Stress scores increase CSQ Calm tends to decrease and vice versa. The items display both within and between participant variability.

Figure 10

Scatterplots of a subset of participants displaying the variability of CSQ Stress and CSQ Calm over time



Covariates of the Concurrent States Questionnaire (CSQ): Stress scale

The analysis contained within this subsection is displayed in Table 28. Concurrent states of stress appear to influence a participant's schizotypal state. However, it is important to establish what, if any, variables influence concurrent feelings of stress and calm. The SSQ total score was a significant covariate of the CSQ Stress scale (b = 0.09 95% CI 0.06 to 0.11, p < .001), each unit increase on the SSQ total predicted an increase of 0.09 on the outcome. This provides further evidence of a relationship between stress and schizotypal states. There was also a significant relationship between the CSQ calm (predictor) and the CSQ stress (b = -0.32 95% CI -0.37 to -0.27, p< .001), in the direction anticipated, a unit increase in CSQ calm served to predict a decrease of 0.32 on the Stress scale. Both ER and SE were significant covariates of concurrent states of stress (ER; b = -0.16 95% CI -0.32 to -0.004, p = 0.044, SE; b = 1.31 95% CI 1.08 to 1.54, p < .001). A one unit increase in ER accounted for a decrease of 0.16 in CSQ stress and a unit increase in SE predicted an increase of 1.31 in the outcome. In the direction anticipated previous stressful events and ER predicted concurrent feelings of stress. However, pleasurable events did not influence the presence of concurrent stress.

Cannabis use per se was found to have no relationship with concurrent stress. Neither did quantity of cannabis consumed within participants which was considered in a different model (b = -0.04 95% CI 0.16 to 0.08, p = .551). This non-significant finding indicates that cannabis is not capable of attenuating feelings of stress. If the model of 'self-medication' described by Kolliakou et al (2011) and Khantzian were to be accepted (see Section 1.6.1) one may expect a significant relationship would have been observed here. However, nicotine use was a significant covariate of the CSQ Stress (b = 0.20 95% CI 0.03 to 0.38, p = .020), for every unit (cigarette) of tobacco used scores on the outcome variable increase by 0.20. Due to the nature of MLM analysis the participant's previous responses have been adjusted for, consequently, the effect of nicotine on CSQ stress should be viewed as independent of previous stress, and previous nicotine use. Consequently, this finding is not likely to be an artefact of prior stress priming for both nicotine use and concurrent stress. Thus this could plausibly indicate an independent effect of nicotine on stress.

Table 28
Parameter estimates for multilevel model of states of stress (outcome) as a function of schizotypal state, calm, stressful events, pleasurable events and cannabis consumption per se

Fixed effect (intercept, slopes)	Estimate	(SE)	Z	P	95% CI	
					Lower	Upper
Intercept	**2.254**	**0.339**	**6.64**	**<.001**	**1.589**	**2.918**
SSQ total	**0.088**	**0.013**	**7.01**	**<.001**	**0.064**	**0.113**
CSQ Calm	**-0.321**	**0.024**	**-13.14**	**<.001**	**-0.367**	**-0.273**
Event Rating (ER)	**-0.162**	**0.080**	**-2.01**	**.044**	**-0.320**	**-0.004**
Stressful Events (SE)	**1.308**	**0.118**	**11.11**	**<.001**	**1.078**	**1.539**
Pleasurable Events (PE)	0.005	0.094	0.05	.957	-0.179	0.189
Cannabis consumed	-0.063	0.140	-0.45	.653	-0.336	0.211
Caffeine	-0.069	0.071	-0.97	.330	-0.208	0.070
Tobacco	**0.203**	**0.088**	**2.31**	**.021**	**0.031**	**0.375**
Alcohol	0.067	0.081	0.82	.410	-0.092	0.226
Time	**-0.002**	**0.001**	**-2.14**	**.032**	**-0.004**	**-0.0002**

Random effects ([co-]variances)		Estimate	(SE)	ICC (%)	95% CI	
					Lower	Upper
Level 1	Intercept	3.712	0.999	50.705	2.190	6.291
Level 2	Intercept	1.805	0.233	24.663	1.402	2.325
	Residual	1.803	0.117		1.588	2.047

Covariates of the CSQ: Calm scale

The previous section described the relationship between the aforementioned predictor variables and measures of concurrent stress, this section will assess the variables as covariates of concurrent feelings of calm (Table 29). There was no significant effect of SSQ total on CSQ Calm, this further vindicates the approach taken to scoring the CSQ. However, there was a significant effect of concurrent feelings of stress on concurrent feelings of calm (*b* =-0.55 95% CI -0.63 to -0.47, *p*<.001). Each unit increase on CSQ Stress scale predicted a decrease of 0.55 on the CSQ Calm scale. The items pertaining to previous events were all significant covariates of concurrent feelings of calm (ER; *b* = 0.37 95% CI 0.15 to 0.58, *p* = .001, SE; *b* = -0.57 95% CI -0.90 to -0.24, *p* = .001, PE; *b* = 0.51 95% CI 0.27 to 0.76, *p* < .001). A unit increase in ER and PE served to predict an increase of 0.37 and 0.51 in SSQ Calm respectively, the same increment increase in SE was related to a decrease of 0.57. These findings suggest the validity of the event related items.

Cannabis consumption per se was a significant covariate of the CSQ Calm (*b* = 0.60 95% CI 0.23 to 0.97, *p* = .002), use in the time period prior to a data entry predicted a 0.60 increase in concurrent feelings of calm. This finding may be explained by cannabis' ability to induce feelings of calm corroborating cannabis' purported anxiolytic effect (Zuardi et al.,1982), and (feasible) improvement to mood (El-Alfy et al., 2010). In an alternative model these findings were replicated in a dose dependent fashion within participants, (*b* = 0.23 95% CI 0.07 to 0.39, *p* = .006), each unit of cannabis consumed predicted an increase of 0.23 in CSQ Calm (see Appendix 33).

No other substance examined produced a significant effect, including nicotine. However, a significant effect of minutes since last data entry was observed, (*b* = -0.004 95% CI -0.006 to -0.001, *p* = .006) each minute (unit) increase above the mean resulted in a decrease of 0.004 in concurrent feelings of calm. As discussed previously, this finding may be interpreted to be as a result of reactivity to the methodology, the longer the time difference in between each data entry the less calm the participant feels. Perhaps the reduction in feelings of calm may be as a result of anticipation of an impending data entry.

Table 29
Parameter estimates for multilevel model of states of calm (outcome) as a function of schizotypal state, stress, stressful events, pleasurable events, and cannabis consumption per se

Fixed effect (intercept, slopes)	Estimate	(SE)	Z	P	95% CI	
					Lower	Upper
Intercept	**13.083**	**0.492**	**26.61**	**<.001**	**12.119**	**14.047**
SSQ total	-0.024	0.017	-1.42	.155	-0.058	0.009
CSQ Stress	**-0.552**	**0.042**	**-13.04**	**<.001**	**-0.635**	**-0.469**
Event Rating (ER)	**0.367**	**0.109**	**3.36**	**.001**	**0.153**	**0.581**
Stressful Events (SE)	**-0.569**	**0.169**	**-3.38**	**.001**	**-0.900**	**-0.239**
Pleasurable Events (PE)	**0.514**	**0.125**	**4.11**	**<.001**	**0.269**	**0.760**
Cannabis consumed	**0.598**	**0.189**	**3.16**	**.002**	**0.226**	**0.969**
Caffeine	-0.036	0.097	-0.37	.711	-0.225	0.154
Tobacco	-0.013	0.119	-0.11	.912	-0.247	0.221
Alcohol	0.119	0.110	1.08	.279	-0.097	0.334
Time	**-0.004**	**0.001**	**-2.85**	**.004**	**-0.006**	**-0.001**

Random effects ([co-]variances)		Estimate	(SE)	ICC (%)	95% CI	
					Lower	Upper
Level 1	Intercept	8.102	2.039	60.090	4.948	13.267
Level 2	Intercept	1.742	0.312	12.917	1.226	2.473
	Residual	3.640	0.238		3.202	4.138

This section has examined factors predicting concurrent states of stress, in which there was no evidence of cannabis' ability to attenuate stressed states. However, analyses in this section suggest that previous cannabis consumption significantly predicts calm states, furthermore, a dose dependent effect was established. This finding supports the notion of cannabis as an anxiolytic, thus providing evidence for Khantzian's model of self-medication (see Section 1.6.1). As evidenced by the use of cannabis conferring some benefit on the user in eliciting calm like states.

3.3.6 Covariates of cannabis use

This section fulfils the second aim of this investigation: to assess temporal priority in the relationship between cannabis and psychotic experience in a naturalistic setting. This aim is fulfilled by examination of factors which predict cannabis consumption. However, information contained in Section 3.3.3 also serves to fulfil

this aim. This section also serves to address the fourth aim of this chapter; to assess factors which may influence the consumption of cannabis. Given cannabis' purported anxiolytic effect (see Section 1.4 pp.55-58) this aim is also considered in Section 3.3.5.

The SSQ and the CSQ scales are concurrent measures, which were administered simultaneously with several retrospective measures (ER, SE, PE, and items pertaining to drug consumption). If a time lag of one data entry is applied to the concurrent measures it is possible to observe their effects on retrospective items or in this case prior action of consuming cannabis.

Covariates of cannabis consumption per se

As discussed previously analyses with a dichotomous outcome variable were computed once with all covariates and for a second time with only the significant predictor variables. Values from the variables that were deemed pertinent to hypotheses testing are displayed in Table 30, and when not significant (at the 0.05 level) refer to the first of the two models, these are the SSQ (and all subscales) and the CSQ stress scale. Apart from these exceptions the values generated by the second model are the ones which are displayed in the text and Tables 30 and 31.

As anticipated time was a significant covariate of cannabis consumption, as the amount of time between each data entry increased by a minute the odds of using cannabis increased by 0.4% (OR =1.004 95% CI 1.001 to 1.007, p = .012). However, SE did not predict cannabis use, suggesting that cannabis users were not consuming cannabis as a result of stressful events. Both ER and PE significantly increased the odds of cannabis consumption (respectively; O.R. =1.68 95% CI 1.32 to 2.12, p < .001; O.R. = 1.89 95% CI 1.43 to 2.04, p < .001). Thus, indicating for every unit increase in PE that had occurred in the moments proceeding a data entry the odds of having consumed cannabis were 89% higher, and for every unit increase on ER the odds of using cannabis increased by 68%.

Caffeine consumption in the moments proceeding a data entry significantly increased the odds that cannabis would be used in the same time frame (OR

=1.60 95% CI 1.26 to 2.04, $p < .001$).For every unit of caffeine consumed (1 cup of tea) the odds of having used cannabis in the same time frame increased by 60%. Whereas, tobacco use significantly reduced the odds of cannabis use (OR = 0.51 95% CI 0.39 to 0.67, $p < .001$), for each unit of tobacco used (1 cigarette) the odds of having used cannabis in the same time frame decrease by 49%. The inferences that can be drawn from the data regarding the relationship between cannabis, caffeine and tobacco are feasibly explained by co-occurring behaviours (e.g. drinking a cup of tea every time cannabis is consumed, or replacing cannabis use with tobacco use) as opposed to causality.

Table 30
Parameter estimates for multilevel model of cannabis consumption per se (outcome) as a function of a schizotypal state, states of stress, stressful events, and pleasurable events

Fixed effect (intercept, slopes)	O.R.	(SE)	Z	P	95% CI	
					Lower	Upper
Intercept	0.981	0.294	-0.06	.949	0.545	1.765
*SSQ total $^{T-1}$	1.034	0.049	0.71	0.478	0.943	1.133
*CSQ Stress $^{T-1}$	1.016	0.040	0.39	0.694	0.940	1.100
Event Rating (ER)	**1.675**	**0.203**	**4.25**	**<.001**	**1.321**	**2.124**
Pleasurable Events (PE)	**1.892**	**0.272**	**4.44**	**<.001**	**1.427**	**2.507**
Caffeine	**1.602**	**0.197**	**3.85**	**<.001**	**1.260**	**2.038**
Tobacco	**0.513**	**0.070**	**-4.90**	**<.001**	**0.392**	**0.669**
Time	**1.004**	**0.002**	**2.50**	**.012**	**1.0009**	**1.007**
Random effects ([co-]variances)	Estimate	(SE)	Median OR	ICC (%)	95% CI	
					Lower	Upper
Level 1	1.636	0.280	4.763	44.621	1.170	2.288
Level 2	0.182	0.580	1.189	0.550	0.0003	95.392

*Computed from previous model

Analysis within this section will allow inferences to be made regarding the 'self-medication' hypothesis described by Kollikaou et al., (2011) or Khantizian, by assessing (see Section 1.6.1) whether distressing states of mind (stress) or psychotic-like states at the previous data entry alter the odds of cannabis consumption prior to the next data entry. CSQ Calm $^{T-1}$ and CSQ Stress $^{T-1}$ did not significantly alter the odds ratio of cannabis consumption. The lack of relationship with CSQ Stress $^{T-1}$ does not provide any corroborating evidence of the self-medication hypothesis (see Section 1.6.1). Concurrent feelings of stress did not

increase the odds of cannabis use, and concurrent feelings of calm did not decrease the odds of cannabis use. This section also sought to assess if a schizotypal state predicts cannabis use. Scores on the SSQ total $^{T-1}$ did not significantly increase the odds ratio associated with cannabis use (Table 30).

To ascertain if the scores on the SSQ subscales would be a significant covariate of cannabis consumption, the model was re-computed utilising the subscales (see Table 31) as opposed to the grand total. Please note that a two level model was utilised as the third level failed to yield an intra-class correlations (ICC) value indicating that this level of the model is not accounting for variability in the data. Thus, suggesting that cannabis consumption remained stable within participants between days, i.e. participants did not tend to consume more on one day in comparison to another. One of the three SSQ subscales was found to have a significant effect. For each unit increase on the SSQ disorganised $^{T-1}$ subscale the odds of cannabis being consumed since the last data entry increased by 14% (OR = 1.25 95% CI 1.05 to 1.25, p = .003). This finding concurs with the notion that a proportion of cannabis use could be attributable to individuals attempting to attenuate some of their distressing symptoms. Thus, within this domain of schizotypy there is some evidence of cannabis 'causing' a schizotypal state.

In this section some of the factors predicting cannabis consumption have been described. Caffeine and tobacco use are both significant covariates of cannabis consumption per se, which feasibly may represent, co-occurring behaviours associated with cannabis use and abstinence of cannabis use. States of stress and states of calm did not significantly increase or decrease the odds of future cannabis consumption. Consequently, this does not provide evidence in support of distress predicting an increase in cannabis consumption. Drug consumption as a means of mitigating psychological distress is a central component of Khantzian's model and the model described by Kollikaou et al., (2011). Thus, the lack of relationship observed between these variables does not support the self-medication hypotheses described.

Table 31
Parameter estimates for multilevel model of cannabis consumption per se (outcome) as a function of a schizotypal state, states of stress, states of calm, stressful events, pleasurable events, and a cannabis-stress interaction

Fixed effect (intercept, slopes)	O.R.	(SE)	Z	P	95% CI	
					Lower	Upper
Intercept	0.905	0.249	-0.36	.718	0.528	1.553
*SSQ inter $^{T-1}$	0.926	0.044	-1.64	.101	0.844	1.015
SSQ dis $^{T-1}$	**1.141**	**0.051**	**2.93**	**.003**	**1.045**	**1.247**
*SSQ cog $^{T-1}$	0.931	0.061	-1.09	.275	0.819	1.058
*CSQ Stress $^{T-1}$	1.010	0.042	0.26	.791	0.933	1.096
Event Rating (ER)	**1.718**	**0.208**	**4.46**	**<.001**	**1.355**	**2.179**
Pleasurable Events (PE)	**1.824**	**0.256**	**4.27**	**<.001**	**1.384**	**2.402**
Caffeine	**1.642**	**0.203**	**4.01**	**<.001**	**1.288**	**2.094**
Tobacco	**0.499**	**0.069**	**-5.05**	**<.001**	**0.381**	**0.654**
Time	**1.004**	**0.002**	**2.60**	**.009**	**1.001**	**1.007**

Random effects ([co-]variances)	Estimate	(SE)	Median OR	ICC (%)	95% CI	
					Lower	Upper
Level 1	1.470	0.253	39.630	4.062	1.049	2.059

*Computed from previous model

The most important data contained in this section pertaining to the 'self-medication' hypotheses is that describing a schizotypal states' propensity to predict future cannabis consumption. Participant's total scores on the SSQ did not indicate any evidence for the 'self-medication hypothesis'. However, further examination of the subscales suggests that distortion of (dis)organisation increases the odds of cannabis consumption. Thus, the findings provide evidence that psychological distress within this domain significantly and positively increases the odds of cannabis consumption. The relationship between distortion of disorganisation and cannabis consumption may be most meaningful when considered in parallel with the finding indicating cannabis consumption significantly co-varies with scores on the disorganised (and interpersonal) subscale. These findings when considered in parallel may represent a synergistic relationship between cannabis and distortion of disorganisation. This notion will be discussed in greater detail in the next section.

3.4 Discussion

3.4.1 Main findings

The current investigation found supporting evidence of cannabis consumption holding temporal priority over increases in schizotypal state, within the domains of interpersonal distortion and disorganisation. This finding was also demonstrated in a dose dependent fashion. Stress (as measured by the CSQ Stress scale) was also a significant covariate of a schizotypal state in all three of the subscales under assessment, thereby supporting the notion that stress may be an antecedent for psychotic like experiences and their persistence (see Section 1.2.3 pp. 37-48). Support was found for a state of calmness decreasing psychotic-like states. However, this only occurred with one of the three subscales under assessment, interpersonal deficits.

Sections 3.3.5 (pp. 230-34) and 3.3.6 (pp. 234-38) elucidated information on what is commonly referred to as the 'self-medication hypothesis'. In examination of stress as a predictor of cannabis consumption no evidence was found of a relationship, thus not supporting the notion of psychological distress within this domain predicating cannabis use. However, some support was found for self-medication. Psychological distress within the domain of distortions of disorganisation significantly and positively predicted cannabis use. However, no significant effect was found in the other SSQ subscales. Previous cannabis consumption (since the last prompt) did not significantly predict decreases in concurrent stress. Thus, no evidence was found for cannabis having an efficacious self-medication effect on states of stress, as would be consistent with self-medication models. Nonetheless, cannabis consumption significantly co-varied with an increase in states of calm. Furthermore, a dose dependent effect was established. Thus, providing support for the self-medication hypothesis and the efficacy of cannabis as an anxiolytic.

A stressed state significantly predicted increases in schizotypal state, and calm states significantly predicted decrease within the interpersonal domain. This indicates that within a continuum model (utilising a cannabis model of psychosis)

stressed and calm states may be determinates of the presentation of psychotic symptomatology.

The notion of a cannabis stress interaction effect mediating the relationship with psychotic experience was also tested in this investigation. A cannabis and stress interaction variable significantly co-varied with increase in a schizotypal state within the domain of interpersonal distortion and disorganisation, thus providing support for an interaction between environmental factors on psychotic states. Moreover, when participants were differentiated on the basis of their concurrent stress, cannabis consumption within the high stress group significantly co-varied with schizotypal state. However, in the low stress group cannabis did not significantly predict schizotypy. These findings indicate that cannabis and stress interact to cause elevations in psychotic-like states, and the presence of both factors may be a necessary requisite for the factors to exert an influence.

3.4.2 Implications and comparison with other research

Schizotypy is commonly considered a stable and enduring personality trait (see Section 1.2.2 pp. 31-37). Nonetheless, in the current investigation several variables under examination were significant predictors of (variance in) a schizotypal state. The relationship between a schizotypal state and trait is poorly understood. Moreover, there is even less information pertaining to how a schizotypal state may infer risk for diagnosable mental illness.

Rössler, Hengartner, Ajdacic-Gross, Haker and Angst (2013) stated “to date, we are still uncertain whether liability to sub-clinical psychosis represents either transient and occasion-specific states or a stable dispositional trait” (pp1-2). Rössler and colleagues in a 30 year follow up investigation found that the proportion of variance in symptomatology attributable to state and trait varies over the course of a person’s life. Nonetheless, Hodgekins et al. (2012) was able to distinguish healthy controls from a patient group recovering from psychosis with a state measure of schizotypy, not dissimilar from that used in the current investigation. Chen et al. (2006) in a review of trait and state markers of schizophrenia concluded that “distinguishing enduring trait markers from transient

state markers for schizophrenia… is helpful for developing neurobiologically and psychologically based intervention strategies" (p.431).

One construct which co-varied with schizotypal state was concurrent stress. There is a compelling body of evidence suggesting that psychosocial stressors play a role in the presentation of psychosis (see Sections 1.2.3 & 3.1). The current investigation provides corroborating evidence for this notion with concurrent stress significantly co-varying with scores on all three domains of schizotypal state under assessment. The results therefore support the notion of a diathesis-stress model, whereby psychosocial stressors function as an antecedent (along with vulnerability) to the development of psychotic disorder (Zubin and Spring, 1977). Additionally, the inverse relationship was observed, with concurrent feelings of calm (CSQ Calm scale) predicting a decrease within the interpersonal domain.

Despite the lack of data pertaining to the mechanism by which one decompensates from schizotypal state to schizophrenia, the relationship between schizotypal state and concurrent stress indicates that stress could potentially contribute to the development of psychotic disorder. Whereas, feelings of calm may serve to (independently) reduce the potential for decompensating. This finding may have wide reaching implications possibly indicating that stress reduction therapies in addition to interventions to increase psychological 'positivity' may have a beneficial effect on the primary symptoms of schizophrenia sufferers. Mindfulness exercises in people with psychosis have been shown to reduce symptomatology (Chadwick, Taylor, & Abba, 2005; Chadwick, Hughes, Russell, Russell, & Dagnan 2009) and enhance "ability to respond mindfully to stressful internal events" (Langer, Cangas, Salcedo, & Fuentes, 2012, p.105). In a recent meta-analysis mindfulness exercises were also found to be effective at reducing anxiety and stress (Khoury et al., 2013).

Cannabis consumption was shown to significantly co-vary with a schizotypal state. Moreover, a dose dependent effect was established. The results suggest that cannabis can serve to independently elevate scores within the interpersonal domain. The literature indicates a relationship between cannabis consumption and

schizotypal personality (e.g. Dumas et al., 2002; Skosnik et al., 2001). However, the nature of this association is poorly understood.

The observed relationship between cannabis and schizotypal state appears at odds with the assertions of Mass et al., (2001) who suggest that highly schizotypal individuals are more prone to using cannabis. Mass and colleagues state that "schizotypal subjects seem to be more likely to use cannabis than the general population. Therefore, cannabis use may be a vulnerability indicator for schizophrenia" (p.209). The results of this investigation indicate that cannabis use may be a contributory factor, as opposed to vulnerability indicator. Mass and colleagues concluded that "schizotypal features… within the cannabis group were related to the drug consumption per se rather than to acute intoxication effects" (p212).

The current investigation allows inferences to be drawn regarding the association between schizotypy and cannabis. The results appear to indicate that cannabis consumption (acute intoxication) serves to elevate a schizotypal state. There is supporting evidence for this notion in the literature with an inverse relationship demonstrated between completion of measures of schizotypy and temporal proximity with cannabis use; the closer the time period to last cannabis use the more schizotypal traits were observed (Baskak et al., 2012). Moreover, in an experimental study design scores on the PSI were significantly increased as a result of a cannabis challenge (Mason et al., 2009). Furthermore, Skosnik et al. (2001) found that current cannabis users exhibited a higher schizotypal personality trait than past users.

The current investigation demonstrated a significant association between cannabis and schizotypal state within the domains of interpersonal deficits and disorganisation, but not within the domains of cognitive-perceptual deficits. Despite temporal priority being established the notion of synergistic maintenance cannot be dismissed wherein psychotic like states prime for and maintain cannabis use, and vice versa. Within the domain of deficits of organisation, reported behaviour consistent with 'self-medication' was observed. Disorganisation as a sub-factor of a schizotypal state co-varied with future cannabis use. Indicating that the

participants' decision as to whether or not to consume cannabis may be in some part based on the occurrence of psychotic-like disorganisation. Nonetheless, disorganised states are in some part influenced by prior cannabis use. Thus, within the domain of disorganisation there is evidence suggesting synergistic maintenance, whereby disorganisation may be a symptom of- and a primer for-cannabis use. Interestingly, within Chapter 2 (Section 2.3.4) participants that were cannabis users displayed significantly more disorganised schizotypal traits than their cannabis naïve counterparts. Taken together the data support the notion that a proportion of the association between schizotypy and cannabis is as a consequence of the user self-medicating disorganised psychotic-like symptomatology.

In the current investigation there was no evidence that cannabis consumption co-varies with psychotic-like states within the realm of cognitive-perceptual distortion. This suggests that, within the time frame observed at least, in habitual users, cannabis does not influence psychotic-like response within this domain. However, it is noteworthy that the sample under consideration was not anticipated to display high vulnerability in comparison to the population. Thus these effects may be a differentiating factor between a healthy and unhealthy sample. The data considered in Chapter 2 suggests that the cognitive-perceptual construct is the only SPQ-b subscale capable of differentiating psychotic populations. This finding provides further evidence that in healthy cannabis users this domain of schizotypy is not elevated.

The transient psychotic-like states observed in this investigation did not appear to be pathological, nor did they result in conversion in the current sample. Nonetheless, the notion that cannabis use may act as an independent developmental antecedent of psychotic illness is supported, particularly for symptoms related to interpersonal deficits. Previous cannabis consumption predicted interpersonal deficits but, previous interpersonal deficits did not predict future cannabis consumption.

The current investigation provides data implicating stress as component of the relationship between cannabis and psychosis. A cannabis stress interaction effect

was a significant predictor of a schizotypal state within the domains of interpersonal deficit and disorganisation. Moreover, cannabis consumption was a significant predictor of a schizotypal state in the participants who experienced the highest states of stress, but not in the ones who experienced the lowest. These findings suggest the possibility of an interaction effect with stress and cannabis in the development of psychotic illness.

Stress and cannabis appear to have a complex, but nonetheless well substantiated relationship. In animal models cannabinoids have been shown to increase the release of adrenocorticotropic hormones and glucocorticoids; a physiological stress response (See Brown & Dobs, 2002 for review). Moreover, the endocannabinoid system is thought to play a role in the regulation of a stress response. Hill and McEwen (2010) summarised in a recent review "...it is becoming increasingly apparent that the endocannabinoid system is an integral regulatory force on HPA [Hypothalamic-Pituitary-Adrenal] axis activation and stress responsivity" (p.795). Endocannabinoid systems regulation of a stress response is thought to occur via GABAergic, glutamatergic and monoaminergic transmission (Häring, Grieb, Monory, Lutz, & Moreira, 2013). Furthermore, the endocannabinoid system has also been implicated in stress related disorders. A dysfunctional endocannabinoid system as a result of "…abnormal CB_1 receptor-mediated anandamide signalling is implicated in the etiology of PTSD" (Neumeister, et al., in press).

There is also data available suggesting an interaction effect between cannabis and stress on a psychosis outcome. Within animal models a cannabinoid stress interaction effect has been demonstrated, ∆-8-THC did not elicit striatal DA release under 'normal' (non-stressed) conditions. However, under 'stressful' conditions (no food for 24 hours) striatal DA was released and behavioural changes occurred (Littleton and Maclean, 1975; Maclean and Littleton, 1977). This may go some way to explain some of the contradictory data pertaining to cannabis' ability to elicit DA release in humans (see Section 1.7.1 pp. 80-84).

In human subjects D'Souza et al., (2008) and Ranganathan et al., (2009) demonstrated increased heart rate (tachycardia) and serum cortisol release as a

consequence of a ∆-9-THC challenge. These physiological changes occurred simultaneously with psychotomimetic effects and perceptual alterations. However, the physiological and the aversive psychological effects were blunted in habitual users in comparison to controls. In epidemiological data from an American sample Houston et al., (2008: 2011), identified an interaction between childhood sexual trauma and cannabis use on a psychosis outcome. Cannabis use alone was not a significant predictor of psychotic illness. In a Greek and Dutch sample an interaction effect was also observed between childhood maltreatment and cannabis use on a psychosis outcome (Konings et al., 2012).

When the results from the current investigation are considered in light of the research outlined above (and in Sections 3.1 & 1.7.4) a developing picture of an interaction between stress and cannabis emerges. This interaction could plausibly be responsible for some cases of psychotic illness. Although, the mechanisms by which such an interaction effect could 'cause' mental illness are still a matter of debate (see Henquet et al., 2008). One proposed mechanism which the current investigation appears to support (in part) is one of 'cross-sensitisation'. Sensitisation is not (typically) considered as a unitary aetiological theory of schizophrenia, but rather a means by which environmental factors may interact with genetic ones (e.g. Henquet et al., 2008; Van Winkel, Henquet et al., 2008). Collip et al., (2008) state "Sensitization refers to the observation that individuals who are exposed repeatedly to an environmental risk factor may develop progressively greater responses over time, finally resulting in a lasting change in response amplitude" (pp. 220-1).

Both stress and cannabis may independently play a role in the sensitisation processes (see Section 1.7.3). The interaction effect outlined by previous investigations, and the current investigation, indicates that if such a sensitisation process was to occur then it is plausible that these processes are interacting i.e. cross-sensitisation. Van Winkel, Stefanis and Myin-Germeys (2008) state "The neurobiological substrate of sensitization may involve dysregulation of the hypothalamus-pituitary-adrenal axis, contributing to a hypothesized final common pathway of dopamine sensitization in mesolimbic areas and increased stress-induced striatal dopamine release" (p.1095). Therein is a plausible mechanism

(supported in part by the current study), in which cannabis, stress and genetic factors may interact to cause psychotic- like states, psychotic symptoms and eventually psychotic disorder.

Nonetheless, the variable nature of cannabis and the myriad of different effects elicited from numerous cannabinoids cannot be ignored. Despite indications that cannabis and stress may interact to the detriment of psychological wellbeing, the data also indicated that cannabis elicited feelings of calm. This appears to support the assertions that cannabis has an anxiolytic effect (Zuardi et al., 1982). Nonetheless, the complex relationship between cannabis and stress means that for most users (in the UK at least) this is not a viable anti-anxiety aid. Most consumers of cannabis in the UK will not have access to the equipment necessary for determining cannabinoid ratios, nor are they likely to be accurately informed of ratios at point of sale (see Section 1.4). It is likely that the calming effect of cannabis is as a consequence of the actions of CBD (see Section 1.4). Thus, in the absence of reliable cannabinoid levels it does not appear that cannabis is appropriate for use in 'self-medication' of anxiety.

The current investigation indicates that the greatest risk to the deleterious effects of cannabis occurs during high periods of stress. However, in a recent meta-analysis examining risk-factors for cannabis consumption, stress-coping was frequently cited as a motivation for cannabis use (Hyman and Sinha, 2009). Given the relatively low prevalence of schizophrenia in comparison to the relatively high prevalence of cannabis use this would appear to suggest that; the most debilitating of the deleterious effects of a cannabis stress interaction are reserved for those at the greatest genetic risk. Further investigation is required to identify genes which confer risk of the development of psychosis (Sullivan, 2005). Nonetheless, the available data indicates that at risk groups (e.g. first degree relatives, those displaying bio-markers etc.) should be warned against utilising cannabis as a stress coping mechanism. This could be adopted within advertisement campaigns focused on the prevention of harm within this population

The findings of this investigation have implications for research, theoretical development, and feasibly illness prevention. Despite the advantages of this

investigation it is not absent of limitations. The next section will focus on the limitations of this investigation and the implications of these limitations on the interpretation of the findings.

3.4.3 Limitations

Representativeness and generalisability

Two limitations which are pervasive in many methodological approaches, of which this study is not an exception, are a self-selecting bias and participant attrition. ESM research places demands on the participants above what is typical within cross-sectional investigation. The participants are required to attend to prompts numerous times throughout the day. Moreover, the pseudo-randomised prompts are designed to capture various psychological states in a variety of environments, whilst a variety of activities are being conducted. Thus, in their very nature they are designed to interrupt participants in their daily activities. The prompts may also distract people other than the participant or cause the participant to feel stigmatised due to the sensitive area of research. As a consequence, the nature of the methodology may further exacerbate the limitations of a self-selecting bias and attrition. “The difficult nature of these tasks might lead certain types of individuals to be over- or underrepresented in ESM studies” (Scollon et al., 2003, p.14). Thus a self-selecting bias has the influence of reducing the generalisability of the results from the sample to the wider population. Moreover, the relatively low *N* although sufficient for an ESM investigation reduces the generalisability of the findings.

The issue of participant attrition has been addressed to some extent in the current investigation. Section 3.3.1 compares two samples from the population; participants who were included in the final sample; and those who initiated the ESM phase, but were not included. Age of cannabis use initiation was significantly earlier in participants that were not included in the final sample. Nonetheless, the mean age of first initiation of those included in the final sample was only two years higher than their counterparts, and age of regular cannabis use was only one year more. Moreover, the mean age of initiation for both groups falls within the parameters of what appears to be an age associated with increased lifetime risk of psychotic illness (Arseneault et al., 2002). Age of initiation aside all of the other indices under assessment indicated no significant differences between the two groups. This suggests that attrition did not cause additional biases within the final sample.

Nonetheless, the exhaustive steps taken to promote a viable research alliance between researcher and participant may have gone some way towards reducing bias as a result of attrition. Ciskszentmihalyi and Larson (1992) suggest that ESM is an appropriate methodology "...provided that a viable research alliance can be established" (p.48). Scollon et al., (2003) suggest that an "effective way of ensuring participant cooperation is to gain participant trust" (p.15). One means by which this can be established is discussed by DeVries (1992, p319), wherein the briefing and debriefing session form a part of developing a research alliance.

In this investigation participants were briefed and de-briefed in a location and time of their choosing. At these sessions (and prior via telephone and email) there was the facility for comprehensive discussion with a researcher regarding the background to the investigation and how the investigation is situated within the wider programme of research. Participants frequently commented that these discussions helped to allay their concerns regarding; findings which unduly portray them or cannabis in a negative light; and the sharing of information with the police. Furthermore, participants were contacted at several time points throughout the investigation and were provided with the opportunity to contact a researcher (virtually) 24-hours a day for the duration of their ESM-phase. The researcher's duties also extended to providing full technical assistance for all apparatus used in the investigation.

There are other aspects of the current investigation which limit the generalisability of the sample. For instance, the use of technology within the study design and recruitment procedure may have served to reduce the likelihood of participation from populations with less confidence or experience of using technology. The factors which may influence the use of technology are broad and wide ranging, but include age (Czaja et al., 2006), ethnicity (Office of Communications, 2013), economic status (Hsieh, Rai & Keil, 2006), and level of education (Sun & Metros, 2011).

The restrictive geographic range from which participants were recruited may have also reduced the variance between the participants, and perhaps most importantly this could have served to reduce the preparations of cannabis available to the

participants. D. Potter et al., (2008) reported that particular preparations of cannabis (i.e. cannabis resin) occurred more frequently in certain geographic locations this appeared most pervasive in samples collected from areas in close proximity to a port. Nonetheless, the proportions of the various preparations of cannabis consumed by the sample are similar to the proportions documented within the population. In the Home Office potency study 81% of samples seized were sinsemilla, 16% cannabis resin, and 3% traditional herbal cannabis (Hardwick & King, 2008). In the current investigation 86.1% of participants reported typically using sinsemilla, 8.3% cannabis resin, and 5.6% traditional herbal cannabis.

Measurement and study duration

Another limitation of the study relates to the quality of the data submitted. A multi-site investigation into ESM, lasting for seven days, did not observe any effects of duration of ESM phase on compliance (Johnson et al., 2009). Nonetheless, Stone, Kessler, and Haythornthwaite (1991) state that "problems of declining data quality…have been documented to occur between 2 and 4 weeks in some diary investigations" (p.592). The current investigations ESM phase lasted for fourteen days. However, it is anticipated that the exhaustive steps taken to develop a research alliance may have mitigated (some of) the potential for declining data quality.

Another limitation which may influence the quality of data is one of validity. Of particular concern is the assessment of quantity of cannabis consumed. Cannabinoid consumption quantity and ratios are dependent on a myriad of variables (see Section 1.4). The current investigation allowed for little control over these variables. There are ethical, legal, and pragmatic reasons which would prohibit ESM study designs in which participants are either given controlled doses of cannabinoids, or in which participants provide samples of the cannabis they consumed. Moreover, such assessments may have reduced ecological validity, making this a less 'naturalistic' investigation. The current investigation utilised retrospective self-report, albeit from a relatively short period of time (see Section 3.2.3). This assessment may be limited in its accuracy and will not provide

information relating to specific cannabinoids. Future, research within the domain could be conducted in locations with less stringent controls on cannabis use, e.g. Amsterdam, Holland. An open (i.e. non-secretive) cannabis market would enable the researcher to procure samples of the same cannabis as that consumed by the participant and subject it to analyses of cannabinoid ratios.

In psychological research there is often a 'trade-off' between the accuracy of measurement and control of variables, and the utilisation of a naturalistic setting. The current investigation has attempted to strike a reasonable balance, between naturalistic research and precision of measurement. Nonetheless, precision of measurement is not only a limitation of items pertaining to quantifiable substances, but psychological constructs as well.

The measures utilised in the current investigation were either constructed or adapted specifically for this investigation. The advantage of such an approach is that it has allowed for the assessment of constructs for which alternative measures may not be appropriate for an intensive ESM study design (e.g. utilising the 48 item PSI for six-fold daily assessment of schizotypal state), or instances where there was no alternative ESM measure (e.g. CEQ). The disadvantage of using such an approach is the measures in question had not been assessed for their validity, prior to this investigation. Evidence of concurrent validity was established for the measures of concurrent stress (CSQ Stress scale) and schizotypal state (SSQ) and to a lesser extent the event related items (ER, SE, and PE). Thus, there are now appropriate measures for future ESM investigations to utilise in the assessment of these constructs. Nonetheless, the efficacy of measurement and process of validation for the stress, calm and event related constructs can be further improved through the use of objective physiological measures of stress (i.e. cortisol).

Modelling of time

One limitation of the current investigation is the consideration of time within the statistical model. Unfortunately, the linear relationships between the incremental units of time are not modelled. To assess the effect of time the current investigation considered the number of minutes that had passed since the last prompt (centred around the mean), in doing so variance in time between prompts is considered within the model. The utilisation of the variable in this manner in theory (see Section 3.2.6) should adjust the betas of the (other) independent variables under consideration so that they are differentiated from the effect of time. However, this is not the optimum solution as it does not consider time as a linear variable throughout the ESM period only between prompts.

Bolger and Laurenceau (2013) recommend "…the influence of time should always be taken into account in your statistical model. That is time should be an explicit factor, or predictor, in any model of interest" (p27). Bolger and Laurenceau, suggest the "spatial power error structure approach" (p.93) as a preferable solution to the modelling of time. However, this method can currently only be administered on one platform (SAS). The advantage of this approach over the one utilised is that a linear relationship between a variable on a macro-scale of the level 2 (see Figure 8) unit can be established. For example, the current investigation can adjust for the linear effect of time on the quantity of cannabis consumed, between prompts. Whereas the approach described by Bolger and Laurenceau within the current investigation could adjust for the linear effect of time on the quantity (or accumulative effect) of cannabis consumed, from initiation to cessation of the ESM phase (day 1-14).

The current investigation has attempted to adjust for the limitations in the approach taken to the measurement of time. A three level data structure inherently models one conceptual element of time (the day level unit). Furthermore, signal-contingent data is only considered within the analysis if there is a valid entry at the previous prompt, within that day. Thus, ensuring that the time gap between responses do not fall outside of pre-determined parameters.

Retrospective assessment

The current investigation utilised some items (e.g. 'Have you used cannabis since the last [prompt]?) and measures (e.g. CEQb) which are pertaining to retrospective information. This may be seen as a limitation of the research. The rationale for the use of these retrospective items (not including the CEQ-b) is to attempt to capture information pertaining to events or drug consumption since the last data entry. If the typical method of consumption of cannabis is considered (i.e. smoking) from the moment the substance is exhaled (unless more is consumed) the participant is no longer *currently* using cannabis. Thus, a concurrent cannabis use item is fraught with poorly defined temporal boundaries, and this may not capture concurrent intoxication. Thus, in this instance retrospective items are the most accurate means of assessing the variable in question.

The use of the CEQ-b as a retrospective measure was based on the impracticalities associated with administering it by other means, for example set 'in the moment' or 'since the last prompt'. According to feedback from the pilot investigation these approaches would likely result in little variability in the data. In addition to making reference to concurrent experiences of intoxication the CEQ-b makes reference to *after-effects*, thus, setting the measure 'in the moment' is not plausible. Administering the CEQ-b six-fold daily pertaining to phenomena 'since the last prompt' would be unsuitable. As it would exceed the maximum time of 2-3 minutes recommended for completion of each data entry (Palmier-Claus, et al., 2011, p.14).

Retrospective items are common place within ESM research (See Christensen et al., 2003) nonetheless, the use of retrospective items are often subject to limitations. Christensen et al. (2003) recommend that retrospective items "should not be used for experiences that are susceptible to retrospective memory bias (e.g. emotions, subjective well-being, or any experiences that are quick to decay)" (p.60). Thus, in the current investigation (with the exception of the CEQb) the items typically refer to tangible and objectively quantifiable constructs. Even the items pertaining to stressful or pleasurable events are not in reference to the frequency of a self-determined pre-defined intensity of experience (i.e. How many *very* stressful events have you experienced since the last prompt?). Instead,

participants were given the specific instruction to document both minor and major stressors, thus reducing the possibility of recall bias. Moreover, this method of collecting data is considered preferable to (some) cross-sectional approaches as "the time of reference is much shorter than with global reports" (Scollon et al., 2003, p.22).

Experience Sampling Methodology

A limitation which is particularly pertinent to retrospective items and is fairly ubiquitous amongst ESM research is that of 'scaling'. Within the current investigation the participants 'prompts' occurred within a relatively short period of time of each other (mean 120.9 minutes, SD 60.68). Nonetheless, this may have resulted in the participants developing a unique scaling based on that time frame. Scollon et al. (2003) outline a case in which scaling may contribute to bias in response;

> The threshold for what is considered an angry state, for example, might be lower when one considers the past few hours as opposed to the past week. Additionally, participants might rate their present state in reference to their previous states (e.g., Compared to my other reports, how happy am I right now?). Thus, the meaning of momentary reports might change compared to between-subject responses. These are empirical questions that, unfortunately, have not received much attention thus far (pp. 22-3).

Experience sampling research does however hold advantages over (typical) cross-sectional research. Experience sampling research is typically capable of making inferences about two of the prerequisites for causality, temporal priority and concomitant variation. Kenny (1979) states "Three commonly accepted conditions must hold for a scientist to claim that X causes Y; 1. time precedence; 2. relationship; 3. nonspuriousness" (p.3). However, Kenny describes a scenario in which although temporal priority is established, previous responses on the dependent variable may have influenced the independent variable. Within the context of the literature outlined in Section 1.6., such a relationship may be as a result of synergistic maintenance. Kenny (1979) states:

> For X to cause Y, X must precede Y in time... To see this let X cause Y with a lag in time, and we then have, X_t causes Y_{t+k} where the subscript refers to time with k > 0. Note that Y_{t+k} cannot cause X_t since this would violate time precedence. (It is true, however, that Y_t could cause X_{t+k}.) (p.3)

ESM and cross-sectional research alike are capable of establishing the second of the conditions of causality, relationship (concomitant variation) (Kenny, 1979). Several analyses herein suggest a relationship between variables, however, the consideration of whether a relationship is significant or not is based on the selection of an arbitrary, yet commonly utilised value of 0.05. Kenny (1979) suggests "in judging whether two variables are related, it must be determined whether the relationship could be explained by chance" (p.5). Although the 0.05 value is utilised to discriminate between related variables and chance occurrence this does not guarantee against making a type 1 or type 2 error.

The third condition of causality, nonspuriousness, cannot be established in this instance. Kenny (1979) states "For a relationship between *X* and *Y* to be nonspurious, there must not be a *Z* that causes both *X* and *Y* such that the relationship between *X* and 2*Y* vanishes once *Z* is controlled" (p.5). In the current investigation the notion of the possibility of a variable *Z* cannot be eliminated. Such a variable could be responsible for explaining any significant relationships between the predictor variables and outcome variables in the analyses contained herein.

The participants perspective

Methodological reactivity is whereby the act of measuring a construct serves to influence a participant's response. A method for assessing methodological reactivity has been proposed a (see Johnson et al., 2009). However, the same approach was also suggested for assessing reliability (Palmier-Claus et al., 2011). Where the distinction between concluding either methodological reactivity or unreliability is arbitrary as the results would be equivocal, thus neither approaches have been adopted. However, modelling time as a function of minutes since last response elucidated significant variance in several measures which co-varied with

intensity of response rate. This may indicate methodological reactivity. Reactivity is typically framed within the context of the participant consciously subverting the data. Within the context of this investigation it would appear that intensity of response independently (and feasibly unconsciously) alters a participant's schizotypal state, within the domain of distortions of (dis)organisation; concurrent stress; and concurrent calmness.

As much as possible an attempt was made to adhere to recommendations for reducing reactivity. DeVries and Delespaul (1992) suggest "randomizing the occurrence of [prompts] throughout the day minimizes subject reactivity" (p.100). In the current investigation only the CEQ-b was not sent according to a pseudo-randomised schedule. Delespaul (1992) recommends that "small devices usually create less reactivity" (p.363). In the current investigation, a small device was utilised. Further attempts were made to reduce reactivity by only administering a minimal number of items. Moreover, it was anticipated that adaptations to item structure, aesthetics and response format as a result of several piloting phases would also reduce reactivity. Nonetheless, it is not known if methodological reactivity may have influenced the quality of data submitted, this is a limitation of this investigation which cannot be addressed. However, it is worthwhile noting that the analyses conducted were sensitive enough to elucidate instances of reactivity itself.

There are of course ethical considerations associated with methodological reactivity and although within the current investigation many different aspects of ethics have been considered, methodological reactivity was not one of them. This could have been measured through other means by utilising the QFQ data. However, this was beyond the scope of this investigation. Nonetheless, it is recommended that future investigations within this domain monitor participants before, after and feasibly even during the ESM period for methodological reactivity.

Despite recommendations that a small device reduces reactivity, in de-briefing sessions the most frequently criticised aspect of the study by the participants was the smartphone. Fiscal constraints limited the investigation to a narrow selection of

apparatus which could have been utilised. As a consequence participants utilised a smartphone with a relatively small display size for a touch screen phone (58 mm x 45 mm). At the de-briefing participants often commented that a phone with more reliable functionality and a larger screen would have made participation easier. It is difficult to assess the impact this may have had as there are no available data comparing ESM on various smartphones. Nonetheless, this may have feasibly reduced participant response rate. However, due to the steps taken to ensure a viable research alliance the smartphone may not have been detrimental to data quality. Moreover, despite the limitations of the technology this method may still have been preferable to the alternative of paper and pen methods (Stone et al., 2002).

3.4.4 Conclusions

Kimhy et al., (2009) highlighted the paucity of research conducted utilising ESM with cannabis users. Perhaps, the relative paucity of research with this population may be partially attributable to researchers' concerns about the participants' ability to follow study protocol. In the current investigation the majority of the equipment (smartphone) was returned (9/12) and the majority of the participants were eligible for inclusion in the main analyses (36/53). Nonetheless, the data indicates that the participants may have experienced some reactivity to the methodology. This investigation has examined the temporal and concomitant relationship between cannabis consumption, schizotypal state, stress, and calmness. Participants submitted, into a smartphone, self-report assessments six times a day for a period of fourteen days. The analysis of the resultant data has elucidated findings which have wider reaching implications than the mere context of this investigation.

This investigation indicates schizotypy consists of state, as well as trait, elements which are influenced by stress and calmness. This implicates stress-reduction exercises as a possible treatment of psychotic symptoms. Cannabis consumption appears to exert some influence on a schizotypal state, particularly within the domains of interpersonal distortion. However, distortion in organisation appears to implicate a system of synergistic maintenance. No evidence was found for cannabis eliciting psychotic-like states from within the cognitive-perceptual

domain. However, a cannabis-stress interaction effect was identified this could implicate a system of cross-sensitisation. It appears that the greatest risk to the deleterious effects of cannabis occurs during high periods of stress. At risk groups who are cannabis users should be warned against using the drug as a coping-mechanism.

Whether via a cross-sensitisation process or not the current study implicates a stress and cannabis interaction as an antecedent of psychotic illness. The relationship between the endocannabinoid system and the Hypothalamic-Pituitary-Adrenal (HPA) axis cannot be ignored, and neither can the relationship between stressful life events and psychosis. The data implicating cannabis as being capable of eliciting DA striatal release has been conflicting (see Section 1.7.1). Perhaps, it is only in instances when ∆-9-THC is combined with psychological stressors that striatal DA release occurs. Psychological stressors (in addition to genetic factors) could feasibly mediate the relationship between cannabis and psychosis. Both psychological stressors and cannabis use serve to activate the HPA axis. The presence of a cannabis induced physiological stress state when accompanied with psychological stressors, could serve to combine with genetic factors to induce psychotic illness. Placing stress as a central component of the relationship between cannabis and psychosis could feasibly account for; mixed laboratory findings; association in epidemiological data; and within person variability in response to cannabis. This interaction effect may prove to be a valuable line of enquiry in elucidating the relationship between cannabis and psychosis.

4. The development of the Cannabis Experiences Questionnaire for assessment of psychotic vulnerability

Brief Overview

This chapter aims to examine evidence for the convergent, discriminant, concurrent and predictive validity of the aversive scales of the CEQ as an assessment of psychotic vulnerability, in addition to assessing the internal reliability and providing inference about the test-retest reliability of the measure. These aims are achieved by drawing on the data discussed in Chapters 2 and 3.

Section 4.1 sumarises the findings from Chapters 2 and 3 which are also relevant to this chapter. Following the introduction there is a brief description of the methodology utilised in this investigation (Section 4.2). A more extensive discussion of methodologies is considered elsewhere in this thesis (Sections 2.2 & 3.2). The results of this investigation are contained within Section 4.3. Section 4.3.1 considers covariates of the aversive scale adapted for the purposes of an ESM investigation. Section 4.3.2 considers the aversive scale and the SPQ-b-L (see Section 3.2.4) administered at T0 (see Table 19) as predictors of schizotypal and stressed states throughout the ESM period. Section 4.3.2 tests the internal consistency of the aversive scale within the CSCU, DD and PD groups. Section 4.3.3 employs the SPQ-b and the CEQ to discriminate between the three aforementioned groups. Section 4.4 contains the discussion of findings, implications, limitations, and conclusions from this chapter.

4.1 Introduction

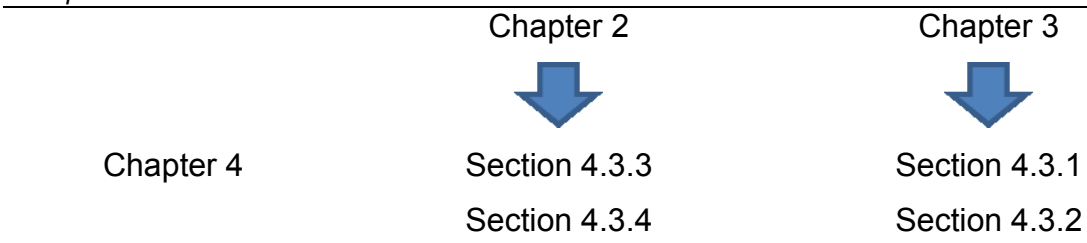
A review and introduction to previous research with the CEQ is considered in Section 2.1. This section will make reference to the results of the two previous research chapters (Chapter 2 & 3) to elucidate information about the CEQ as a measure of psychotic vulnerability. The CEQ disaggregates into three independent scales (Section 2.2.3 & Appendix 1). The scale which appears most relevant to psychosis proneness (e.g. Stirling et al., 2008) contains twenty items; seventeen concurrent effects and three after effects. The items consider a range of psychotomimetic phenomena, which could feasibly represent attenuated positive psychotic (e.g. feeling threatened by an unknown force), disorganised (e.g. disturbed in your thinking), and negative (e.g. depressed) symptomatology.

Section 2.3.5 considers group differences in the aversive scale. Cannabis users with a self-reported diagnosis of a psychotic disorder (PD) scored significantly higher than both a community sample (CSCU) and a sample with a self-reported diagnosis of depression (DD) (Tables 13 & 14). The aversive scale was also assessed for covariance with a self-reported diagnosis of psychosis (Section 2.3.6). The aversive scale was a significant covariate of the PD group in comparison to the DD group, and the CSCU group when unreported or undiagnosed mental illness is being controlled for (Section 2.3.8) or seemingly being controlled for (Section 2.3.7). However, it would appear that in comparison of the CSCU and PD groups the SPQ-b subscales and the aversive scale may be assessing a similar underlying factor (see Table 16).

This chapter will utilise the data set derived from Chapter 3 to provide further information about the aversive scale of the CEQ. An examination of a daily measure of aversive cannabis experiences (CEQ-b) will be performed to assess the scale as both a predictor and an outcome of a schizotypal state (Section 4.3.1). That section will also assess whether the CEQ-b predicts schizotypal states as a consequence of within or between participant variance. The data described in Chapter 3 will also be utilised to assess the CEQ's aversive scale as a predictor of schizotypal states (Section 4.3.2). Furthermore, this data will be used to assess the aversive scale and the SPQ-b as predictors of a stressed state.

This chapter will also utilise the data described in Chapter 2 to assess the internal reliability of the aversive scale in; a community sample of cannabis users (CSCU); cannabis users with a self-reported diagnosis of depression (DD); and cannabis users with a self-reported diagnosis of a psychotic disorder (PD) (Section 4.3.3). This chapter will conclude by utilising the data from Chapter 2 to assess the CEQ and the SPQ-b as predictors of psychotic illness (Section 4.3.4). This section will utilise a discriminant function analysis (DFA) to assess whether the participants group status (CSCU, DD or PD) can be predicted from their data. To facilitate interpretation of which investigation has contributed data to this chapter please refer to Figure 11.

Figure 11
Demonstrating which datasets have contributed to the analyses contained within chapter 4



4.1.1 Aims of this chapter

Information contained within the literature review, discussing the development of a measurement scale, is particularly pertinent to this chapter (Section 1.3), which had two primary aims:

1. To assess evidence for the reliability of the aversive scale of the CEQ as an assessment of psychotic vulnerability.
2. To assess evidence for the convergent, concurrent and predictive validity of the aversive scale of the CEQ.

4.2 Methodology

The discussion of the methodology and analytical procedures associated with Chapter 3 are contained within Section 3.2. As stated within this section, the assessment of cannabis experiences in the ESM investigation was slightly different to that of the other variables. The CEQ-b is an adapted version of the aversive scale of the CEQ. The principal adaptation being that the CEQ-b has a much shorter time of reference than the CEQ items. The CEQ-b items refer to cannabis induced phenomena experienced in a 24-hour period, whereas the CEQ refers to experiences over the participant's lifetime.

It is important to note that because of the CEQ-b's period of reference (previous 24-hours) it was administered in a slightly different manner to the other ESM items. The CEQ-b was administered with the participant's last response of the day, within one hour of their predicted bed time. The items of the CEQ-b were pertaining to cannabis experiences the participant had experienced within a 24 hour period. This is the same sampling period as the assessment of the other variables. Thus, the CEQ-b should not be presumed to have temporal priority, except in instances where a time lag has been applied.

The discussion of the methodology considered for analyses conducted in Sections 4.3.3 and 4.3.4, is in Section 2.2. However, unlike the data considered in Chapter 2, the data analysed within this chapter utilised data analysis software STATA 12.1 (StataCorp).

4.3 Results

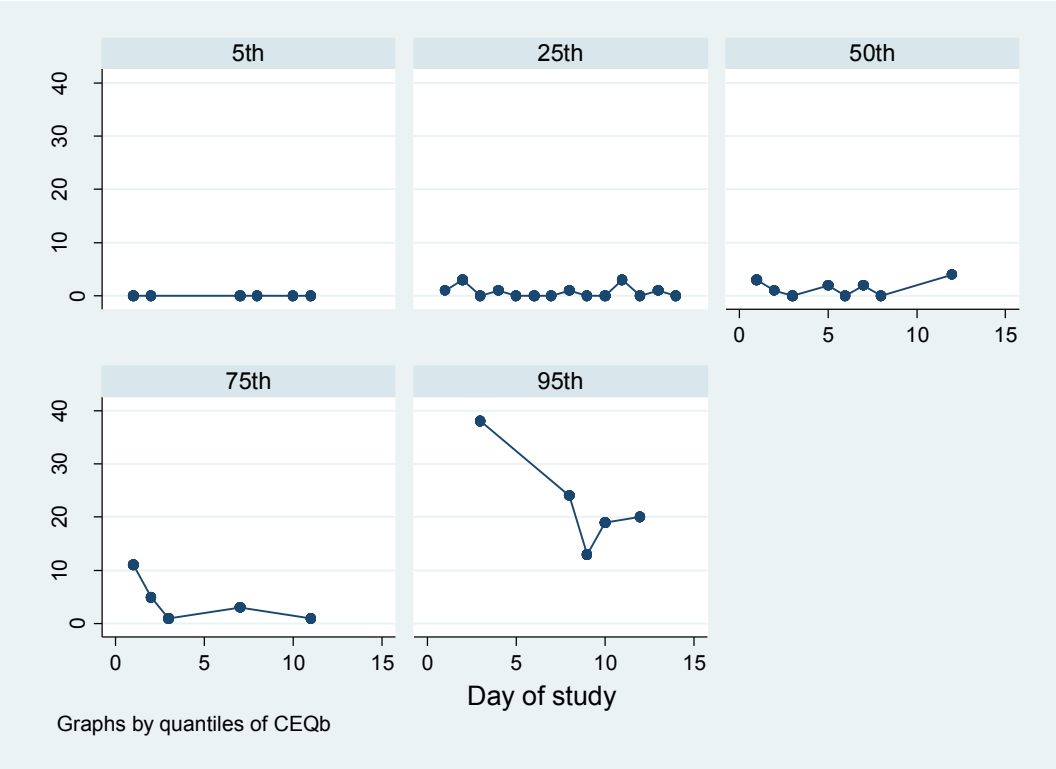
4.3.1 Covariates of aversive cannabis experiences: An ESM investigation

Fluctuations in daily assessments of aversive cannabis experiences

A subset of five participants were selected on the basis of their mean score on the CEQb over the ESM-phase, at the 5th, 25th, 50th, 75th and, 95th percentile, see Figure 12. These participant's scores on the CEQ-b were then mapped over the duration of the 14 days investigation. The CEQ-b displayed variability both between participants and in the majority of the cases within participants.

Figure 12

Scatterplots of a subset of participants displaying the variability of aversive cannabis experiences over time



Covariates of the Cannabis Experiences Questionnaire-Brief

Analyses contained within this subsection are contained within Table 32. The SSQ total was a significant covariate of the CEQ b (b = 0.17 95% CI 0.11 to 0.23, p < .001), each unit increase in the SSQ total co-varies with a 0.17 increase on the CEQ b. This finding indicates that schizotypal states co-vary with aversive cannabis experiences, suggesting a possible link between psychotic illness and

these experiences. Furthermore, the CSQ Stress scale was a significant covariate of the CEQ b (*b* = 0.23 95% CI 0.06 to 0.41, *p* = .009), each unit increase of concurrent stress co-varies with an increase of 0.23 on the CEQb. This suggests a relationship between states of stress and aversive cannabis experiences, however, it cannot be ascertained as to which of these variables possesses temporal priority. Consequently, it may be deemed that aversive cannabis experiences are influenced by stress, or, aversive cannabis experiences may be influencing stress. Nonetheless, this finding provides convergent validity and further evidence for the utility of the CEQb.

The cannabis-stress interaction variable was also a significant covariate of the CEQb (*b* = 0.40 95% CI 0.22 to 0.57, *p* < .001), each unit increase on the CSQ stress scale when combined with cannabis co-varies with an increase of 0.40 on the CEQ-b. This finding indicates that there is a relationship between the stress-cannabis interaction effect and aversive cannabis induced experiences. As discussed previously this does not infer temporal priority consequently numerous explanations of the finding may be possible. The cannabis-stress interaction may be influencing the aversive cannabis experiences or the experiences may in turn be promoting the cannabis-stress interaction. Nonetheless, this finding provides further corroborating evidence of a cannabis and stress interaction effect.

Cannabis consumption per se was also considered within this model, which was a significant covariate of the CEQb (*b* = 0.81 95% CI 0.10 to 1.52, *p* = .026). This finding could plausibly indicate that an increase in incidence of consumption could increase the propensity to experience aversive cannabis experiences. However, in an alternative model the quantity of cannabis consumed (within participants) did not significantly co-vary with the CEQb (*b* = 0.22 95% CI -0.10 to 0.53, *p* = .18). Neither, were, SSQ Calm, ER, SE, or PE significant covariates of the CEQb. However, caffeine consumption per se co-varies with a reduction of scores on the CEQ-b (*b* = -0.42 95% CI -0.80 to -0.04, *p* = .028). Each unit of caffeine consumed (1 cup of tea, ½ cup of coffee) co-varies with a decrease of 0.42 on the CEQ-b. Tea has been shown to lower post-stress cortisol and induce greater subjective relaxation, which may explain the relationship between caffeine and the CEQb (Steptoe et al., 2007).

Table 32
Parameter estimates for multilevel model of daily assessments of aversive cannabis experiences (outcome) as a function of schizotypal states of stress, states of calm, stressful events, pleasurable events, cannabis consumption per se and a cannabis-stress interaction

Fixed effect (intercept, slopes)	Estimate	(SE)	Z	P	95% CI	
					Lower	Upper
Intercept	**3.091**	**0.693**	**4.46**	**<.001**	**1.733**	**4.449**
SSQ total	**0.169**	**0.029**	**5.73**	**<.001**	**0.111**	**0.227**
CSQ Stress	**0.232**	**0.088**	**2.62**	**.009**	**0.059**	**0.405**
CSQ Calm	0.078	0.064	1.22	.224	-0.047	0.202
Event Rating (ER)	0.068	0.218	0.31	.754	-0.359	0.496
Stressful Events (SE)	0.463	0.320	1.44	.149	-0.165	1.091
Pleasurable Events (PE)	-0.242	0.239	-1.01	.312	-0.712	0.227
Cannabis X Stress	**0.395**	**0.087**	**4.52**	**<.001**	**0.224**	**0.567**
Cannabis consumed	**0.809**	**0.363**	**2.23**	**.026**	**0.097**	**1.520**
Caffeine	**-0.421**	**0.192**	**-2.19**	**.028**	**-0.797**	**-0.044**
Tobacco	-0.424	0.238	-1.79	.074	-0.890	0.041
Alcohol	0.226	0.223	1.01	.310	-0.211	0.663
Time	0.003	0.003	0.94	.345	-0.003	0.008

Random effects ([co-]variances)		Estimate	(SE)	ICC (%)	95% CI	
					Lower	Upper
Level 1	Intercept	3.941	0.534	52.801	3.021	5.141
	Residual	3.726	0.108		3.521	3.943

Daily Aversive cannabis experiences as a covariate of a schizotypal state

One means of assessing the CEQ-b's utility as an assessment of psychosis proneness is to assess it as a covariate of a schizotypal state. As discussed in Section 4.2 the CEQ-b is administered at the end of every day and the measure is in reference to that day's cannabis experiences (i.e. today have you had the following experiences). Consequently temporal priority between the variables cannot be established through conventional means. Nonetheless, the CEQ-b's ability to co-vary with measures of schizotypal states is informative.

The analysis described within this section is very similar to that displayed in Table 23 and discussed in Section 3.3.3, thus the relevant table is contained within

Appendix 34. The most notable difference between these models is the significance value of PE has decreased dramatically from .163 to .007. The rationale for this decrease is not known. Nonetheless, the CEQ-b was a significant covariate of the SSQ total (*b* =0.29 95% CI 0.16 to 0.42, *p*<.001) each unit increase on the CEQ-b co-varies with an increase of 0.29 on the SSQ total. This finding indicates that the cannabis experiences documented at the end of the day significantly predicts schizotypal states throughout the day. However, without establishing temporal priority this finding cannot be considered causal, nonetheless, this provides convergent evidence of the validity of the CEQ-b at identifying potentially pathological experiences.

Temporal priority between the CEQ-b and the other variables under consideration cannot be established through conventional means. However, one means in which it is possible to establish temporal priority and to consider the duration of disturbance is by lagging the CEQ-b variable by a day (CEQ-b_{T-1}). The CEQ-b was administered at equidistant time points consequently no additional procedures need to be adopted to control for time differences between days. However, as discussed (see Section 3.2.8), time since last data entry will be considered within the model. For brevity and to avoid repetition this analysis is not contained within a table (see Appendix 35). The CEQ-b_{T-1} was a significant predictor of a schizotypal state total (*b* = 0.23, 95% CI 0.12 to 0.34, *p* < .001). In this instance temporal priority can be established: the CEQ-b was capable of predicting schizotypal states that occurred on the following day. This finding provides further evidence for the utility of the CEQ-b at predicting experiences which may indicate susceptibility to psychotic illness, thus providing evidence of the measures predictive validity.

Further, examination of the lagged variable was undertaken to model between and within participant effects. To this end CEQ-b_{T-1} was split into two orthogonal components this procedure has been described in Section 3.2.8 and in Bolger and Laurenceau (2012, p.78). These variables were recomputed into the previous model described, the output is identical to that contained in Appendix 35, with the exception of the variance predicted by the CEQ-b_{T-1}. Both within (*b* = 0.22, 95% CI 0.10 to 0.33, *p* < .001) and between (*b* = 0.66, 95% CI 0.06 to 1.27, *p* = .033) participant effects of the CEQ-b_{T-1} were significant positive predictors of

schizotypal state. Each unit increase from the participants mean score predicted a 0.22 unit increase on the SSQ total score. Each unit increase above the samples mean predicted a 0.66 unit increase on the SSQ total score.

4.3.2 Schizotypal trait and the Aversive scale as covariates of momentary experience

The full length CEQ and the SPQ-b-L were completed prior to the briefing session. These measures were not administered as ESM items, but as cross-sectional measures. Nonetheless, the aversive scale of the CEQ and the cognitive-perceptual, disorganised, and interpersonal subscales of the SPQ-b-L can be considered as covariates within a multilevel model. The SPQ-b-L is assessing a personality construct and the aversive scale could also feasibly be assessing a stable construct (see Section 2.4). Some of the momentary variables under assessment may be influenced by these stable constructs, thus to observe the effect of these constructs it is necessary to omit some variables. Schizotypal state, states of calm, states of stress, the interaction term considering stress (CXS) and perception of events may all be influenced by schizotypal traits and the same constructs that promote aversive cannabis phenomena. Thus, the variables pertaining to these momentary phenomena will be omitted.

Schizotypal state (SSQ total) was assessed as an outcome variable (see Table 33). Given that schizotypal trait and state are likely to be highly related the SPQ-b subscales were not considered within the initial model in order to assess the aversive scale independently. The model considered the consumption of cannabis, alcohol, caffeine and tobacco, time, and the aversive scale. The aversive scale was not a significant predictor of a schizotypal state (b = 0.09, 95% CI -0.37 to 0.55, p = .71) (see Appendix 36). The model was re-computed with the three SPQ-b subscales included as predictors. The cognitive-perceptual subscale of the SPQ-b was a significant predictor of a schizotypal state (b = 0.75, 95% CI 0.01 to 1.48, p = .046), however, the disorganised and interpersonal subscales were not.

Table 33
Parameter estimates for multilevel model of a schizotypal state (outcome) as a function of aversive cannabis experiences, schizotypal trait and cannabis consumption per se

Fixed effect (intercept, slopes)	Estimate	(SE)	Z	P	95% CI Lower	95% CI Upper
Intercept	**14.202**	**1.866**	**7.61**	**<.001**	**10.544**	**17.859**
Aversive scale	-0.026	0.253	-0.10	.917	-0.521	0.468
SPQ: Cog-per	**0.745**	**0.374**	**1.99**	**.046**	**0.0121**	**1.477**
SPQ: inter	-0.186	0.419	-0.044	.657	-1.008	0.635
SPQ: dis	-0.651	0.524	-1.24	.214	-1.677	0.376
Cannabis consumed	**0.812**	**0.357**	**2.28**	**.023**	**0.113**	**1.512**
Caffeine	0.139	0.198	0.70	.484	-0.250	0.527
Tobacco	0.107	0.243	0.44	.661	-0.370	0.583
Alcohol	0.270	0.224	1.21	.227	-0.168	0.709
Time	-0.005	0.003	-1.93	.053	-0.01	0.0001

Random effects ([co-]variances)		Estimate	(SE)	ICC (%)	95% CI Lower	95% CI Upper
Level 1	Intercept	118.673	28.711	80.932	73.861	190.673
Level 2	Intercept	13.108	1.710	8.939	10.151	16.927
	Residual	14.851	0.909		13.172	16.744

Stress is thought to be a contributory factor in the presentation of psychotic illness (see Section 1.2.3 pp. 37 -40), and presented in Sections 3.3.3 (pp. 217-26) and 3.3.4 (pp. 227-229) there is evidence of an interaction between cannabis and stress on schizotypal state. Thus, stressed states (CSQ stress) were assessed as an outcome variable, of the aforementioned predictor variables (Table 34). The aversive scale was a significant and positive predictor of the amount of concurrent stress documented throughout the ESM period (b = 0.15, 95% CI 0.05 to 0.24, p = .002). However, neither the cognitive-perceptual, interpersonal, or disorganised subscales were significant predictors of stress. This provides some supporting evidence of the predictive validity of the CEQ.

Table 34
Parameter estimates for multilevel model of a stressed state (outcome) as a function of Aversive cannabis experiences, schizotypal trait and cannabis consumption per se

Fixed effect (intercept, slopes)	Estimate	(SE)	Z	P	95% CI	
					Lower	Upper
Intercept	**2.267**	**0.359**	**6.32**	**<.001**	**1.564**	**2.969**
Aversive scale	**0.147**	**0.048**	**3.04**	**.002**	**0.053**	**0.242**
SPQ: Cog-per	0.008	0.0714	0.11	.914	-0.132	0.148
SPQ: inter	-0.047	0.080	-0.59	.556	-0.204	0.110
SPQ: dis	-0.048	0.102	-0.47	.638	-0.248	0.152
Cannabis consumed	**-0.427**	**0.167**	**-2.56**	**.011**	**-0.755**	**-0.100**
Caffeine	0.011	0.093	0.012	.904	-0.171	0.193
Tobacco	**0.431**	**0.114**	**3.77**	**<.001**	**0.207**	**0.655**
Alcohol	0.014	0.105	0.13	.897	-0.193	0.220
Time	-0.001	0.001	-0.81	.419	-0.003	0.001

Random effects ([co-]variances)		Estimate	(SE)	ICC (%)	95% CI	
					Lower	Upper
Level 1	Intercept	3.738	1.061	33.837	2.143	6.521
Level 2	Intercept	4.139	0.459	37.467	3.330	5.144
	Residual	3.170	0.191		2.817	3.567

4.3.3 Assessments of internal reliability of the Aversive scale

The aversive scale of the CEQ was assessed for internal reliability with the three groups of cannabis users discussed in Chapter 2; a community sample (CSCU); a sample with a self-reported diagnosis of depression (DD); a sample with a self-reported diagnosis of a psychotic disorder (PD). The aversive scale displayed good internal reliability in the CSCU group (Cronbach's α = .932), DD group (Cronbach's α = .917) and the PD group (Cronbach's α = .939). Thus, the measure indicated a small amount of error variance in the three groups (respectively, 13.14%, 15.91%, & 11.83%). In the CSCU group no item deletion would have served to elevate alpha (see Appendix 37). In the DD group the deletion of two items may have served to elevate alpha, however, the largest increase is very small (0.002) (see Appendix 37). In the PD group the deletion of three items may have served to elevate alpha, however, the largest increase is also very small (0.002). This indicates that group identity (CSCU, DD, or PD) appears to have little effect on the internal reliability of the aversive scale. Despite

the PD group and the CSCU group presumably having differences in neuropharmacology they both respond consistently within groups on the CEQ. Unfortunately, there are insufficient participants within the PD group to assess the factorial structure of the CEQ. However, the assessments of Cronbach's alpha do not indicate that any of the items have been misallocated to the scale.

4.3.4 Using the Cannabis Experiences Questionnaire and the Schizotypal Personality Questionnaire-brief to predict psychotic illness

Utilising the data reported in Chapter 2, a discriminant function analysis (DFA) was performed. Whilst using a linear DFA the analysis tests a linear combination of variables to model group classification. However, as described in Section 2.3.1 the data do not meet the requisite assumptions necessary for parametric statistical procedures. The principle limitation of using non-parametric DFA is that the canonical discriminant coefficients are based on parametric assumptions (linear estimation), and thus cannot be computed. Nonetheless, a non-parametric discriminant function analysis utilising the Kth nearest neighbour (KNN) method was administered.

The KNN method (in this instance) predicts group membership from the membership of the nearest data point. The aversive and intoxicated scales of the CEQ, and the SPQ-b subscales were considered within the model. The Euclidean distances between the participant's data points on the aforementioned measures will be utilised to calculate their nearest neighbour in (Euclidean) geometric space. In this investigation the *two* nearest neighbours will be utilised to calculate the group classification. In the instance of a tie between the two nearest neighbours, the tie will be decided by selecting the neighbour with the closest proximity to the dependent variable. In the presentation of the results both the true value classification will be considered as will the leave-one-out (LOO) method. The LOO method considers the results "where the observation in question is omitted and its result is predicted from the rest of the data" and thus is more conservative than the true value classification (StataCorp, 2011, p203).

The results of the DFA classification table (Table 35) indicate that the model computed in the most conservative estimation (LOO) correctly classified 98.14% of

the HCU group, 32.94 % of the DD group and 16.67% of the PD group. The total error rate value for this model was 11.33%, thus the model correctly classified participants 88.67% of the time (Table 36). At the least conservative estimates (i.e. not utilising the LOO method) the model correctly classified 94.77% of the HCU group, 94.12% of the DD group and 83.33 % of the PD group. This produced an error rate of 8.30%, correctly assigning participants 91.70% of the time.

Table 35

kth nearest neighbour discriminant function analysis assessing group membership as a function of the SPQ-b and aversive and intoxicated cannabis induced experiences

True Group (%)		Classified Group (%)					
		HCU		DD		PD	
		All data	LOO	All data	LOO	All data	LOO
CSCU	All	816 (94.77)		45 (5.23)		0	
	LOO		845 (98.14)		14 (1.63)		2 (0.23)
DD	All	5 (5.88)		80 (94.12)		0	
	LOO*		53 (62.35)		28 (32.94)		3 (3.53)
PD	All	3 (6.25)		5 (10.42)		40 (83.33)	
	LOO		29 (60.42)		11 (22.92)		8 (16.67)
Total		824	927	130	53	40	13
Observed %		82.90	93.26	13.08	5.33	4.02	1.31
Predicted %		86.62		8.55		4.83	

*One participant unclassified

Table 36

Count error rate of kth nearest neighbour discriminant function analysis

	Count error rate			
	CSCU	DD	PD	Total
All %	6.74	15.15	24.07	8.30
LOO %	1.86	66.67	83.33	11.33
Predicted %	86.62	8.55	4.83	

The data presented in Sections 2.3.4 and 2.3.6 suggests that the cognitive-perceptual subscale of the SPQ-b is adept at identifying those who have had a

psychological disturbance. The data presented in Sections 2.3.5 and 2.3.6 suggests the aversive scale may be adept at distinguishing between those who have and have not had a psychotic mental illness. This suggests that one feasible means of identifying people with a psychotic disorder may be to administer the SPQ-b to initially identify psychological disturbance. Those who are affirmatively identified could be differentiated into psychotic (or not) by the use of the aversive scale. To test this notion a KNN DFA with the three SPQ-b subscales as independent variables was conducted. This test was performed with a dichotomous outcome variable differentiating between participants who were in the community sample of cannabis users (CSCU) and those that have reported a diagnosis of mental illness (DD and PD) (Table 37). The predicted category was saved as a variable and only those participants predicted to suffer with mental illness were re-computed in the next model. The second model utilised the aversive scale of the CEQ to differentiate between participants who had been diagnosed with a psychotic illness and the participants still left in the model (CSCU and DD). The more conservative LOO model will be presented.

Table 37
Table displaying discriminant function analyses predicting psychopathology per se as a function of schizotypal personality

Mental illness		Classified		
		No	Yes	Total
True value	No	837 (97.21)	24 (2.79)	861
	Yes	110 (82.71)	23 (17.29)	133
Error rate (%)		2.787	82.707	13.481
Observed %		95.27	4.73	
Predicted %		86.62	13.38	

Table 38
Table displaying discriminant function analyses predicting psychotic disorder as a function of aversive cannabis experiences

Psychotic mental illness		Classified		
		No	Yes	Total
True value	No	17 (70.83)	7 (29.17)	24
	Yes	6 (26.09)	17 (73.91)	23
Error rate (%)		29.167	26.087	27.660
Observed %		48.94	51.06	
Predicted %		51.06	48.94	

Table 38 indicates that the proportion (relative percentage) of correctly assigned data is lower than the previous approach of considering all predictor variables in one model. However, the number of participants correctly assigned to the PD group has increased from 16.67% of the sample (8), to 35.42% of the sample (17). Suggesting that by administering the SPQ-b to identify those ill and those not ill, before using the aversive subscale to identify those psychotic or not is a more accurate means of assessing group membership.

4.4 Discussion

4.4.1 Main findings

This chapter utilised data derived from the investigation described in Chapter 3 to elucidate information about the CEQ. The aversive scale of the CEQ was utilised to assess cannabis experiences that had occurred within a 24 hour period (CEQ-b). The aversive cannabis experiences were assessed as an outcome variable of events and states that had occurred in the previous 10-16 hours (Section 4.3.1, Table 32). A schizotypal state, (psychotomimetic phenomena) was a significant positive covariate of the CEQ-b. An assessment of concurrent stress was also a significant positive covariate as was the interaction term from the measure of stress and cannabis consumption. Aversive cannabis experiences (CEQ-b) significantly and positively co-varied with the items most related to psychosis proneness. This provides evidence of concurrent and convergent validity of these aversive cannabis experiences as assessments of psychosis proneness.

The CEQ-b was also found to be a significant positive predictor of future (>8 hours <23 hours) schizotypal state. The aversive cannabis experiences were found to hold temporal priority over momentary increases in psychotomimetic experience, indicating that the CEQ-b has predictive validity. Moreover, both the within and between participant effects of the CEQ-b were found to be significant positive predictors of future schizotypal state. This indicates that the CEQ-b could plausibly be assessing both; pharmacological vulnerability (see Section 2.4.4) as seen in the significant between participant differences; and environmental risk factors as demonstrated by significant within participant effects.

The aversive scale (CEQ full version) was assessed as a predictor of a schizotypal state and was not found to be a significant covariate. However, the cognitive-perceptual subscale of the SPQ-b was. This indicates that the CEQ may not be appropriate for the assessment of proneness to momentary increases in psychotomimetic phenomena. However, given that these experiences commonly occur and it is the persistence of experience which appears most clinically relevant, this finding may not indicate an absence of predictive validity (van Os et al., 2009). Nonetheless, the aversive scale was a significant predictor of self-

reported states of stress. This indicates that the aetiology of aversive cannabis induced experience may be common or related to stress liability/evaluation.

This chapter also utilised data from Chapter 2. The aversive scale of the CEQ displayed good internal reliability (all α > .9) in the cannabis users; from a community sample (CSCU); with self-reported depression (DD); and with self-reported psychotic illness (PD). A discriminant function analysis was utilised to assess the various measures ability to predict group membership (CSCU, DD or PD) from the participant's data. The CEQ aversive and intoxicated scales and the SPQ-b subscales, correctly predicted 88.67% of group membership. However, the most effective means identified of discriminating those with psychotic illness involved a two-step process: first utilising the SPQ-b subscales to differentiate those who have received a diagnosis of a mental illness, and then subsequently using the aversive scale of the CEQ to identify those with psychotic illness.

4.4.2 Implications and comparison with other research

Experience Sampling and the Cannabis Experiences Questionnaire- brief version

The CEQ-b significantly and positively co-varied with a schizotypal state, concurrent perception of stress and an interaction term between concurrent stress and cannabis consumption. Propensity for schizotypal states have been shown to be increased in psychosis prone cannabis users (Mason et al., 2009). Stressful life events have been shown to predict increases in psychotic symptoms in patients (Docherty et al., 2009). Moreover, in Sections 3.3.3 and 3.3.4 there is data indicating that a cannabis stress interaction effect may be a contributing factor to psychotic like experience. Therefore, this indicates convergent validity for the CEQ-b as an assessment of psychosis proneness.

The CEQ-b was a significant predictor of schizotypal states that occurred the following ESM study day (>8 hours <23 hours). One of the pre-requisites for causality, temporal priority can be established here (Bradford-Hill, 1965). However, it may be possible that schizotypal states are priming for aversive cannabis

experiences. Nonetheless, this finding indicates the predictive validity of the CEQ-b as an assessment of proneness to psychotic like experience.

This investigation also demonstrated that both within and between participant effects of the CEQ-b were significant predictors of schizotypal states the following day. The between participant significant effect of the CEQ-b provides some evidence in support of the test-retest reliability of the CEQ. The significant relationship of, between participant variance and schizotypal state indicates that despite within participant variance the measure still accounts for a significant proportion of the variance in schizotypal state.

Prior to this investigation it was unclear as to whether aversive cannabis experiences represent stable 'schizotaxic' vulnerability or aversive environmental factors, or both. The significant effect of the within participant differences indicates that there are plausibly environmental factors which influence aversive cannabis induced experiences relationship with future schizotypal states. The relationship documented between the CEQ-b and stress, suggests that this could be one environmental factor which may prime for aversive cannabis induced experience and schizotypal state. In an ESM investigation another factor (emotional reactivity) has been shown to interact with stress to correlate with positive psychotic symptoms in patients with psychotic illness and their relatives (Lataster et al., 2010). However, Lataster et al. (2010) also found that emotional-reactivity to stress tended to cluster in families which could suggest genetic factors.

The between participant significant effect of the aversive scale indicates that a stable construct may influence the relationship between the predictor and future psychotic-like experience. An increased sensitivity to the psychotomimetic effects of cannabis has been documented to have a familial link with psychotic illness (GROUP, 2011) and aversive cannabis experiences occur most frequently in those psychosis prone (Barkus, et al., 2006; Stirling et al., 2008). Henceforth, it is likely that a proportion of the between participant variance is as a consequence of a genetic component. Nonetheless, there are feasibly relatively stable environmental factors which may account for some of the effect (e.g. urbanicity, see Krabbendam & van Os, 2005). However, the significant within and between

participant effects of the CEQ-b appears to indicate that the measure reflects both environmental and genetic processes.

Experience sampling and the aversive scale of the cannabis experiences questionnaire (full version)

The aversive scale (administered prior to the ESM phase) was not found to be a significant predictor of schizotypal state. However, the cognitive-perceptual subscale of the SPQ-b was. This provides evidence of the predictive validity of the cognitive-perceptual subscale, but not the aversive scale. Section 2.3.4 suggests that of the three SPQ-b subscales the cognitive-perceptual one is most adept at identifying self-reported psychotic illness, these results support that notion. Moreover, other research has demonstrated that highly schizotypal cannabis users have displayed elevated psychotic like experience (Mason et al., 2009). The non-significant relationship between the aversive scale and schizotypal state indicates that the measure cannot significantly predict the propensity to momentary psychotic-like experience. However, this does not discount the scales proficiency in feasibly; assessing propensity to more enduring clinically relevant psychotic symptoms; or assessing other related momentary constructs.

The CEQ aversive scale was however, a significant predictor of a stressed state. This implicates that the expression of aversive cannabis induced phenomena may share a common aetiology with reactivity to stressors, and/or a stressful environment. Collip et al., (2013) demonstrated that individuals with persistent psychotic experiences had higher levels of reactivity to stress in comparison to individuals with transient psychotic experiences. One review concluded that "aberrant emotional reactivity to daily stress may constitute part of the liability to psychosis" (Myin-Germeys & van Os, 2007, p.420). Thus, the relationship between the aversive scale and a stressed state could plausibly be a better indicator of the scales ability at predicting enduring illness than the (lack of) relationship with a schizotypal state. Nonetheless, the relationship between susceptibility to a stressed state and the aversive scale provides evidence of the convergent validity (and in some regards predictive validity) of the measure at assessing psychotic vulnerability.

Discriminating between cannabis users

The aversive scale of the CEQ displays good internal reliability in the three groups of cannabis users; a community sample (CSCU); those with self-reported depression (DD) and those with a self-reported psychotic disorder. This suggests that the scale is appropriate for use in both clinical and non-clinical populations. The results of the discriminant function analysis indicate that perhaps the optimum way to utilise the SPQ-b and the aversive scale is in a two-step process. First utilising the SPQ-b to identify psychopathology, then secondly utilising the aversive scale to identify those with a psychotic illness. As it is hoped that the measures under assessment may be utilised as a self-report predictor of psychotic vulnerability, it is necessary to adopt the most conservative approach. Thus, only the results from the Leave One Out (LOO) method will be discussed. Even with the optimum means of discriminating between participants described, only around a third of participants were correctly identified as having a self-reported psychotic diagnosis. This finding and the associated R^2 values of the regression models (Sections 2.3.7-9) indicate that the variables under assessment only account for a small amount of variance in diagnosis. Thus, indicating that other factors may account for a large proportion of variance in the data.

Schizophrenia has been associated with environmental risk factors such as: obstetric conditions (Byrne, et al., 2007), prenatal illness (Brown, Cohen, Greenwald, & Susser, 2000), childhood trauma (Heins et al., 2011), acquired brain injury (see Clarke et al., 2012), and urbanicity (Krabbendam & van Os, 2005) amongst others. Feasibly, hundreds of genetic SNP may each confer a small additive risk (Purcell et al., 2009) in what has been described as a "hyper-complex" model (Sullivan, 2005, p212). If the various psycho-social and genetic risk factors had been considered in the current investigation they would have in all likelihood accounted for some of the variance in the data. The measuring and assessment of such a quantity of variables is implausible for most investigations, and the current investigation is not an exception. Despite the myriad of factors that contribute to a risk of a diagnosis of a psychotic disorder, the psychotomimetic phenomenology documented in measures of schizotypy are thought to represent an expression of an individual's genetic risk to the development of psychosis, the "schizophrenic phenotype" (Rado, 1960 p.87). The current investigation has

served to demonstrate that the psychotomimetic phenomenology assessed by the aversive scale may also reflect an expression of one or several genetic and psycho-social determinates of psychotic liability.

A differential sensitivity to the psychotomimetic effects of cannabis expressed as psychotic like experience has been demonstrated in individuals diagnosed with psychotic illness (D'Souza et al., 2005), their first degree relatives (GROUP, 2011) and individuals prone to psychosis (Barkus, et al., 2006; Barkus & Lewis, 2008; Henquet et al., 2005; Mason et al, 2009; Stirling et al., 2008). The association between cannabis and schizophrenia may feasibly occur as a result of an interaction between genetic (Caspi et al., 2005) and/or psychosocial processes (Houston et al., 2008). Moreover, cannabis is thought to be an independent developmental antecedent to schizophrenia (Arseneault et al., 2007). Thus, it would stand to reason that psychosis prone individuals may be identifiable by their response to cannabis. The current investigation has added further to this area of research by demonstrating that people with self-reported psychotic illness can be identified by their experiences with cannabis. This indicates that cannabis-induced experience may be one means by which psychotic vulnerability can be assessed.

A differential sensitivity to the psychotomimetic effects of cannabis may represent one of several endophenotypes which may independently contribute to different pathways to psychotic illness (e.g. see Myin-Germeys & van Os, 2007). This could plausibly indicate that the aversive scale might be incapable of identifying disorder that originates from vulnerability to other pathways. Those diagnosed with cannabis induced psychotic disorder have displayed significantly more aversive cannabis induced experiences (Stirling, 2011). Cannabis users who have been diagnosed with schizophrenia appear to be substantively different to their non-cannabis using counterparts (Meijer et al., 2012). Moreover, around half of those diagnosed with a cannabis-induced psychotic disorder progress to develop a schizophrenia-spectrum disorder (Arendt et al., 2005). Thus, as opposed to assessing psychotic vulnerability per se, the aversive scale could plausibly be assessing the 'psychotic vulnerability' of the cannabinoid system. Identifying such sensitivity can have wide reaching implications by enabling the assessment of individual risk to cannabis. Moreover, given the relationship between the

endocannabinoid system and stress (see Section 1.7.4 pp. 91-95 & Sections 3.3.3-4 pp. 217-29) aversive cannabis induced experiences could be reflective of a psychotic sensitivity to psychological stressors. If this were the case the aversive scale may be useful in assessing allocation of stress reduction treatment in psychotic patients.

4.4.3 Limitations

The limitations of this investigation have already been discussed in depth in Sections 2.4.3 (pp. 155-57) and 3.4.3 (pp. 247-257) and will not be repeated here. However, there is a limitation specific to comparing the CEQ-b to the aversive scale of the CEQ. The items of the CEQ-b and the aversive scale are the same, except for an altered rubric. However, the time frame in which the items refer to is very different. The CEQ-b refers to events that have taken place over the last 24 hours. However, the aversive scale of the CEQ refers to the participant's 'lifetime' experience with cannabis. Although the CEQ-b can allow for inferences to be made about the aversive scales stability and validity, caution should be applied. At present there is not enough data to suggest what, if any, difference exists between these two measures in their assessment of psychosis vulnerability. Nonetheless, it would be erroneous to assume that they were entirely equivocal.

4.4.4 Conclusions

This chapter has considered the data of two separate investigations. These data have provided information regarding the validity and reliability of the CEQ aversive scale as an assessment of psychotic vulnerability. This investigation has demonstrated both convergent and predictive validity of the CEQ-b, which plausibly infers validity of the aversive scale of the full CEQ. The cannabis induced experiences assessed by the CEQ-b appear to be influenced by both stable (between participants) and transient (within participant) effects. This is a similar notion that has been discussed in relation to drug induced experiences since the 1960s called the "set-setting theory" (Leary, 1966, p.84). The CEQ-b is reflecting both the innate vulnerability ('mind-set') and environmental stressors (setting) which constitute a risk for psychotic-like experience. This may indicate that the

aversive scale of the CEQ (full version) is assessing genetic and environmental risk factors.

The aversive scale of the CEQ (full version) was a significant predictor of a stressed state in the ESM investigation. This indicates that the aversive scale may share a common or closely related construct with liability to stress reactivity. It has been proposed that altered emotional reactivity to stress may constitute an endophenotype for psychosis (Myin-Germeys & Van Os, 2007). Thus, perhaps aversive cannabis induced phenomena may be experienced more regularly in individuals with this particular propensity. This demonstrates convergent and predictive validity of the aversive scale as a predictor of psychotic vulnerability.

This investigation has demonstrated that, by quantifying cannabis induced experience it is possible to discriminate between participants who have or have not been diagnosed with a psychotic illness. This indicates that cannabis-induced experiences may be an appropriate means to assess risk of psychotic vulnerability. These experiences did however only account for a small proportion of variance in the data.

In assessment of psychotic liability; interviewing, psychiatric assessment, and genetic analyses are costly, often impractical and can be imprecise. Thus, one of the most common means to assess vulnerability is via self-report questionnaire such as the SPQ-b. However, assessments of schizotypy may highlight a gamut of (attenuated) symptomatology even if they originate from non-psychotic illness (see Section 2.4.2 pp. 147-54). This could feasibly indicate that conventional measures of psychosis proneness are not appropriate with cannabis using populations who have been diagnosed with-, or an increased risk of- non-psychotic illness. However, assessment of cannabis induced phenomena may circumvent this problem without increasing demands on resources. Cannabis consumption may allow for the assessment of vulnerability to environmental (psychotic) stressors, in a similar manner to the use of a tilt-table test in the diagnosis of syncope.

The aversive scale of the CEQ has previously provided evidence of its concurrent and convergent validity with assessments of psychotic vulnerability (Stirling et al.,

2008). Moreover, the CEQ has previously displayed good test-retest reliability (Stirling, unpublished data). The aversive scale has now provided further evidence of its convergent validity (Sections 4.3.1 pp. 263-67 and 4.3.2 pp. 267-69), discriminant validity (Section 4.3.4 pp.270-73), and predictive validity (Section 4.3.2), as an assessment of psychotic vulnerability. Moreover, the aversive scale has demonstrated internal reliability in both clinical respondents and a community sample (section 4.3.3 pp. 269-70) and there is further evidence suggesting test-retest reliability (section 4.3.1).

5. Summary of the main findings in relation to aims and implications

This chapter serves to highlight the means by which each of the research chapters (Chapters 2, 3 & 4) individual aims have been fulfilled. This chapter also discusses how each respective chapter has contributed to accomplishing the overall aim of this body of research. It will also highlight to the reader some of the main implications of each of the individual chapters and the thesis as a whole.

5.1 Chapter 2

Four groups of participants were assessed on measures of schizotypy (SPQ-b) and cannabis induced phenomena (CEQ), where applicable. These groups of participants consisted of a community sample who were cannabis naïve (CSCN, n = 306); a community sample who were cannabis users (CSCU, n = 861); cannabis users with self-reported depression (DD, n = 85); cannabis users with a self-reported psychotic disorder (PD, n = 48).

In pairwise comparison the PD group scored significantly higher than the DD group on only one of the three SPQ-b subscales (cognitive-perceptual). The PD group had significantly more aversive cannabis experiences than both the DD group and the CSCU group. However, the DD group had significantly more appetitive cannabis experiences than both the PD group and CSCU group. The various regression models and the pairwise comparison contained within this chapter indicate that the cognitive-perceptual subscale of the SPQ-b and the aversive scale of the CEQ display evidence of convergent validity and specificity to assessment of psychotic vulnerability.

5.1.1 Aims of Chapter 2

1. To assess variance in schizotypal trait related to cannabis use and reported mental illness

2. To assess the presence of a differential sensitivity to the psychotomimetic effects of cannabis in those with psychotic illness
3. To assess the utility of assessments of cannabis induced experience and schizotypal trait as predictors of psychotic illness in cannabis using populations

The first aim of the chapter was acheived in Section 2.3.4 (pp.127-31), through pairwise comparison of the aforementioned groups of participants on assessments of schizotypy. The second aim of this chapter was fulfilled in Section 2.3.5 (pp. 132-33) via pairwise comparison of the CSCU group, DD group, and PD group on the CEQ. A differential sensitivity of cannabis was observed, which feeds into the second aim of this thesis. The third aim was partially acheived in Section 2.3.5 (pp. 131-33) via assessment of group differences in the CEQ. The analyses contained within Sections 2.3.6-8 (pp.134-45) also provide evidence towards aim 3. In these sections cannabis induced experiences and schizotypal trait were assessed within various regression models for their ability to significantly predict psychotic disorder.

5.1.2 Implications of Chapter 2

The SPQ-b subscales may not all equally contribute to an increased predisposition to psychosis in cannabis using populations and thus, future investigations should apply caution when assessing participant's total score on the SPQ-b. Moreover, the interpersonal and disorganised SPQ-b subscales may not be appropriate for the accurate assessment of psychosis proneness in cannabis using populations when other mental illness is present. Henceforth future investigations should consider other means of assessing psychotic vulnerability when conducting research with this population, such as by assessing differential sensitivity to cannabis. However, the cognitive-perceptual subscale of the SPQ-b and the aversive scale of the CEQ appear promising at discriminating between cannabis users who have increased psychotic liability and those with liability to other mental illness. These scales may prove useful in future investigations wishing to assess psychosis proneness in cannabis using populations.

This chapter has substantiated the notion of a differential sensitivity to the psychotomimetic effects of cannabis on the basis of psychotic vulnerability. Participants with self-reported psychotic disorder had significantly more aversive experiences than a community sample, and cannabis users with self-reported depression. Interestingly, a differential sensitivity in the subjective effects of cannabis was also elucidated in those with reported depression. Participants who reported experience of this disorder also had significantly more pleasurable effects of cannabis. A dysfunctional endocannabinoid system may play a role in the presentation of depression. This is evinced by the results of previous investigations (see Section 2.4.2 pp. 147 -54) and the results of this chapter, which revealed cannabis users with self-reported depression experiencing a differential sensitivity to appetitive cannabis induced phenomena. This may suggest an antidepressant effect of cannabis. However, the current investigation failed to establish if the appetitive cannabis experiences occurred whilst experiencing the symptoms of their mood disorder. Further investigation is necessary to establish if participants who are currently presenting with depressive symptomatology also frequently experience appetitive cannabis induced phenomena. This notion may be tested through an ESM study design with recreational/self-medicating cannabis users suffering with depression in order to assess the momentary relationship (temporal priority) between cannabis consumption, depressive symptomatology, and appetitive cannabis experience.

5.2 Chapter 3

Chapter 3 considered the data from 36 healthy regular cannabis users applying an ESM study design. Over a two week period the participants completed multiple assessments of a stressed state, a calm state and a schizotypal state. Participants also completed items pertaining to their previous events and drug consumption.

This investigation demonstrated methodological reactivity as displayed by frequency of data entry significantly and positively co-varying with schizotypal state. In various models a stressed state was also found to be a significant positive covariate of a schizotypal state, conversely, a calm state was a significant negative covariate of interpersonal schizotypal states. Cannabis consumption and quantity of cannabis consumed significantly increased scores on the calm scale. This finding could be taken as evidence in support of the drug conferring an anxiolytic effect. Cannabis consumption and quantity of cannabis consumed significantly predicted schizotypal states in the domains of interpersonal distortion and disorganisation. However, elevations in the disorganised domain of schizotypal state significantly predicted cannabis consumption. This indicates that elevations within this domain may be as a consequence of synergistic maintenance. However, cannabis appears to exert an independent effect on interpersonal distortions. Stress and cannabis consumption also significantly interacted to predict a schizotypal state.

5.2.1 Aims of Chapter 3

1. To assess whether schizotypy has state like components that are altered by cannabis intoxication
2. To assess the evidence for temporal priority in the relationship between cannabis and psychotic experience in a naturalistic setting.
3. To assess the effect of a stressed and calm state on psychotic-like states utilising a cannabis challenge to facilitate a model of psychosis.
4. To assess factors which may influence the consumption of cannabis
5. To assess the plausibility of an interaction between cannabis and psychological stressors on psychotic (like) experience

The first aim of this chapter is in part substantiated by the consideration of scatterplots of the participant's scores on the SSQ (see Section 3.3.3 pp. 217-26 & Figure 9). Schizotypal states displayed both within and between participant variance. The first aim of this investigation is fulfilled in analyses contained within Section 3.3.3 in which cannabis consumption was shown to significantly predict schizotypal states.

Analyses contained within Section 3.3.3 also served to accomplish aim 2, along with analyses contained within Section 3.3.6 (pp. 234-238). These analyses assessed whether cannabis consumption significantly predicted psychotic-like states and in-turn whether psychotic-like states significantly predicted cannabis consumption. Given the repeated measures study design these analyses were capable of establishing temporal priority.

Analyses contained within Section 3.3.3 assisted to acheive the third aim of this investigation. The analyses contained in Section 3.3.3 assessed stressed and calm states as predictors of psychotic-like states. The data indicated that stressed states significantly increased schizotypal states, and calm states decreased interpersonal schizotypal states.

Aim four was addressed by assessing variables which increase the O.R. of cannabis consumption (Section 3.3.6). These analyses assessed psychotic-like states and stressed states as predictors of cannabis consumption. The fourth aim was also attained by analyses contained within Section 3.3.5 (pp. 230-34) which investigated whether cannabis may serve to confer a beneficial effect on the participant's perception of stressed or calm states. These analyses could be said to be assessing aspects of the self-medication hypothesis.

Aim five of the investigation was addressed in Section 3.3.3 in which a cannabis stress interaction variable was assessed as a predictor of a psychotic-like state. The fifth aim of this investigation was reached by the analysis contained in Section 3.3.4. (pp. 226-29) In this section participants that displayed the least and most

stressed states throughout the investigation were assessed independently for an effect of cannabis consumption on psychotic-like states.

The first, second, fourth and fifth aims of this investigation contribute to the thesis' first overall aim of adding to discussions of causality in the relationship between cannabis and psychosis. The first aim of this body of research is fulfilled through; the establishment of the temporal sequence of cannabis and psychotic-like states; establishing the presenece of a beneficial (possibly self-medicative) anxiolytic effect of cannabis; and providing supporting evidence of a plausible mechanism.

5.2.2 Implications of Chapter 3

This investigation has demonstrated some evidence of methodological reactivity, whereby the act of measurement in itself serves to alter the variable under assessment. This indicates that whilst undertaking future investigation with this population attention should be paid to both monitoring and attempting to diminish methodological reactivity. Nonetheless, the majority of the participants that initiated the investigation completed it and the majority of the equipment was returned. Thus, indicating that ESM research is a viable methodology with this population.

Stressed states increase psychotomimetic experience and calm states independently decrease psychotomimetic experience. This may plausibly indicate stress reduction exercises as a useful approach in controlling psychotic symptoms. However, further investigation is required to understand whether the relationship between stress and psychotic experience displayed in this healthy sample has a similar effect in a clinical population.

Cannabis consumption elevates schizotypal states which implicates a causal relationship between cannabis and psychotic illness. However, this appears restricted to 'symptoms' from within the interpersonal domain. There is still a need to assess whether such elevations in such schizotypal states translate to an increased risk of decompensating into psychotic disorder. Disorganised schizotypal states were both predicted by cannabis consumption and predicted

cannabis consumption. This may implicate both a self-medication type action, and a cannabis-psychosis causal action; a synergistic self-maintaining model. Intriguingly in Chapter 2 the community sample cannabis users and non-users were only differentiated by schizotypal traits within the disorganised domain. These findings, when combined, may indicate that psychotic-like states from within this domain are synergistically maintained (as evinced in the ESM investigation). However, the exacerbation of schizotypal traits within the community sample of cannabis users could indicate; permanent alteration as a consequence of cannabis; or attempts to self-medicate a pre-existing vulnerability / pathology. Nonetheless, cannabis appears highly related to both disorganised schizotypal state and trait. Further, investigations could seek to elucidate this relationship by conducting multi-staged research consisting of both ESM assessment of schizotypal state and longitudinal follow-up phases (similar to that described in Collip et al., 2013). To assess the persistence of the transient psychotomimetic effects of cannabis.

This investigation has also provided some support for the 'self-medication hypothesis' cannabis appears to induce calm like states in the user. This could plausibly indicate that the cannabis users may use cannabis in an attempt to mitigate the effects of adverse psychological states. Nonetheless, cannabis appears to confer no benefit on psychotic-like symptoms, or stressed states. However, calm states attenuate interpersonal schizotypal states. This indicates that a proportion of the association between cannabis and schizophrenia could plausibly be as a consequence of self-medication. Future investigations attempting to establish causal inference should consider taking a measure of the anxiolytic effects of the drug.

This investigation has elucidated an interaction effect between cannabis and stressed states. This could be the mechanism by which cannabis use could contribute to psychotic breakdown and excacerbate symptoms. However, further research is required to this effect. Nonetheless, this indicates that individuals at highest risk of psychotic illness should be advised against using cannabis as a stress reduction aid.

5.3 Chapter 4

The aversive scale of the CEQ has demonstrated evidence of its convergent validity (Sections 4.3.1 pp. 263-67 and 4.3.2 pp. 267-69), discriminant validity (Section 4.3.4 pp. 270-73), and predictive validity (Section 4.3.2) for assessment of psychotic vulnerability. Moreover, the aversive scale has established internal reliability in both clinical respondents and a community sample (Section 4.3.3 pp.269-70) and there is further evidence suggesting test-retest reliability (Section 4.3.1).

5.3.1 Aims of Chapter 4

1. To assess evidence for the reliability of the aversive scale of the CEQ as an assessment of psychotic vulnerability.
2. To assess evidence for the convergent, concurrent and predictive validity of the aversive scale of the CEQ.

5.3.2 Implications of Chapter 4

The data presented in this section suggests that the aversive scale of the CEQ is adept at assessing psychotic vulnerability. The psychotic vulnerability displayed however, may only be representative of one of several functional pathways to psychosis. This measure could feasibly be assessing the cannabinoid pathway to psychotic disorder. Nonetheless, the measure appears to reflect both genetic and environmental factors. Given that cannabis use is one of the few controllable risk factors there is a need to undertake a prospective cohort study assessing cannabis experiences as a predictor of psychotic illness. Such an endeavour may be utilised to reduce the incidence of psychosis in a population known to be at an increased risk.

Cannabis is the most frequently consumed illicit drug. Thus, the assessment of cannabis induced phenomenology could represent an opportunity for the rapid and wide spread assessment of psychotic vulnerability. This thesis highlights the need

for a prospective cohort based study examining the predictive ability of the aversive scale at assessing vulnerability to psychosis.

5.4 Aims and implications of this thesis

The thesis as a whole possessed two primary aims:

1. To contribute to discussions relating to 'causal inference' in the relationship between cannabis and psychosis
2. To assess the reliability and validity of a measure of psychotic vulnerability based on differential sensitivity to cannabis

The first aim of this thesis is addressed in Chapter 3. Chapter 3 allowed for the assessment of temporality of numerous variables of interest. Within a continuum model of psychosis, analyses contained in Sections 3.3.3, 3.3.5, 3.3.6 assessed the validity of the; self-medication hypothesis; a causal model of association; and a synergistic model of association (see Section 1.6 pp. 61-79). Evidence supported the existence of all three of these models of association. In addition to temporality, the data considered within this chapter also allowed for the assessment of another aspect of causality, plausibility. The presence of a cannabis and stress interaction effect were assessed, with evidence found in support of the notion that such an effect may play a role in a plausible mechanism of decompensating. Thus, this thesis has served to contribute to discussions pertaining to; whether cannabis use causes psychotic illness; and the mechanism by which cannabis use may (interact with other factors to) cause psychotic illness. There is a paucity of research within this area which can establish temporality (Kimhy et al 2009), or assess the plausibility of a cannabis stress interaction effect (see Henquet et al., 2008). Thus, this investigation represents a significant contribution to knowledge.

The second chapter helped to fulfil the second primary aim of this thesis. This chapter served to substantiate the notion of a differential sensitivity to the psychotomimetic effects of cannabis in those vulnerable to psychosis. Such a differential sensitivity to cannabis has only been demonstrated in a small number of investigations previously (see Section 2.1 pp. 102-05), and to the authors knowledge never previously utilising both a community sample control and clinical control (reported depression). Thus, such a finding contributes to this area of research. The data contained within the fourth chapter provided evidence of the validity and reliability of the aversive scale.

The aversive scale could plausibly represent psychotic sensitivity of the endocannabinoid system and / or psychotic sensitivity to psychological stressors. The ability to assess sensitivity of the endocannabinoid system is a worthwhile endeavour, as cannabis use is one of the few purported independent developmental antecedents of psychotic disorder which is preventable. Furthermore, if the aversive scale *is* assessing psychotic sensitivity to stress, the measure could be capable of identifying individuals who are likely to have the biggest diminution of psychotic symptomatology in response to stress reduction techniques. The investigations within this thesis and that of previous investigations (see Section 2.1) indicate that the aversive scale is appropriate for assessment of; psychotic vulnerability; and adverse (psychotic) reaction to cannabis. Therefore, the aversive scale may be useful in the future; in drug education programmes and risk assessment in recreational cannabis users; in screening for medicinal cannabis prescription; in screening for research trials with cannabinoids or other known psychotomimetics; and in the allocation of psychological intervention for cannabis dependence, and (possibly) stress-reduction in those with disorder or at ultra-high risk. Thus, the development of the aversive scale of the CEQ (and consequently this thesis) may have implications for research, education and clinical care. The development of a scale for assessment of psychotic vulnerability based on differential sensitivity to the psychotmimetic effects of cannabis is a significant contribution to this area of research.

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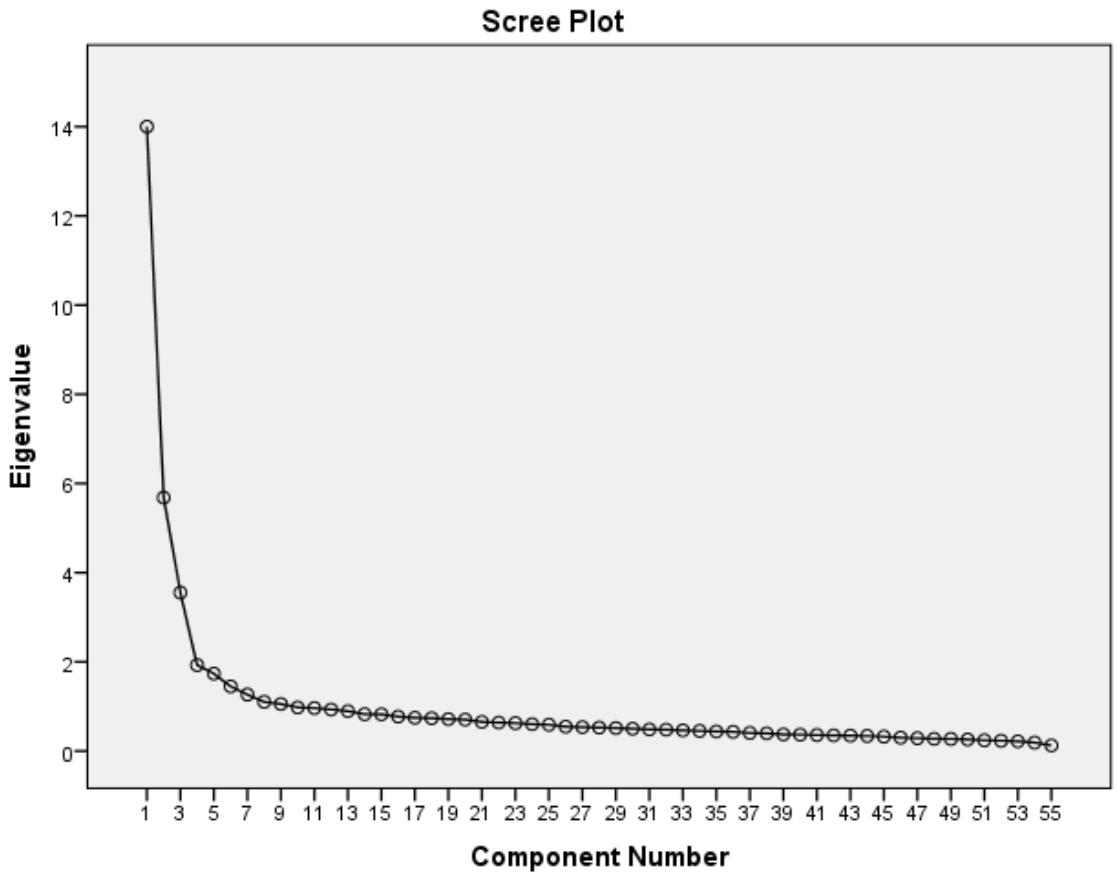
7. APPENDICES

Appendix 1 Principal component analysis of the cannabis experiences questionnaire

Considering the data from a community sample of 892 cannabis users a principal component analysis (PCA) with oblimin rotation was performed on the cannabis experiences questionnaire. Any factor scoring an eigenvalue higher than two was retained in the model. As demonstrated by the associated scree plot a three factor solution emerged (Figure 13).

Figure 13

Scree plot of principal component analysis of the cannabis experiences questionnaire



Any factor with a unique loading of 0.4 was retained in the model the putative names assigned are displayed in the associated pattern matrix with the full list of the CEQ items (Table 39).

Table 39
Table the pattern matrix of a principal component analysis of the Cannabis Experiences Questionnaire

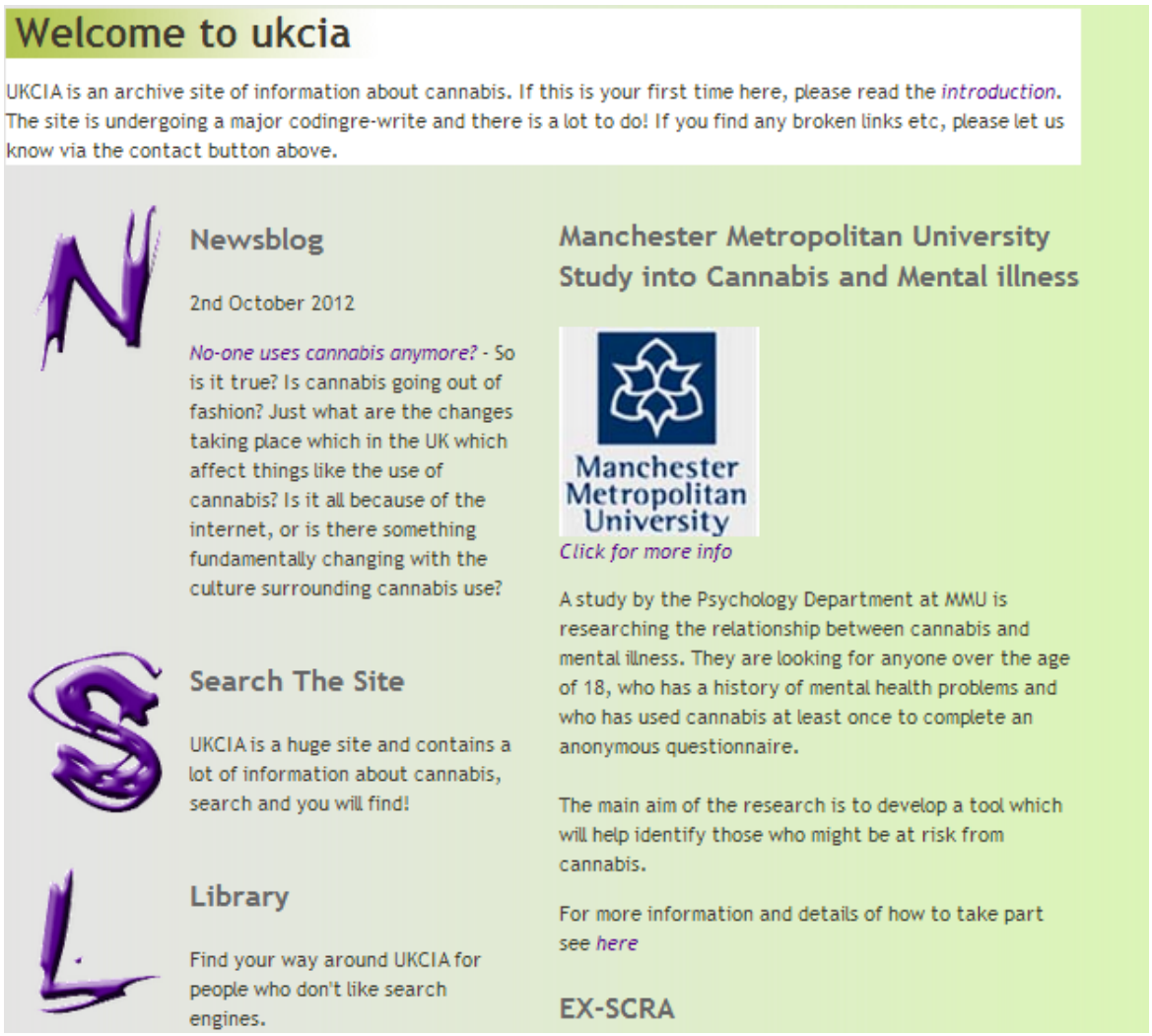
	Aversive	Appetitive	Intoxicated
Feeling happy	-.490	.529	.167
Being relaxed	-.590	.428	.366
Excited	.005	**.594**	-.034
Sleepy	-.110	-.007	**.573**
Energized	-.051	**.641**	-.248
Powerful	.240	**.513**	-.186
Laid back	-.599	.428	.383
Sentimental	.046	**.452**	.196
Felt all powerful, like you could do anything	.241	**.520**	-.142
Religious	.278	.292	-.121
Full of Plans	-.018	**.704**	.070
Ecstatic	.014	**.684**	-.087
Feel more creative	-.144	**.740**	.104
Able to understand the world better	-.056	**.650**	.184
Enhanced perceptual awareness	.042	**.548**	.143
Looking for excitement	.066	**.551**	-.019
Out of body experiences	**.469**	.262	-.125
Full of ideas	-.026	**.714**	.095
Obsessive (or fixed on something)	.332	.363	.216
Fearful	**.617**	-.074	.143
Angry	**.606**	.180	-.066
Paranoid	**.592**	-.107	.230
Uncomfortably sleepy	.255	-.050	.374
Anxious	**.694**	-.143	.185
Like there was something you had to do no matter what	.386	.319	.039
Depressed	**.616**	-.003	.194
Deluded	**.464**	.248	.056
Rapid flow of thoughts	.237	**.530**	.128

Table 38 continued

	Aversive	Appetitive	Intoxicated
Threatened by unknown force	**.690**	.017	.045
Lethargic	.038	.053	**.547**
Sad	**.582**	.037	.149
Disturbed in your thinking	**.587**	.003	.241
Nervy	**.601**	-.010	.239
Speech becomes slurred	.218	.117	.285
Slowing of time	.173	.130	.355
Auditory hallucinations	**.467**	.184	.044
Visual hallucinations	**.499**	.174	-.064
Things not feel right on your skin	**.564**	.052	.139
Losing a sense of reality	**.451**	.177	.228
Feeling like you no longer know yourself	**.689**	.005	.106
Fearful that you are going mad	**.743**	.007	.059
Reduced level of consciousness	.175	.066	.360
Increased appetite	-.110	.217	**.466**
Disinhibition AE	.312	.157	.335
Don't want to do anything AE	.069	-.076	**.780**
Feel Generally slowed down AE	.086	-.121	**.817**
Loss of motivation AE	.109	-.048	**.740**
Feel that your thinking has been slowed down AE	.187	-.117	**.738**
Cannot concentrate AE	.198	-.080	**.698**
Slowing of time AE	.199	-.035	**.557**
Paranoid without reason AE	**.633**	-.088	.285
Suspicious without reason AE	**.635**	-.031	.255
Felt depersonalised AE	**.566**	.028	.283
Cannot remember events AE	.046	.149	.255
Have reduced attention AE	.181	-.009	**.670**

AE = After Effect

Appendix 2 An example of study advertisement in a virtual environment



Appendix 3 Study advertisement (hard copy)

Help needed for a study by the Research Institute for Health and Social Change

We in the Psychology Department at MMU, England are researching the relationship between cannabis and mental illness. We are looking for anyone over the age of 18, who has a history of mental health problems and who has used cannabis at least once to complete an **anonymous** questionnaire.

The main aim of our research is to develop a tool which will help identify those who might be at risk to some of the adverse effects of cannabis. This tool could hopefully prevent, or delay some people becoming unwell.

If you would like to take part or for further information, then please go to: www.hpsc.mmu.ac.uk/street-drugs-research

At this time we are only interested in the recreational (or non-medically prescribed) use of natural (non-synthetic) cannabis products. If you have ONLY had experience of synthetic cannabis products (e.g. Spice), or medically prescribed natural cannabis products (e.g. Sativex) you would not be eligible to take part.

Appendix 4 Demographic information & mental health questionnaire

This questionnaire will ask for some basic information about yourself and your mental health. Any responses that you give will be treated in the strictest confidence. Please circle or fill in the boxes where appropriate.

1	Sex	Female	Male
2	Age		
3	I am currently psychologically well.	Yes	No
4a	I am currently receiving treatment for a nervous / psychological disorder.	Yes	No
4b	(If previous answer was YES) What nervous / psychological disorder(s) are you being treated for?		
5a	I have received treatment for a psychological disorder in the past	Yes	No
5b	(If previous answer was YES) What nervous or psychological disorder(s) have you received treatment for?		
6a	I am currently taking medication to treat a psychological disorder.	Yes	No
6b	(If previous answer was YES) What medication(s) are you currently taking?		

7a	I have been prescribed medication to treat a psychological in the past that I am not currently taking.	Yes		No		
7b	(If previous answer was YES) Please give the name(s) of the medication that you were prescribed.					
8	If you are/were taking medication, did/do you take your medication as often as the doctor or pharmacist told you to? (please circle one of the boxes or complete the 'other' option)	Rarely or never	From time to time	Sometimes Yes and sometimes No	More often than not	Always or almost always
		Other:_____				
9a	Are you currently receiving treatment for a nervous or psychological disorder that is not medication?	Yes		No		
9b	(If previous answer was YES) What (none medication) treatment are you currently receiving?					
10a	Have you ever received treatment for a nervous or psychological disorder that was not medication?	Yes		No		
10b	(If previous answer was YES) Please indicate what treatment you have received for a psychological disorder that was not medication.					

Cannabis use and mental health

This questionnaire takes an average of 15 minutes to complete and will typically take less than 40 minutes to complete. The questionnaire comprises of four sections the first looking at mental health, the second looking at a personality trait known as schizotypy, the third looking at recreational drug use and the fourth looking at cannabis use and people's experiences with cannabis.

0%
100%

Recreational Drug Use

In this section of the questionnaire you will be asked to list drugs that you have taken recreationally, other than cannabis.

•Have you ever taken any drug recreationally?
(Not including alcohol, nicotine and cannabis)

◉ Yes ○ No

Please select from the list any of the following drugs that you have taken and can you please indicate whether you consider yourself a current or past user.

Please select whether you are a current or past user

	Current	Past	Selection checked in error
Acid (AKA LSD)	○	○	○
Aerosols	○	○	○
Alcohol	○	○	○
Amphetamine (AKA Speed, whizz)	○	○	○
Amyl nitrite (AKA poppers)	○	○	○
Anabolic steroids	○	○	○
Benzodiazepine	○	○	○
2CB	○	○	○
Crystal Methamphetamine	○	○	○
Cocaine	○	○	○
Chat	○	○	○
2-CT-7	○	○	○
Dexamphetamine (AKA Dexies)	○	○	○
Diablo	○	○	○
Downers (AKA Tranquilisers)	○	○	○

Dihydrocodeine (opiate)	○	○	○
Ecstasy (AKA MDMA)	○	○	○
Fly agaric (AKA Magic mushrooms)	○	○	○
GBL	○	○	○
GHB	○	○	○
Heroin	○	○	○
Ivory wave	○	○	○
Isobutyl nitrite (AKA Poppers)	○	○	○
Ketamine	○	○	○
Khat	○	○	○
	Current	**Past**	**Selection checked in error**
Liberty Caps (AKA Magic mushrooms)	○	○	○
LSD	○	○	○
Magic Mushrooms	○	○	○
Mephedrone (AKA Meph, Drone, 4-MMC, Meow meow)	○	○	○
Methadone	○	○	○
Naphyrone (AKA NRG-1)	○	○	○
Opium	○	○	○
PMA	○	○	○
Pills (AKA ecstasy)	○	○	○
Piperazines	○	○	○
Salvia	○	○	○
Solvents	○	○	○
Tobacco	○	○	○
Other Depressant	○	○	○
Other hallucinogen	○	○	○
Other stimulant	○	○	○

<< Previous Next >> [Exit and clear survey]

Appendix 6 Screen shot: Participant Information Sheet

Psychosis and recreational drugs research group

Information for Participants

Do I have to take part?

There is no obligation on you to contribute to our research. If you get halfway through completing our questionnaires and wish to withdraw at that point you are free to do so and we will then simply discard your incomplete data.

What will happen to me if I agree to take part?

If you would like to help us with our research, you can either access and complete the necessary questionnaires by clicking on this link Take Part, or if you are based within the UK contact us and we will send you an information sheet, paper copies of our questionnaire, and a stamped addressed envelope in order to return the completed forms to us.

We would enter your information onto a secure computer database which could only be accessed by a member of our research group. Data entry is completely anonymous, cookies are not downloaded on to your computer and your ISP address is not logged in anyway. No personal identification data is stored.

What are the possible disadvantages and risks of taking part?

Taking part in this study will not change any care or services which you are currently receiving. In all honesty the associated risks are very low. However, it is possible that some people may find some of the questions asked distressing. To date more than 2000 people have completed the questionnaires none of which have indicated that they have experienced any distress or harm as a result of taking part in the study.

Useful Links

Many thanks to the following organisations for their support of this research. If you wish to receive information guidance and support about mental health problems and the issues surrounding them, then please click on one of the following links.

PsyWeb

PsyWeb.com is one of the world's largest sites dedicated to depression and mental health. Our goal is to bring people together around the issues of addictions by providing concise, up-to-date information and a meeting place for patients, their friends and families, and professionals who offer pathways to recovery.

Schizofriend

Schizofriend.me is a social network for anyone affected by schizophrenia. Share experiences, post art, make friends and feel better.

MyAddiction

MyAddiction.com is the world's fastest-growing addiction community. Our goal is to bring people together around the issues of addictions by providing concise, up-to-date information and a meeting place for addicts, their friends and families, and professionals who offer pathways to recovery.

www.makingspace.co.uk - Since 1982, Making Space has been working with people affected by mental health conditions, and with their carers, to help them shape their lives

What are the possible benefits of taking part?

You will be contributing to the greater understanding of the effects of cannabis use on people. The ongoing debate surrounding the illicit status of the social use of cannabis is complex and is beyond the remit of this study. However, the development of cannabis policy should be based on a proper understanding of the risks and benefits of its use. Identifying those at risk from cannabis, which may be possible through the experiences people have, is the ultimate aim of this study. Cannabis use will continue irrespective of the legal status of the drug and whether or not there will be changes to this legal status, we hope the knowledge we collect will help prevent what may be avoidable harm.

Will my taking part in this study be kept confidential?

All data recorded 'on-line' will be entirely anonymous. We do not need to know who you are. If you complete paper copies of our questionnaires, these too will be anonymous.

based on their own personal aspirations and circumstances.

www.rethink.org - the leading national mental health membership charity, works to help everyone affected by severe mental illness recover a better quality of life.

www.schizophrenia.com - Started in 1995, Schizophrenia.com is a leading non-profit web community dedicated to providing high quality information, support and education to the family members, caregivers and individuals whose lives have been impacted by schizophrenia.

For information about cannabis and help with addiction please see the following websites:

Appendix 7 Screen shot: Context of the investigation

Psychosis and recreational drugs research group

Past Research

The widespread use of cannabis amongst people has raised concerns amongst health practitioners about its possible role in the development of mental health problems. The role which cannabis plays in the onset of psychosis is of particular interest and still a source of debate. Previous studies have focused on the amount, frequency and time of day cannabis is used to determine whether these factors influence proneness to developing psychosis. An alternative approach is to focus on the experiences which people report in relation to cannabis use. Our research group has developed a questionnaire that seeks to record these experiences; we have called this the Cannabis Experiences Questionnaire (CEQ). The CEQ is now in its 8th version and has been completed by over 1800 people, both online and in hard copy. We have consistently found that volunteers who have a proneness to psychosis, are much more likely to report negative experiences such as hallucinations (seeing and hearing things which are not there) and other unusual thoughts and beliefs when they use cannabis. This indicates that people who experience more negative effects of cannabis may be at higher risk for later development of psychosis.

To further our understanding of the link between cannabis and psychosis we have decided to do this piece of research. We hope that by looking at how people with a history of mental health problems answer the CEQ we can work out which cannabis related experiences may increase someone's risk of developing a mental illness. Below are references to some of our past research published in the area of cannabis experiences with a link to where a brief summary can be read:

Barkus EJ, Stirling J, Hopkins RS, Lewis S. (2006). Cannabis-induced psychotic-like experiences are associated with high schizotypy. Psychopathology 39:175-178.

Barkus E, Lewis S. (2008) Schizotypy and psychosis-like experiences from recreational cannabis in a non-clinical sample. Psychological Medicine, 38: 1-10.

Stirling, J., Barkus, E.J., Nabosi, L., Irshad, S., Roemer, G., Schreudergoldheijt, B., & Lewis, S. (2008). Cannabis-Induced Psychotic-Like Experiences Are Predicted by High Schizotypy. Psychopathology 41: 371-8

Useful Links

Many thanks to the following organisations for their support of this research. If you wish to receive information guidance and support about mental health problems and the issues surrounding them, then please click on one of the following links.

PsyWeb
PsyWeb.com is one of the world's largest sites dedicated to depression and mental health. Our goal is to bring people together around the issues of addictions by providing concise, up-to-date information and a meeting place for patients, their friends and families, and professionals who offer pathways to recovery.

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www.makingspace.co.uk - Since 1982.

Appendix 8 Screen shot: Participant information about the study ethics

Ethics

Click a topic title below to find information on:

Ethical Approval; *who has approved us to do this research*

Our research group has general ethical approval from both Manchester University and Manchester Metropolitan University. This project has specific ethical approval from Manchester Metropolitan University faculty of Psychology and Social Care.

Participant protection; *what are we doing to ensure that your rights are protected throughout your taking part in this research*

You can stop taking part in the study at any time all you have to do is close the window that popped up when you clicked on the TAKE PART link. If you have any comments, concerns or criticisms please visit the Contact Us page and tell us about it.

Confidentiality; *how we ensure that there are no breaches of information*

We do not need you to give us your name, address or email if you don't want to. You will be given the option to leave contact information if you wish to take part in future research, however this is not necessary for you to take part. If you send us a question, query or comment via email we will respond and then delete your contact information.

Data protection; *how we ensure secure storage of your data*

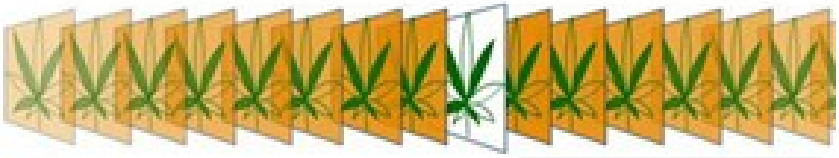
Your responses will be stored on a secure server that only named members of the research team will have access to. Once we have finished collecting responses, the information will be stored on a password protected computer in a locked room.

Funding; *how this project is funded*

At present this study is not officially funded, however this study would not have been possible without resources from Manchester Metropolitan University faculty of Psychology and Social Care and the Research Institute for Health and Social Change.

Appendix 9 Screen shot displaying researcher contact details

Psychosis and recreational drugs research group



Contacts

We welcome contact from people about this project, but please note this is not a broad discussion forum and we are not able to give specific psychological or medical advice.

Please send any questions, queries, thoughts and comments about this project to Ronan Morris, who is acting as 'lead researcher' and can be contacted via **email**
by phone: +44 (0)161-247-2415
or by post:
Ronan M. Morris
Department of Psychology
Faculty of Health, Psychology & Social Care
Manchester Metropolitan University
Elizabeth Gaskell Campus
Hathersage Road
M13 0JA
England

We will endeavour to respond as quickly as possible, however if there is a large volume of responses there may be some delay. The other members of the research team are Dr. John Stirling, Mr. John Cavill and Dr. Emma Barkus.

Useful Links

Many thanks to the following organisations for their support of this research. If you wish to receive information guidance and support about mental health problems and the issues surrounding them, then please click on one of the following links.

PsyWeb
PsyWeb.com is one of the worlds largest sites dedicated to depression and mental health. Our goal is to bring people together around the issues of addictions by providing concise, understable information and a meeting place for patients, their friends and families, and professionals who offer pathways to recovery.

Schizofriend
Schizofriend.me is a social network for anyone affected by schizophrenia. Share experiences, post art, make friends and

Appendix 10 Screen shot displaying consent form

Take Part

By clicking the 'Take Part' button below you have agreed that we, the investigators, have permission to use your data. The data does not enable anyone to identify you and will not be used for any purpose other than this investigation.

Please be aware that you have the right to withdraw from this investigation, simply close the window presenting the questions.

If you wish to be informed of the findings of this investigation, please revisit this website at a later date where a summary of the findings will be posted, it is anticipated this will be in mid 2013.

Alternatively you can contact the researcher and request to have a summary of the findings sent to your email address.

As an informed participant of this study, I understand that:

I am at least 18 years old.
My participation is voluntary and if at any point I am disturbed by any of the items presented in the questionnaire I do not have to continue.
I am aware of what my participation involves.
I have read and understood the above, and give consent for my data to be analysed.

At this time we are only interested in the recreational (or non-medically prescribed) use of natural (non-synthetic) cannabis products. If you have ONLY had experience of synthetic cannabis products (e.g. Spice), or medically prescribed natural cannabis products (e.g. Sativex) you would not be eligible to take part.

Click the Take Part button to accept the above and to move on to the survey page.

Take Part

Cannabis use and mental health

This questionnaire takes an average of 15 minutes to complete and will typically take less than 40 minutes to complete. The questionnaire comprises of four sections the first looking at mental health, the second looking at a personality trait known as schizotypy, the third looking at recreational drug use and the fourth looking at cannabis use and people's experiences with cannabis.

If for any reason you have started this questionnaire without clicking on a consent form can you please go to:
http://www.hpsc.mmu.ac.uk/street-drugs-research/index.php?key=55

If you want to go back or forth between your answers then please use the previous and next buttons at the bottom of the screen rather than the back and forward buttons in your browser.

Please try and **answer all the questions displayed,** if you cannot complete the questionnaire in one sitting you are welcome to come back and try and complete it at a later date.

Although there are 108 possible questions you will in all likelihood answer less, the amount will depend on your responses to previous questions.

Thank you for your time and effort.

There are 108 questions in this survey.

A note on privacy

This survey is anonymous.
The record kept of your survey responses does not contain any identifying information about you unless a specific question in the survey has asked for this. If you have responded to a survey that used an identifying token to allow you to access the survey, you can rest assured that the identifying token is not kept with your responses. It is managed in a separate database, and will only be updated to indicate that you have (or haven't) completed this survey. There is no way of matching identification tokens with survey responses in this survey.

Next >> [Exit and clear survey]

Appendix 12 Tests of normality on participant characteristics

Table 40

Showing tests of normality on participant characteristics

					Kolmogorov-Smirnov		
		n	Skewness	Kurtosis	D	DF	*p*- value
PD	Frequency of use	40	0.82	-0.63	0.230	40	<.001
	Weekly Expenditure	45	-0.37	-1.655	0.202	45	<.001
	Age of first use	48	2.718	13.016	0.169	48	<.001
	Age	48	0.756	-0.390	0.142	48	.017
	Number of lifetime uses	48	4.759	21.624	0.538	47	<.001
DD	Frequency of use	79	1.21	0.40	0.333	79	<.001
	Weekly Expenditure	85	-0.294	-1.494	0.229	85	<.001
	Age of first use	85	1.596	3.799	0.166	85	<.001
	Age	85	1.166	1.092	0.145	85	<.001
	Number of lifetime uses	77	9.220	85.0	0.428	77	<.001
CSCU	Frequency of use	845	0.072	-1.08	0.159	845	<.001
	Weekly Expenditure	685	0.606	-1.24	0.257	685	<.001
	Age	861	2.643	8.533	0.239	861	<.001

Appendix 13 Tests of homogeneity of variance in participant characteristics

Table 41

Showing Levene's tests of homogeneity of variance on participant characteristics

		DF	*F*	*P* - value
Frequency of use	2	961	1.147	.318
Weekly Expenditure	2	812	5.199	.006
Age of first use	1	31	2.727	.101
Age	2	991	36.581	<.001
Number of lifetime uses	1	122	1.206	.274

Appendix 14 Tests of normality on the SPQ-b

Table 42

Showing tests of homogeneity of variance on the SPQ-b

		Skewness	Kurtosis	Kolmogorov-Smirnov		
				D	DF	*p*- value
PD	Cognitive-perceptual	-0.279	-0.564	0.203	48	<.001
	Interpersonal	-0.335	-1.098	0.159	48	.004
	Disorganised	-0.12	-1	0.152	48	.007
	SPQ-b Total	-0.238	-0.885	0.142	48	.017
DD	Cognitive-perceptual	-0.33	-1.031	0.143	85	<.001
	Interpersonal	-0.33	-1.031	0.165	85	<.001
	Disorganised	0.041	-1.078	0.147	85	<.001
	SPQ-b Total	0.06	-0.709	0.07	85	.20
CSCU	Cognitive-perceptual	0.592	-0.416	0.149	861	<.001
	Interpersonal	0.583	-0.712	0.163	861	<.001
	Disorganised	0.578	-0.717	0.182	861	<.001
	SPQ-b Total	0.624	-0.244	0.102	861	<.001
CSCN	Cognitive-perceptual	0.627	-0.439	0.149	306	<.001
	Interpersonal	0.488	-0.439	0.135	306	<.001
	Disorganised	0.933	-0.022	0.206	306	<.001
	SPQ-b Total	0.676	-0.083	0.135	306	<.001

Appendix 15 Tests of homogeneity of variance on the SPQ-b

Table 43

Showing Levene's tests of homogeneity of variance on the SPQ-b

	DF		F	*p*- value
Cognitive-perceptual	3	1296	0.508	.68
Interpersonal	3	1296	0.685	.56
Disorganised	3	1296	0.860	.46
SPQ-b Total	3	1296	1.252	.29

Appendix 16 Tests of normality on the CEQ

Table 44

Showing tests of homogeneity of variance on the CEQ

		Skewness	Kurtosis	Kolmogorov-Smirnov		
				D	DF	*p*- value
PD	Aversive	0.896	-0.044	0.137	48	.024
	Appetitive	0.67	-0.626	0.194	48	<.001
	Intoxicated	0.422	-0.623	0.145	48	.013
DD	Aversive	1.568	2.813	0.154	85	<.001
	Appetitive	-0.185	-0.053	0.069	85	.20
	Intoxicated	0.584	0.012	0.099	85	.039
CSCU	Aversive	1.27	1.138	0.146	861	<.001
	Appetitive	0.214	0.203	0.056	861	<.001
	Intoxicated	0.203	-0.716	0.07	861	<.001

Appendix 17 Tests of homogeneity of variance on the CEQ

Table 45

Showing Levene's tests of homogeneity of variance on the CEQ

	DF		F	*p*- value
Aversive	2	991	7.030	.001
Appetitive	2	991	5.134	.006
Intoxicated	2	991	3.563	.029

Appendix 18 Tests of multicolinearity variance proportion tables SPQ-b

Table 46
Showing variance proportion table of the SPQ-b total and the aversive and intoxicated scales

Dimension	Eigenvalue	Condition Index	Variance proportions			
			Constant	SPQ-b	Aversive	Intoxicated
1	3.421	1.0	.01	.02	.02	.01
2	0.295	3.407	.13	.08	.68	.00
3	0.197	4.168	.10	.80	.01	.18
4	0.087	6.260	.75	.11	.29	.81

Appendix 19 Tests of multicolinearity variance inflation factors SPQ-b

Table 47
Showing variance inflation factors of the SPQ-b total and the aversive and intoxicated scales

	Tolerance	VIF
SPQ-b	.844	1.184
Aversive	.625	1.600
Intoxicated	.682	1.467

Appendix 20 Tests of multicolinearity variance proportion tables SPQ-b subscales

Table 48
Showing variance proportion table of the SPQ-b subscales and the aversive and intoxicated scales

Dimension	Eigenvalue	Condition Index	Variance proportions					
			Constant	Cog-Per	Inter	Dis	Aversive	Intoxicated
1	4.834	1.000	.01	.01	.01	.01	.01	.01
2	0.403	3.463	.00	.02	.15	.15	.27	.06
3	0.269	4.241	.27	.04	.00	.07	.38	.06
4	0.206	4.839	.00	.68	.50	.00	.07	.00
5	0.198	4.938	.01	.24	.33	.77	.00	.01
6	0.089	7.379	.71	.01	.01	.00	.28	.86

Appendix 21 Tests of multicolinearity variance inflation factors SPQ-b subscales

Table 49
Showing variance inflation factors of the SPQ-b total and the aversive and intoxicated scales

	Tolerance	VIF
Cognitive-perceptual	.617	1.620
Interpersonal	.681	1.468
Disorganised	.669	1.495
Aversive	.692	1.445
Intoxicated	.659	1.517

Help needed for a study into the link between cannabis and mental illness by the Research Institute for Health and Social Change

Manchester Metropolitan University

We in the Psychology Department at MMU, are researching the relationship between **cannabis** and mental illness. We are looking for people over the age of 18, who are current cannabis users to take part in our research. Our study will last for two weeks and you will be required to answer some questions several times a day, taking about 20 minutes of your time each day.

The main aim of our research is to develop a tool which will help identify those who might be at risk to some of the adverse effects of cannabis. This tool could hopefully prevent, or delay some people becoming unwell.

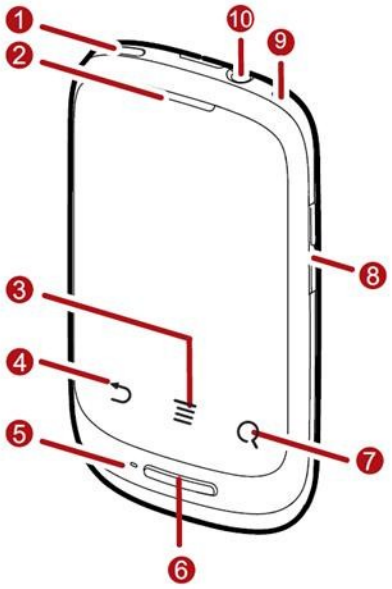
We are giving £20 Love to Shop gift vouchers as a 'thank you' to people who complete the full study.

If you would like to take part or for further information please go to:
www.hpsc.mmu.ac.uk/street-drugs-research/esm-screening

Or contact Rohan Morris via email R.Morris@mmu.ac.uk or on 0161 247 2415 (please leave a message if there is no response)

Appendix 23 How to guide part 1

Using the phone and connecting to data services– FAQs



1 Power key 2 Earpiece

3 Menu key 4 Back key

5 Microphone 6 Home key

7 Search key 8 Volume control keys

9 Wrist strap hole 10 Headset jack

How do I switch the phone on and off?

On– Press and hold the power key (1).

Off– As above, until a menu appears then select power off.

How do I enter/exit aeroplane mode?

Press and hold the power key (1) until a menu appears then select airplane mode.

How do I go to the home screen?

By pressing the home key (6).

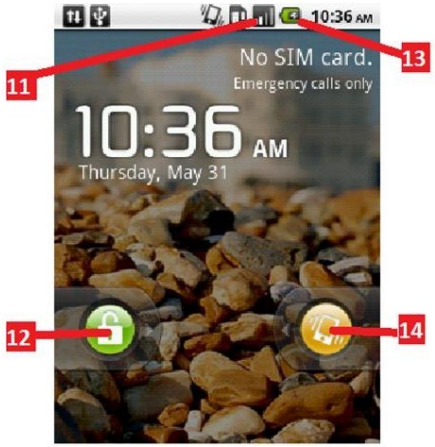
How do I go back?

To go to the previous screen, hide the (on screen) keyboard, or exit an application press the back key (4)

How do I turn the phone ringtone up and down?

On the home screen use the volume control keys (8)

Using the phone and connecting to data services– FAQs



How can I tell if the phone has signal?

Via an icon in the notification bar (11).

How do I lock/unlock the phone?

Lock– Press (don't hold) the power key (1).

Unlock– Slide the green padlock (12) to the right.

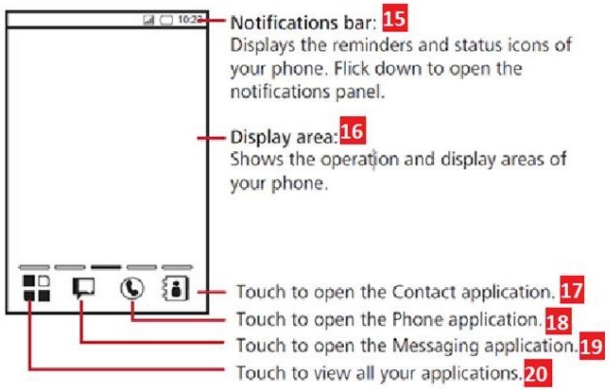
How can I tell how much battery is left?

Via an icon in the notification bar (13).

How do I mute/unmute the phone?

Slide the orange /grey icon (15) to the left.

Using the phone and connecting to data services– FAQs



How can I tell if data services are enabled?

From the home screen (6), slide down the notifications bar (15). If data services are disabled click on the notice to enable.

How do I make a phone call?

From the home screen (6), press the phone icon (18) dial number or access contacts and press the green button.

How do I access text messages?

From the home screen (6), click on the messaging icon (19). If a thread is already open then press the back button (4) to view all messages. Options to delete and compose new messages can be brought up via the menu key (3).

How do I access other applications on the phone e.g. calculator, games, settings, wifi setup?

From the home screen press the view applications button (20).

Using the phone and connecting to data services– FAQs

How do I connect the phone to a wifi network?

From the home screen (6), click to view all applications (20). Scroll the page down and click on the settings icon.

- Select the first option, wireless & networks.
- Then select wi-fi settings.

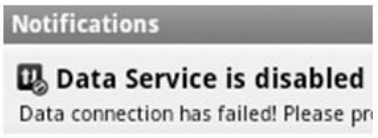
- Click turn on wi-fi.
- Click on the appropriate network.

- If necessary enter password, this can usually be found on the wireless hub. Password may be case sensitive.
- You should now be connected. Whenever you see this  in the notification bar it means that the phone is connected to a wi-fi network.

How do I connect to a none wifi network?

- Pull the notification bar (15) down.
- Scroll through till you find the notice that says Data service is…. If it says data service is enabled then you are already connected.

- If it says data service is disabled then click on the notification to enable data.



Appendix 24 How to guide part 2

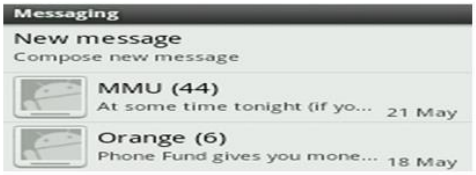
Part 2– Answering the questionnaire(s)

Starting the questionnaire – step by step

Step 1a- Click on the messaging icon (19), when you receive a text message (7 times daily).

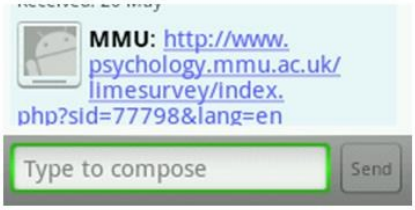
Note– *The green number on the messaging icon tells you how many unread messages you have.*

Step 1b- Once a day (if you have used cannabis) complete the CEQ. Simply click on the desktop icon (22) and it will start (move on to next page for further info).



Step 2- Select the message sent from MMU. Dependant on whether there is a message thread open or not this step may be skipped.

Note– *Any messages sent from us will either be sent from MMU or Rohan Morris (stored in phone contacts).*



Step 3- Click on the message text itself.

Note- *The newest message is at the bottom.*

Part 2– Answering the questionnaire(s)

Navigating the questionnaire and entering text– FAQs

How do I zoom in and out (re-size an image)? (*When the questionnaire starts you may need to zoom out to see all the answer options.)*

To zoom simply place two fingers (or thumb) on the screen and pinch together (to zoom out) or push apart (to zoom in).

How do I scroll round the page?

After a short time the questionnaire will load. To move round the page (up or down & left or right) place one finger on the screen and move in the opposite direction to where you want the page to scroll i.e. push down to scroll up.

How do I turn the orientation of the screen (landscape to portrait or vice versa)?

Whilst holding the device simply turn it on a 90 degree angle.

Note– *This function can become unresponsive during answering the questionnaire. It is recommended that changes to orientation are performed before starting to answer the questionnaire.*

Part 2– Answering the questionnaire(s)

How do I enter text into a box?

Click on the box where you wish to enter text and a keyboard will come up on the screen.

Note *To enter numbers click* ?123

How do I exit the on screen keyboard?

This can be done in two ways either by touching the screen anywhere (except the keyboard or text box) or by pressing the back button (4) on the phone (do not double tap this button).

What do I do when I have finished answering all the questions?

To send the data to us, you must press the submit button. The submit button can be found at the bottom of the last page. If everything has been done correctly a thank you page will load up.

Part 2– Answering the questionnaire(s)

Closing browser tabs

Every time you answer a questionnaire the web browser opens up a new tab, much like a web browser on a computer can have multiple tabs. It is necessary to close some of these tabs after answering the questionnaire several times.

To close a browser tab (if not in full screen mode skip step 1)-

Step 1- Drag the toolbar (23), at the top of the screen, down to display the tabs.

Step 2- Press the x symbol displayed on the tabs (24) until all tabs are close and only the home page remains.

Appendix 25 Schizotypal States Questionnaire items

This is an example of the SSQ items however please note these were displayed on a mobile device not paper format.

		Strongly disagree	disagree	Neutral	Agree	Strongly Agree
Right now I feel:	People would think me aloof					
	Unseen forces are around me					
	My behaviour is unusual					
	Other people can read my mind					
	Things have special meanings for me					
	Rather bizarre					
	I should be wary of others					
	That if I spoke, I'd seem vague/elusive					
	Threatened/put down					
	Others are looking at me oddly					
	Uneasy about being with others					
	Astrology and fortune telling make sense					
	I could use words in an odd way					
	I don't want to reveal much about myself					
	I want to keep in the background					
	I can hear things others cannot					
	people are taking advantage of me					
	I cannot get close to others					
	I'm a rather odd unusual person					
	I cannot express myself clearly					
	uneasy just talking					
	I should keep my feelings private					

Appendix 26 Concurrent States Questionnaire items

This is an example of the SSQ items however please note these were displayed on a mobile device not paper format.

		Not at all	a bit	so so	quite a lot	very much so
Right now I am feeling:	chilled out					
	on edge					
	Calm					
	Worried					
	Content					
	anxious					
	Relaxed					
	concerned					
	Happy					
	agitated					
	Stressed					

Appendix 27 ESM Participant information sheet

Participant Information Sheet

Study title: Momentary assessment of aversive cannabis experiences, a schizotypal state and perceived stress

Researchers: Rohan Morris, John Cavill, Chris Wibberley, and Laura Brown
(Manchester Metropolitan University)

Invitation: We would like to invite you to take part in our research study. Before you decide, we would like you to understand why the research is being done and what it would involve for you. One of our research team will be available to go through the information sheet with you (if you so wish) and answer any questions you may have. We'd suggest this should take about 20 minutes. Talk to others about the study if you wish.

What is the purpose of the study? To be able to look at the relationship between people's experiences with cannabis, their experiences which are related to an aspect of personality known as schizotypy (schizotypal state), and how stressed a person feels. It is hoped that this study will provide data that will enable us to identify people who are at the greatest risk of experiencing some of the negative psychological effects of cannabis.

Why have I been invited? We are trying to recruit 60 people who are over the age of 18 and are current cannabis users. You have been invited because we believe that you may be eligible to participate.

Do I have to take part? It is entirely up to you to decide whether or not to take part in the study. We will be available to describe the study and go through the information sheet with you. If you agree to take part we will ask you to sign a consent form, however (as with our previous research in this area) you do not have to use your real name. You are free to withdraw (leave) at any time, without giving a reason.

What will happen to me if I take part? Initially you will be asked to complete two questionnaires; one looking at your past experiences with cannabis (the cannabis experiences questionnaire) and the other measuring your score on a personality trait known as schizotypy (schizotypal personality questionnaire). After you have completed these questionnaires you will be asked to meet with one of the researchers. This can be done at a time and location at your convenience, and will take approximately 30 minutes. The researcher will explain in detail exactly what is required of you for the next stage of the study, answer any questions that you may have, and loan you the necessary equipment.

The second stage will involve you carrying a mobile device around with you for a period of two weeks. The mobile device will prompt you at various times completing a short questionnaire on the mobile device. You will be requested to complete the questions 6 times a day when prompted by a signal from the mobile device. This phase will last for a period of two weeks and will require on average between 10 and 20 minutes per day.

Expenses and payments:
As a thank you for those that complete the second phase of the study (inputting data on a daily basis into a mobile device) we will give **you £20 (in Love2Shop gift vouchers)** upon completion of the

study and return of the mobile device. In addition the mobile device will be pre-loaded with **£10 mobile phone credit and 400 text messages** for you to use, this is to ensure you can contact a member of the research team free of charge. However, will not be able to cover any associated costs which you may incur including, but not exclusive to, your time, and electricity consumption (as the mobile device will require charging).

What will I have to do?
For the first phase simply answer our questionnaires and return them (or submit it if in an electronic format). For the second phase for the most part you will continue with your typical routine. You will receive a prompt on your mobile device at random times (except for times that you have indicated you will be unavailable e.g. when you are asleep). After you have received the prompt we request that you use the device to access our questionnaire and respond to the questions presented.

What are the possible disadvantages and risks of taking part?
The associated risks of taking part are very low. You will be requested to complete a questionnaire containing items relating to your experiences of drug use. There is a small possibility that some participants might find this mildly distressing, for instance by being asked to focus on feelings that you found unpleasant.

Another possible disadvantage of taking part in this research is that some participants may find the methodology intrusive. As the study may require a response at a random time point it may distract you from your normal daily activity. However, you will not be expected to respond if you are unavailable (e.g. in a meeting or a class) or if it would be dangerous to do so (e.g. whilst driving). Furthermore, if you are unavailable and wish to not be disturbed you can always put the device on to a silent or vibrate only setting, or alternatively turn the device off.

What are the possible benefits of taking part?
For you personally, probably none, although our work may alert you to some of the dangers of using cannabis, and make you think about the wisdom of continuing to use it if you are concerned that it might be doing you harm. In the wider context, you will have the satisfaction of having contributed to our research efforts which have the ultimate goal of having practical health benefits for cannabis users.

What will happen when the research study ends?
When the study ends we will arrange a convenient time and location to meet with you and collect the mobile device from you.

What if there is a problem?
If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer you questions (see contact details beneath). If you remain unhappy and wish to complain formally you can do this by contacting John Cavill on 0161 247 2867 or j.cavill@mmu.ac.uk

Will my taking part in the study be kept confidential?
Yes. We will follow ethical and legal practice and all information about you will be handled in the strictest confidence. Only the named researchers will have access to any identifying information you have supplied us. However, it is not necessary for you to use your real name. Identifying information and contact details will be stored separately from your data on password-protected computer, which is kept in a locked office. Data will be sent to our secure server which is physically located on the university campus. Our IT team regularly update security to prevent any malicious access to our

server. Once downloaded from the server data will be stored on a password-protected computer (in a locked office) that only the researchers will have access to.

What will happen if I don't want to carry on with the study? You can withdraw from the study at any time during participation. Additionally if you so wish we can destroy any data that you have already submitted to us up to a two week period after your completion.

What will happen to the results?
To acknowledge the time and effort our participants put into our research we will always endeavour to publish our findings. By publishing our research our participants can have a direct impact on scientific knowledge and understanding. In any publications produced from this research it will not be possible to identify you or any other participant in this study.

Who is funding the research?
This research is being funded by the Research Institute for Health and Social Change, Manchester Metropolitan University (MMU), and is being supported by the Department of Psychology, MMU.

Who has reviewed this study?
This study has been reviewed and approved by the MMU faculty of Health, Psychology and Social Care ethics committee.

Thank you for taking the time to read this,

Rohan Morris
Department of Psychology
Elizabeth Gaskell
Manchester Metropolitan University
Hathersage Rd
M13 OJA
0161 247 2415
R.Morris@mmu.ac.uk

Please note we are in no way responsible for or connected with any of the organisations beneath:

If you have any concerns about drug addiction or want information about drugs, then please contact one of the following organisations who may be able to provide you with help and support:

Talk to Frank- http://www.talktofrank.com/ or 0800 77 66 00
Drugs Line- http://www.drugsline.org/ or 0808 1 606 606
Erowid- http://www.erowid.org/

If you have any concerns about mental health problems or want further information about mental health issues, then please contact one of the following organisations who may be able to provide you with help and support:

www.makingspace.co.uk
www.mentalhealth.org.uk
*www.rethink.org or **0845 456 0455***

Appendix 28 ESM Participant consent form

Momentary assessment of aversive cannabis experiences, a schizotypal state and perceived stress

CONSENT FORM

- I confirm that I have read and understood the information sheet for the project with the above title.
- I understand that my agreement to take part in the research is voluntary and that I am free to withdraw from the research, without giving any reason.
- I also understand that I am free to withdraw any data I may have submitted at any point during my participation and two weeks after my participation in this research.
- I understand that any information given to the research team will remain confidential and that my anonymity will be protected.
- I give my consent for the data I provide to be analysed and am aware that the results of such an analysis may be reproduced in any report or publication of the research. However, this will not be in any way in which I may be identified.

I agree to take part in the research

Date _____

Participant signature
(May use pseudonym) _____

Contact details _____

_____

_____
(phone number, email or address)

Appendix 29 Validating the ESM items

Validating measures of a schizotypal state

Please note for the validation items (the PSI and WSI) no system of pro-rating was adopted hence the N varies from analysis to analysis.

Table 50
Results of a Pearson's r correlation displaying the relationship between scores on the PSI and SSQ administered at Day 0 of the investigation.

		SSQ total	SSQ Cog	SSQ Dis	SSQ Int
Cronbach's Alpha		α=0.91	α=0.79	α=0.76	α=0.88
PSI total	N	**51**	**51**	**52**	**52**
	r	**.626**	**.445**	**1.000**	**.567**
	p	**<.0001**	**.001**	**<.0001**	**<.0001**
PSI DT	N	**51**	51	52	**52**
	r	**.473**	.501	.258	**.338**
	p	**<.001**	**<.001**	.064	**.014**
PSI PD	N	**51**	51	**52**	**52**
	r	**.5632**	.462	**.478**	**.508**
	p	**<.0001**	**<.001**	**<.001**	**<.001**
PSI CD	N	**51**	51	**52**	**52**
	r	**.460**	.247	**.482**	**.471**
	p	**<.001**	.080	**<.001**	**.003**
PSI An	N	**51**	51	**52**	52
	r	**.448**	.237	**.354**	.162
	p	**.001**	.094	**.01**	.251
PSI Ma	N	**51**	51	**52**	**52**
	r	**.354**	.262	**.332**	**.279**
	p	**.011**	.063	**.016**	**.045**
PSI Pa	N	**51**	**51**	**52**	**52**
	r	**.500**	**.310**	**.303**	**.448**
	p	**<.001**	**.027**	**.029**	**<.001**

Table 51
Results of a Pearson's r correlation displaying the relationship between scores on a re-test of the PSI and SSQ administered at day 4 of the investigation.

		SSQ total	SSQ Dis	SSQ Cog	SSQ Int
PSI total	n r p	**37** **.818** **<.0001**	**37** **.772** **<.0001**	**38** **.737** **<.0001**	**38** **.772** **<.0001**
PSI DT	n r p	**37** **.553** **<.001**	**37** **.496** **.002**	**38** **.639** **<.0001**	**38** **.452** **.004**
PSI PD	n r p	**37** **.638** **<.0001**	**37** **.560** **<.001**	**38** **0.702** **<.0001**	**38** **0.547** **<.001**
PSI CD	n r p	**37** **.719** **<.0001**	**37** **.756** **<.0001**	**38** **.582** **<.001**	**38** **.620** **<.0001**
PSI An	n r p	**37** **.543** **<.001**	**37** **.447** **.006**	**38** **.391** **.015**	**38** **.655** **<.0001**
PSI Ma	n r p	**37** **.690** **<.0001**	**37** **.664** **<.0001**	**38** **.641** **<.0001**	**38** **.643** **<.0001**
PSI Pa	n r p	**37** **.806** **<.0001**	**37** **.744** **<.0001**	**38** **.599** **<.001**	**38** **.789** **<.0001**

Validating momentary measures of stress

Prior to analysis the relationship between the two proposed scales/sub-scales of the CSQ had not been assessed as a consequence two scoring approaches were adopted. One approach was to consider the two scales as related along a continuum, i.e. feelings of calmness are the opposite to feelings of stress. Another approach was to consider the two constructs as independent, i.e. feeling calm and feeling stress are not related and could co-occur. Therefore, the CSQ was consider as a sum of the six items pertaining to stress, and the five items pertaining to calmness (with scores reversed), referred to herein as CSQ total. The CSQ was also considered as consisting of two independent scales, the six items assessing stress and the five items assessing calmness referred to as CSQ Stress and CSQ Calm.

The CSQ total was assessed as a predictor on the outcome variables of WSI Event (Table 52) and WSI Impact (Table 53). The CSQ total did not predict scores on the WSI Event scale. However, the predictor accounted for a significant increase on the WSI Impact, (b = 0.11, 95% CI 0.05 to 0.17, p < .001), a one unit increase on the CSQ total predicted an increase of 0.11 in the outcome variable. These results demonstrate evidence of convergent validity between the CSQ total and the impact of stressful events.

Table 52
Parameter estimates for multilevel model of the event scale of the Weekly Stress Inventory (outcome) as a function of scores on the CSQ total

Fixed effect (intercept, slopes)	Estimate	(SE)	Z	P	95% CI	
					Lower	Upper
Intercept	**11.684**	**0.821**	**14.23**	**<.001**	**10.075**	**13.293**
CSQ total	0.017	0.009	1.90	.057	-0.0005	0.032

Random effects ([co-]variances)		Estimate	(SE)	ICC (%)	95% CI	
					Lower	Upper
Level 1	Intercept	4.411	0.582	87.628	3.406	5.712
	Residual	1.657	0.037		1.587	1.731

Table 53
Parameter estimates for multilevel model of the impact scale of the Weekly Stress Inventory (outcome) as a function of scores on the CSQ total

Fixed effect (intercept, slopes)	Estimate	(SE)	Z	P	95% CI	
					Lower	Upper
Intercept	**21.509**	**2.504**	**8.59**	**<.001**	**16.602**	**26.417**
CSQ total	**0.109**	**0.029**	**3.69**	**<.001**	**0.051**	**0.166**

Random effects ([co-]variances)		Estimate	(SE)	ICC (%)	95% CI	
					Lower	Upper
Level 1	Intercept	13.446	1.777	85.244%	10.378	17.422
	Residual	5.594	0.123		5.358	5.841

Despite the relationship between the CSQ total and the WSI Impact it is still necessary to assess the relationship between the CSQ Calm and CSQ Stress items. The effects of CSQ Calm and CSQ Stress were considered simultaneously as predictors of scores on the WSI Event and WSI Impact. There was no significant effect of CSQ Calm and CSQ Stress on WSI Event (see Table 54). There was also no significant effect of CSQ Calm on WSI Impact, however, CSQ Stress was a significant predictor of the scale (b = 0.21, 95% CI 0.07 to 0.35, p =

.004). A one unit increase in the CSQ Stress scale predicted an increase of 0.21 on the WSI Impact scale (see Table 55).

Table 54

Parameter estimates for multilevel model of the event scale of the Weekly Stress Inventory (outcome) as a function of scores on the CSQ calm and CSQ Stress scales

Fixed effect (intercept, slopes)	Estimate	(SE)	Z	P	95% CI	
					Lower	Upper
Intercept	**11.683**	**0.821**	**14.23**	**<.001**	**10.074**	**13.292**
CSQ Calm	-0.014	0.019	-0.72	.475	-0.051	0.024
CSQ Stress	0.020	0.021	0.93	.352	-0.022	0.062

Random effects ([co-]variances)		Estimate	(SE)	ICC (%)	95% CI	
					Lower	Upper
Level 1	Intercept	4.411	0.582	87.628	3.406	5.712
	Residual	1.657	0.037		1.587	1.731

Table 55

Parameter estimates for multilevel model of the impact scale of the Weekly Stress Inventory (outcome) as a function of scores on the CSQ calm and CSQ Stress scales

Fixed effect (intercept, slopes)	Estimate	(SE)	Z	P	95% CI	
					Lower	Upper
Intercept	**21.514**	**2.493**	**8.63**	**<.001**	**16.628**	**26.399**
CSQ Calm	-0.023	0.065	-0.36	.719	-0.150	0.103
CSQ Stress	**0.207**	**0.072**	**2.86**	**.004**	**0.065**	**0.348**

Random effects ([co-]variances)		Estimate	(SE)	ICC (%)	95% CI	
					Lower	Upper
Level 1	Intercept	13.385	1.769	85.153	10.330	17.344
	Residual	5.589	0.123		5.353	5.836

The findings outlined above demonstrate evidence of the independence of concurrent experiences of calmness and concurrent experiences of stress. The fact that CSQ Stress was capable of distinguishing stressful weeks, and CSQ Calm was not is testimony to the fact.

Validating event related items

To assess an appropriate means of scoring the items ER, SE and PE two approaches were adopted. One approach was to consider the normalised (Z-score) of the three items as related along a continuum, i.e. stressful events have an antagonistic relationship with pleasurable events. This approach consists of the

addition of standardised scores for ER (reversed), PE (reversed), and SE, referred to herein as the Events Questionnaire (EQ). Another approach is to consider the two constructs as independent, i.e. pleasurable events and stressful events are not related and could co-occur within one event. This approach consists of ER, PE, and SE being considered independent factors. EQ was not a significant predictor of the WSI Event scale (see Table 56). Neither was there a significant effect of EQ on WSI Impact (see Table 57).

Table 56
Parameter estimates for multilevel model of the event scale of the Weekly Stress Inventory (outcome) as a function of scores on the Events Questionnaire

Fixed effect (intercept, slopes)	Estimate	(SE)	Z	P	95% CI	
					Lower	Upper
Intercept	**11.734**	**0.838**	**14.00**	**<.001**	**10.091**	**13.377**
EQ	0.054	0.040	1.33	.182	-0.025	0.133
Time	0.002	0.001	1.47	.142	-0.0005	0.004
Random effects ([co-]variances)		Estimate	(SE)	ICC (%)	95% CI	
					Lower	Upper
Level 1	Intercept	4.493	0.596	88.781	3.464	5.827
	Residual	1.597	0.048		1.506	1.694

Table 57
Parameter estimates for multilevel model of the impact scale of the Weekly Stress Inventory (outcome) as a function of scores on the Events Questionnaire

Fixed effect (intercept, slopes)	Estimate	(SE)	Z	P	95% CI	
					Lower	Upper
Intercept	**21.665**	**2.610**	**8.30**	**.000**	**16.550**	**26.780**
EQ	0.212	0.140	1.51	.130	-0.062	0.486
Time	**0.007**	**0.004**	**2.02**	**.044**	**0.0002**	**0.015**
Random effects ([co-]variances)		Estimate	(SE)	ICC (%)	95% CI	
					Lower	Upper
Level 1	Intercept	13.971	1.858	86.356	10.766	18.130
	Residual	5.553	0.167		5.236	5.889

In the consideration of the items ER, SE and PE as independent constructs none of the variables significantly predicted scores on the WSI event scale (see Table 58 & 59), neither, did they significantly predict scores on the WSI Impact scale.

Table 58
Parameter estimates for multilevel model of the event scale of the Weekly Stress Inventory (outcome) as a function of Pleasurable Events, Stressful Events and an Event Rating

Fixed effect (intercept, slopes)	Estimate	(SE)	Z	P	95% CI	
					Lower	Upper
Intercept	**11.735**	**0.8400**	**13.97**	**<.001**	**10.089**	**13.382**
Event Rating (ER)	-0.101	0.091	-1.12	.264	-0.279	0.077
Stressful Events (SE)	0.054	0.102	0.52	.601	-0.147	0.254
Pleasurable Events (PE)	0.088	0.111	0.79	.427	-0.130	0.307
Time	0.001	0.001	1.27	.204	-0.0007	0.003
Random effects ([co-]variances)		Estimate	(SE)	ICC (%)	95% CI	
					Lower	Upper
Level 1	Intercept	4.502	0.597	88.84	3.471	5.839
	Residual	1.596	0.048		1.505	1.692

Table 59
Parameter estimates for multilevel model of the impact scale of the Weekly Stress Inventory (outcome) as a function of Pleasurable Events, Stressful Events and an Event Rating

Fixed effect (intercept, slopes)	Estimate	(SE)	Z	P	95% CI	
					Lower	Upper
Intercept	**21.68**	**2.613**	**8.30**	**<.001**	**16.559**	**26.801**
Event Rating (ER)	-0.344	0.315	-1.09	.275	-0.963	0.274
Stressful Events (SE)	0.254	0.356	0.72	.475	-0.443	0.951
Pleasurable Events (PE)	0.473	0.387	1.22	.221	-0.285	1.232
Time	0.006	0.004	1.72	.085	-0.0009	0.014
Random effects ([co-]variances)		Estimate	(SE)	ICC (%)	95% CI	
					Lower	Upper
Level 1	Intercept	13.986	1.860	86.419	10.777	18.149
	Residual	5.544	0.166		5.228	5.880

The inability of aforementioned items to reliably predict scores on the WSI may have occurred for several reasons. One possibility is that the items developed for the purposes of this investigation do not possess construct validity and as a consequence no convergent validity was observed. PE and ER are not directly pertaining to stressful events and as consequence it could be viewed as unremarkable their inability to predict stressful weeks. The lack of relationship between SE and WSI Event score perhaps may be indicative of cultural differences between the current sample and the sample which was used in the creation of the WSI. The WSI was developed in the United States of America, item

retention was based on the item being endorsed by at least 10% of the sample (Brantley, Jones, Boudreaux & Catz, 1997). Perhaps, in using a measure developed in another culture some of the daily minor stressors experienced may be different.

The validity of the aforementioned items can be assessed through means other than the WSI. It would be anticipated that stressful events would predict concurrent stressed states and pleasurable events would predict concurrent calm states. Consequently, the effect of EQ, ER, SE, and PE were estimated as predictors of the CSQ scales.

EQ was capable of significantly predicting scores on the CSQ stress scale (*b* = 0.75, 95% CI 0.65 to 0.84, *p* < .001) each unit increase on the independent variable predicted an increase of 0.75 on the outcome variable. EQ was also a significant predictor of CSQ Calm (*b* = -0.98, 95% CI -1.10 to -0.87, *p* < .001) for each unit increase on EQ there was a decrease of 0.98 on the dependent variable. This finding provides further evidence of convergent validity; the Events Questionnaire is capable of predicting stressed and calm states.

Table 60
Parameter estimates for multilevel model of the CSQ Stress scale (outcome) as a function of scores on the Events Questionnaire

Fixed effect (intercept, slopes)	Estimate	(SE)	Z	P	95% CI	
					Lower	Upper
Intercept	**2.334**	**0.373**	**6.26**	**<.001**	**1.604**	**3.064**
EQ	**0.748**	**0.049**	**15.31**	**<.001**	**0.652**	**0.844**
Time	0.0009	0.001	0.78	.434	-0.001	0.003

Random effects ([co-]variances)		Estimate	(SE)	ICC (%)	95% CI	
					Lower	Upper
Level 1	Intercept	4.154	1.193	44.011	2.600	7.498
Level 2	Intercept	2.862	0.361	28.522	2.234	3.665
	Residual	2.756	0.176		2.431	3.124

Table 61
Parameter estimates for multilevel model of the CSQ Calm scale (outcome) as a function of scores on the Events Questionnaire

Fixed effect (intercept, slopes)	Estimate	(SE)	Z	p	95% CI	
					Lower	Upper
Intercept	**12.935**	**0.559**	**23.13**	**<.001**	**11.839**	**14.031**
EQ	**-0.984**	**0.060**	**-16.40**	**<.001**	**-1.101**	**-0.866**
Time	**-0.003**	**0.001**	**-2.48**	**.013**	**-0.006**	**-0.0007**

Random effects ([co-]variances)		Estimate	(SE)	ICC (%)	95% CI	
					Lower	Upper
Level 1	Intercept	10.631	2.639	60.729	6.535	17.293
Level 2	Intercept	2.057	0.379	11.751	1.434	2.952
	Residual	4.817	0.309		4.248	5.463

As discussed previously it is necessary to evaluate the independence of stressful and pleasurable events, consequently the items ER, PE, and SE, were tested as predictors of CSQ Stress and CSQ Calm. Both ER (b = -0.42, 95% CI -0.59 to -0.24, p < .001) and SE predicted (b = 2.03, 95% CI 1.78 to 2.27, p < .001) significant changes on the CSQ Stress. A one unit increase in ER resulted in a decrease of 0.42 units of the CSQ stress and a unit increase in SE resulted in a 2.03 unit increase in the outcome variable. PE did not significantly predict scores on the CSQ Stress. However, all explanatory variables assessed were significant predictors of scores on CSQ Calm. A one unit increase in ER resulted in an increase of 0.67 units of the CSQ Calm (b = 0.67, 95% CI 0.43 to 0.90, p < .001), a unit increase in SE resulted in a 1.78 unit decrease in the outcome variable (b = -1.78, 95% CI -2.10 to -1.46, p < .001), and a unit increase in PE equated to an increase of 0.73 (b = 0.73, 95% CI 0.47 to 1.0006, p < .001).

Table 62
Parameter estimates for multilevel model of scores on the CSQ Stress scale (outcome) as a function of Pleasurable Events, Stressful Events and an Event Rating

Fixed effect (intercept, slopes)	Estimate	(SE)	Z	P	95% CI	
					Lower	Upper
Intercept	**2.371**	**0.342**	**6.93**	**<.001**	**1.701**	**3.042**
Event Rating (ER)	**-0.416**	**0.090**	**-4.63**	**<.001**	**-0.592**	**-0.240**
Stressful Events (SE)	**2.027**	**0.125**	**16.18**	**<.001**	**1.782**	**2.273**
Pleasurable Events (PE)	-0.136	0.103	-1.32	.187	-0.339	0.066
Time	-0.001	0.001	-0.94	.346	-0.003	0.001
Random effects ([co-]variances)		Estimate	(SE)	ICC (%)	95% CI	
					Lower	Upper
Level 1	Intercept	3.690	1.021	42.333	2.145	6.348
Level 2	Intercept	2.630	0.330	30.173	2.056	3.364
	Residual	2.397	0.154		2.113	2.719

Table 63
Parameter estimates for multilevel model of scores on the CSQ Calm scale (outcome) as a function of Pleasurable Events, Stressful Events and an Event Rating
CSQ Calm

Fixed effect (intercept, slopes)	Estimate	(SE)	Z	P	95% CI	
					Lower	Upper
Intercept	**12.920**	**0.554**	**23.34**	**<.001**	**11.834**	**14.005**
Event Rating (ER)	**0.670**	**0.120**	**5.59**	**<.001**	**0.435**	**0.904**
Stressful Events (SE)	**-1.781**	**0.163**	**-10.93**	**<.001**	**-2.101**	**-1.462**
Pleasurable Events (PE)	**0.733**	**0.137**	**5.37**	**<.001**	**0.465**	**1.0006**
Time	**-0.003**	**0.001**	**-2.01**	**.045**	**-0.006**	**-0.00006**
Random effects ([co-]variances)		Estimate	(SE)	ICC (%)	95% CI	
					Lower	Upper
Level 1	Intercept	10.415	2.590	60.614	6.397	16.955
Level 2	Intercept	2.054	0.380	11.957	1.429	2.953
	Residual	4.713	0.304		4.153	5.348

The results displayed in Tables 62 and 63 provide evidence of convergent validity between measures of concurrent stress and pleasure and previous stressful and pleasurable events. The anchors assigned to the ER item, incorporating both ‘very pleasant’ (0) and ‘very unpleasant’ (4) may have attempted to assess two constructs with one item. However, the ability of ER to predict scores on both the CSQ Calm and CSQ Stress in the direction anticipated suggests that perhaps the item is assessing one construct which is a correlate of both stress and pleasure;

event evaluation. The results displayed in Table 62 can also help make inferences about the independence of stressful events and pleasurable events. SE were capable of significantly predicting scores on the CSQ Stress, however, PE had no such effect. The non-significant finding indicates that there is no relationship between previous pleasurable events and concurrent feelings of stress.

The independence of stress and pleasure

Some of the analyses outlined in this appendix provide evidence for the independence of feelings of stress and feelings of calm. Concurrent feelings of stress (CSQ stress) predicted scores on the WSI Impact scale. However, no such significant relationship was observed with concurrent feelings of calm (CSQ calm). If CSQ Stress and CSQ Calm were pertaining to the same underlying factor one would expect the variables to both exert an influence on the same outcome variable. SE and ER were capable of predicting scores on the CSQ Stress scale, however, PE did not have a significant relationship. Despite this EQ significantly predicted concurrent states of calm and stress. Furthermore, SE significantly reduced and PE significantly increased scores on the CSQ Calm, thus seemingly displaying an antagonistic relationship. It is possible to further evaluate the independence of the items, however, this is unlikely to yield any definitive answers. Furthermore, such an analysis is beyond the scope of this current study. As there is (some) evidence suggesting that the CSQ total and EQ are potentially assessing more than one independent constructs, for the purposes of this body of research, the scales will be considered as assessing independent constructs. Considering the constructs as independent even if they are assessing one underlying concept will not typically result in the loss of any information. The instance where *information* loss may occur, would be in the case of collinearity. However, within the MLM the variables are assessed for collinearity and any that are deemed to be are omitted from the model. The alternative approach would be to encounter the possibility of utilising composite scores of two (or more) unrelated concepts, if this were to occur the variables would cease to assess a construct and would instead assess a mean of two independent scores, resulting in the loss of meaning (information). Consequently, CSQ Stress and CSQ Calm are considered as independent, as are ER, SE, and PE.

Appendix 30 quantity of cannabis consumed predicting SSQ total

Table 64
Parameter estimates for multilevel model of schizotypal state (outcome) as a function of states of stress, states of calm, stressful events, pleasurable events, quantity of cannabis consumed and a cannabis-stress interaction

Fixed effect (intercept, slopes)		Estimate	(SE)	Z	p	95% CI	
						Lower	Upper
Intercept		**14.141**	**1.813**	**7.80**	**<.001**	**10.589**	**17.694**
CSQ Stress		**0.689**	**0.091**	**7.58**	**<.001**	**0.511**	**0.867**
CSQ Calm		-0.071	0.071	-0.99	.320	-0.211	0.069
Event Rating (ER)		-0.120	0.210	-0.57	.569	-0.532	0.292
Stressful Events (SE)		-0.081	0.333	-0.24	.807	-0.735	0.572
Pleasurable Events (PE)		0.327	0.252	1.30	.194	-0.166	0.820
Cannabis	Between	2.939	2.190	1.34	.180	-1.353	7.231
Quantity	Within	**0.439**	**0.160**	**2.74**	**.006**	**0.125**	**0.754**
Caffeine		0.140	0.186	0.75	.451	-0.225	0.506
Tobacco		-0.269	0.229	-1.17	.241	-0.19	0.180
Alcohol		0.208	0.214	0.97	.331	-0.211	0.628
Time		**-0.006**	**0.003**	**-2.17**	**.030**	**-0.010**	**-0.001**

Random effects ([co-]variances)		Estimate	(SE)	ICC (%)	95% CI	
					Lower	Upper
Level 1	Intercept	114.706	27.779	83.440	71.359	184.385
Level 2	Intercept	10.134	1.450	7.372	7.656	13.415
	Residual	12.632	0.831		11.103	14.371

Appendix 31 quantity of cannabis predicting interpersonal psychotic like states

Table 65
Parameter estimates for multilevel model of interpersonal distortions (outcome) as a function of states of stress, states of calm, stressful events, pleasurable events, quantity of cannabis consumed and a cannabis-stress interaction

Fixed effect (intercept, slopes)		Estimate	(SE)	Z	p	95% CI	
						Lower	Upper
Intercept		**6.063**	**0.767**	**7.90**	**<.001**	**4.559**	**7.566**
CSQ Stress		**0.279**	**0.050**	**5.62**	**<.001**	**0.181**	**0.376**
CSQ Calm		**-0.093**	**0.039**	**-2.39**	**.017**	**-0.170**	**-0.017**
Event Rating (ER)		0.035	0.116	0.30	.765	-0.193	0.262
Stressful Events (SE)		-0.030	0.183	-0.17	.869	-0.389	0.329
Pleasurable Events (PE)		-0.180	0.138	-1.30	.192	-0.451	0.091
Cannabis Quantity	Between	0.698	0.927	0.75	.451	-1.118	2.515
	Within	**0.245**	**0.088**	**2.77**	**.006**	**0.071**	**0.418**
Caffeine		0.076	0.103	0.74	.459	-0.125	0.278
Tobacco		-0.151	0.126	-1.19	.233	-0.398	0.097
Alcohol		0.048	0.118	0.40	.686	-0.184	0.279
Time		-0.002	0.001	-1.35	.178	-0.005	0.001

Random effects ([co-]variances)		Estimate	(SE)	ICC (%)	95% CI	
					Lower	Upper
Level 1	Intercept	20.270	4.992	75.298	12.508	32.847
Level 2	Intercept	2.730	0.427	10.143	2.010	3.709
	Residual	3.919	0.261		3.439	4.663

Appendix 32 quantity of cannabis predicting disorganised psychotic like states

Table 66
Parameter estimates for multilevel model of distortions of disorganisation (outcome) as a function of states of stress, states of calm, stressful events, pleasurable events, quantity of cannabis consumed and a cannabis-stress interaction

Fixed effect (intercept, slopes)		Estimate	(SE)	Z	P	95% CI	
						Lower	Upper
Intercept		**4.105**	**0.548**	**7.49**	**<.001**	**3.030**	**5.180**
CSQ Stress		**0.195**	**0.032**	**6.18**	**<.001**	**0.133**	**0.257**
CSQ Calm		-0.011	0.025	-0.43	.667	-0.060	0.038
Event Rating (ER)		-0.142	0.075	-1.90	.057	-0.288	0.004
Stressful Events (SE)		-0.035	0.117	-0.30	.765	-0.265	0.195
Pleasurable Events (PE)		**0.298**	**0.089**	**3.37**	**.001**	**0.125**	**0.472**
Cannabis Quantity	Between	1.171	0.662	1.77	.077	-0.127	2.470
	Within	**0.156**	**0.057**	**2.75**	**.006**	**0.045**	**0.267**
Caffeine		0.080	0.066	1.21	.226	-0.049	0.210
Tobacco		-0.053	0.081	-0.65	.514	-0.212	0.106
Alcohol		**0.160**	**0.076**	**2.10**	**.036**	**0.011**	**0.308**
Time		**-0.003**	**0.001**	**-3.06**	**.002**	**-0.005**	**-0.001**

Random effects ([co-]variances)		Estimate	(SE)	ICC (%)	95% CI	
					Lower	Upper
Level 1	Intercept	10.444	2.539	79.781	6.485	16.820
Level 2	Intercept	1.004	0.171	7.667	0.719	1.401
	Residual	1.643	0.111		1.440	1.875

Appendix 33 quantity of cannabis predicting calm states

Table 67
Parameter estimates for multilevel model of states of calm (outcome) as a function of schizotypal state, stress, stressful events, pleasurable events, and quantity of cannabis consumed

Fixed effect (intercept, slopes)		Estimate	(SE)	Z	P	95% CI	
						Lower	Upper
Intercept		**13.084**	**0.491**	**26.64**	**<.001**	**12.122**	**14.047**
SSQ Total		-0.025	0.017	-1.42	.156	-0.058	0.009
CSQ Stress		**-0.552**	**0.042**	**12.99**	**<.001**	**-0.635**	**-0.468**
Event Rating (ER)		**0.391**	**0.109**	**3.60**	**<.001**	**0.178**	**0.605**
Stressful Events (SE)		**-0.568**	**0.169**	**-3.35**	**.001**	**-0.900**	**-0.236**
Pleasurable Events (PE)		**0.503**	**0.127**	**3.96**	**<.001**	**0.254**	**0.751**
Cannabis Quantity	Between	0.570	0.594	0.96	.337	-0.595	1.736
	Within	**0.231**	**0.083**	**2.77**	**.006**	**0.068**	**0.394**
Caffeine		-0.028	0.097	-0.29	.772	-0.218	0.162
Tobacco		-0.373	0.119	-0.31	.753	-0.270	0.195
Alcohol		0.069	0.111	0.62	.537	-0.150	0.287
Time		**-0.004**	**0.001**	**-2.75**	**.006**	**-0.006**	**-0.001**

Random effects ([co-]variances)		Estimate	(SE)	ICC (%)	95% CI	
					Lower	Upper
Level 1	Intercept	8.102	2.020	59.606	4.888	13.134
Level 2	Intercept	1.779	0.316	13.233	1.256	2.519
	Residual	3.651	0.239		3.210	4.152

Appendix 34 CEQ-b as a predictor of a schizotypal state

Table 68
Parameter estimates for multilevel model of schizotypal state (outcome) as a function of states of stress, states of calm, stressful events, pleasurable events, cannabis consumption per se, a cannabis-stress interaction, and aversive cannabis experiences

Fixed effect (intercept, slopes)	Estimate	(SE)	Z	P	95% CI	
					Lower	Upper
Intercept	**14.337**	**1.783**	**8.04**	**<.001**	**10.842**	**17.830**
CSQ Stress	**0.403**	**0.106**	**3.82**	**<.001**	**0.196**	**0.610**
CSQ Calm	-0.099	0.075	-1.32	.186	-0.245	0.048
Event Rating (ER)	-0.076	0.232	-0.33	.743	-0.530	0.378
Stressful Events (SE)	0.116	0.363	0.32	.748	-0.595	0.827
Pleasurable Events (PE)	**0.716**	**0.267**	**2.68**	**.007**	**0.191**	**1.240**
CEQ-b	**0.286**	**0.066**	**4.32**	**<.001**	**0.156**	**0.416**
Cannabis Consumed	**0.940**	**0.384**	**2.45**	**.014**	**0.188**	**1.693**
Cannabis X Stress	**0.433**	**0.092**	**4.69**	**<.001**	**0.252**	**0.613**
Caffeine	-0.027	0.202	-0.13	.895	-0.422	0.369
Tobacco	-0.395	0.258	-1.53	.125	-0.901	0.110
Alcohol	-0.118	0.239	-0.49	.623	-0.586	0.351
Time	-0.004	0.003	-1.44	.150	-0.010	0.001

Random effects ([co-]variances)		Estimate	(SE)	ICC (%)	95% CI	
					Lower	Upper
Level 1	Intercept	110.735	27.118	84.219	68.523	178.951
Level 2	Intercept	8.716	1.449	6.629	6.292	12.072
	Residual	12.033	0.846		10.485	13.811

Appendix 35 Time lagged CEQ-b as a predictor of a schizotypal state

Table 69

Parameter estimates for multilevel model of schizotypal state (outcome) as a function of states of stress, states of calm, stressful events, pleasurable events, cannabis consumption per se, a cannabis-stress interaction, and aversive cannabis experiences from the previous day

Fixed effect (intercept, slopes)	Estimate	(SE)	Z	P	95% CI	
					Lower	Upper
Intercept	**13.277**	**1.807**	**7.35**	**<.001**	**9.735**	**16.818**
CSQ Stress	**0.485**	**0.117**	**4.13**	**<.001**	**0.255**	**0.715**
CSQ Calm	-0.115	0.084	-1.37	.170	-0.279	0.049
Event Rating (ER)	-0.019	0.268	-0.07	.944	-0.544	0.507
Stressful Events (SE)	-0.307	0.417	-0.74	.462	-1.124	0.510
Pleasurable Events (PE)	0.410	0.316	1.30	.195	-0.209	1.029
CEQ-b $_{T-1}$	**0.232**	**0.057**	**4.09**	**<.001**	**0.121**	**0.342**
Cannabis Consumed	**1.135**	**0.432**	**2.63**	**.009**	**0.288**	**1.981**
Cannabis X Stress	**0.470**	**0.097**	**4.83**	**<.001**	**0.279**	**0.661**
Caffeine	-0.028	0.230	-0.12	.903	-0.478	0.422
Tobacco	-0.504	0.300	-1.68	.093	-1.091	0.084
Alcohol	0.102	0.297	0.34	.732	-0.480	0.684
Time	-0.005	0.003	-1.53	.126	-0.011	0.001
Random effects ([co-]variances)		Estimate	(SE)	ICC (%)	95% CI	
					Lower	Upper
Level 1	Intercept	109.284	27.721	84.777	66.472	179.670
Level 2	Intercept	6.895	1.414	5.349	4.613	10.308
	Residual	12.729	1.001		10.911	14.850

Appendix 35 Aversive scale as a predictor of a schizotypal state

Table 70

Parameter estimates for multilevel model of schizotypal state (outcome) as a function of Aversive cannabis experiences, and cannabis consumption per se

Fixed effect (intercept, slopes)	Estimate	(SE)	Z	P	95% CI	
					Lower	Upper
Intercept	**14.328**	**1.957**	**7.32**	**<.001**	**10.492**	**18.164**
Aversive scale	0.088	0.234	0.37	.708	-0.371	0.547
Cannabis consumed	**0.814**	**0.357**	**2.28**	**.023**	**0.114**	**1.514**
Caffeine	0.140	0.198	0.70	.481	-0.249	0.528
Tobacco	0.097	0.243	0.40	.689	-0.379	0.574
Alcohol	0.272	0.224	1.21	.225	-0.167	0.710
Time	-0.005	0.003	-1.93	.054	-0.010	0.0001
Random effects ([co-]variances)		Estimate	(SE)	ICC (%)	95% CI	
					Lower	Upper
Level 1	Intercept	135.050	32.61	82.847	84.131	216.785
Level 2	Intercept	13.111	1.710	8.043	10.153	16.930
	Residual	14.851	0.909		13.172	16.744

Appendix 36 Internal reliability of the aversive scale

Table 71
Table displaying internal reliability of aversive cannabis experiences

	Cronbach's α if item deleted		
	CSCU	DD	PD
Out of body experiences	.932	.919	.936
Feeling fearful	.929	.910	.935
Angry	.930	.916	.940
Paranoid	.928	.912	.934
Anxious for no reason	.927	.911	.934
Depressed	.928	.913	.937
Deluded (believing in something which afterwards you knew not to be true)	.931	.914	.934
Feeling threatened by an unknown force	.928	.912	.934
Sad	.929	.914	.937
Disturbed in your thinking	.928	.910	.933
Nervy	.927	.914	.937
Hearing things other people couldn't hear (auditory hallucinations)	.931	.915	.940
Having visions (like visual hallucinations)	.931	.918	.941
Things not feeling 'right' on your skin or in your body	.929	.911	.936
Losing your sense of reality	.930	.912	.938
Feeling like you no longer know yourself	.927	.912	.934
Fearful that you are going crazy/mad	.927	.910	.933
Paranoid without reason (AE)	.927	.911	.933
Suspicious of people, events or things without reason (AE)	.927	.910	.934
Feeling depersonalised (AE)	.928	.915	.935