

Volume 1

Prodromal symptoms in skunk users

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D.Clin.Psy. thesis, 2008
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Overview

This thesis aims to explore the effects of “Skunk,” a high potency variety of cannabis which now accounts for 81% of the cannabis sold in the UK. A causal link between cannabis use and schizophrenia has been established but little is known about the impact of skunk or whether users experience psychotic-like or prodromal symptoms. Skunk has a higher percentage of tetrahydrocannabinol (Δ -9-THC), the main psychoactive ingredient in cannabis, than traditional cannabis. Acute exposure to Δ -9-THC has been shown to cause transient psychotic symptoms in healthy individuals. However, despite the prevalence of its use, no study to date has explored the impact of skunk cannabis on recreational users. Part one of the thesis is a literature review of the evidence of how cannabis use might contribute to prodromal symptomatology of schizophrenia. It focuses on the neurobiological and cognitive effects of cannabis and how these are mediated by specific vulnerability factors. The review highlights the need for greater understanding of higher potency cannabis that dominates the UK market today.

Part two is an empirical paper that reports a study of prodromal symptoms of schizophrenia in daily skunk users. The study was part of a larger study investigating the impact of drugs being carried out at UCL. It is connected to two other DClinPsy theses separately investigating the effects of cocaine (Lisa Monaghan, Royal Holloway) and ketamine (Suzanna Duffin, UCL). To index prodromal and psychotic-like symptoms, 27 heavy skunk users and 20 non skunk using controls completed the Schizophrenia Proneness Instrument – Adult version (SPIA), the Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE) the Peters Delusion Inventory (PDI)

and the Dissociative Experiences Survey (DES). They were also administered prose recall, fluency and superstition tasks as these are key areas of cognitive impairment reported in the prodrome and psychosis. The paper reports the distinct pattern of prodromal symptomatology found in daily skunk users and highlights the need for further longitudinal studies to investigate what happens to these “prodromal” skunk users.

Part 3 comprises a critical appraisal of and reflections on the research as a whole.

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Acknowledgements

I would like to thank Val Curran, Oliver Mason and Celia Morgan for all of their support throughout the research. Thank you to the UCL graduate school for funding the research. I owe big thanks to Suzanna Duffin and Lisa Monaghan for keeping me going and keeping me sane. Finally, thank you to Simon and my family for all of their support.

Part 1

Literature Review

“How might cannabis use contribute to prodromal symptoms of schizophrenia?”

Abstract

Epidemiological studies have associated cannabis use with schizophrenia for decades. In the past decade meta-analyses of this research have helped to establish a causal link between cannabis use and the onset of psychotic symptoms as a result of both acute experimental studies and longitudinal studies of recreational use. Despite this, there is limited understanding of the mechanisms by which cannabis might contribute to the symptoms of schizophrenia. This review presents research on the effects of cannabis in relation to the symptoms of those found in the prodromal phase of schizophrenia, individuals at high risk of developing full psychotic episodes. The importance of investigating the prodrome is outlined before some of the similarities of the phenomenological experiences of the prodrome and those caused by cannabis are illustrated. The paper reviews the cognitive, neurobiological and structural evidence of how cannabis might contribute to the prodrome. The review includes the vulnerability factors that have been shown to mediate these effects. Finally, the paper highlights the evidence that the psychoactive potency of cannabis in the British market has grown and the absence of research into the effects of the recreational use of “skunk,” a high potency variety of cannabis which accounts for 81% of the cannabis sold in the UK today.

1. Introduction

This review investigates the association reported between cannabis and schizophrenia by looking at how cannabis might contribute to prodromal symptoms of schizophrenia. The paper presents the importance of investigating the prodrome and reviews the neurobiological and cognitive changes found in individuals who have been identified to be in the prodromal phase of schizophrenia. It illustrates the common neurobiological and cognitive changes that have been reported as a result of both acute administration and recreational use of cannabis. It then reviews vulnerability factors that have been shown to mediate these changes such as genotypes, schizotypy, life-events and the age of first use of cannabis as well as the dose-response findings. Finally, the paper highlights the lack of literature on the use of high potency cannabis, “skunk,” that currently dominates British cannabis consumption, and the need for further investigation.

For the purpose of this review the databases MEDLINE and PsychINFO 1966-2007 were searched and the parameters used provided papers with any one of the following key words: cannabis, marijuana, tetrahydrocannabinol, Δ -9-THC , prodrome, ultra high risk with any of these key words: cognition, neurobiology, neuropsychology.

2. Cannabis

Cannabis is the most widely used, illegal drug in the world (World Health Organisation, 2007). Cannabis use dates back to the Neolithic age (Mikuriya, 1969; Rudgeley, 1999) and it is the third most common drug of choice in Europe after alcohol and tobacco (Calafat et al., 1999). According to the European Monitoring

Centre for Drugs and Drug Addiction (EMCDDA, 2007) it is now second only to heroin as the primary substance of misuse in those seeking treatment of addiction.

The co-morbidity of substance abuse and schizophrenia is approximately 50% (Gentil, 2003). Until recently, the direction of causality between cannabis use and the experience of psychotic symptoms associated with schizophrenia has been under debate (Thornicroft, 1990). However, there has been an increase in clinical, experimental, prospective and epidemiological evidence indicating that cannabis use is a significant risk factor for the emergence of schizophrenia (van Os et al., 2002; Fergusson et al., 2006). Systematic reviews and meta-analyses have suggested that there is a causal relationship between cannabis and psychosis (Arsenault, 2004; Moore et al., 2007; Semple et al., 2005). The most recent meta analysis found an increased risk of any psychotic outcome to be approximately 40% in individuals who had ever used cannabis (pooled odds ratio = 1.41, 95%). This figure was elevated to a 50-200% increase in the risk for participants who used cannabis most heavily (Moore et al., 2007). There is also good evidence that cannabis intoxication may lead to brief psychotic episodes or recurrence of psychotic symptoms in individuals with a history of schizophrenia (Mathers and Ghodse, 1992; Fletcher and Honey, 2006). In the last two decades cannabis use has significantly increased among adolescents, and the age of first use has fallen considerably in many countries (Aust, 2002).

Both Boydell et al. (2006) and Moore et al. (2007) suggest that increased cannabis consumption may be related to the increasing prevalence of schizophrenia. Boydell et al. (2006) showed a steady increase in the number of patients who reported using

cannabis before their first episode of psychosis between 1965 and 1999 in south London. Indeed, Moore et al. (2007) estimate that 14% of those currently diagnosed with schizophrenia would not have been if they had not used cannabis.

The primary psychoactive constituent of the hemp plant *Cannabis Sativa* is the cannabinoid, delta-9-tetrahydrocannabinol (Δ -9-THC). Cannabinoids have a long history of consumption for recreational, religious and medical reasons. In humans, cannabinoids are known to produce euphoria, pain relief, enhancement of sensory perception, tachycardia, antinociception, difficulties in concentration and impairment of memory (Solowij, 1998). Taken in high doses (acutely), Δ -9-THC has been reported to produce psychotic symptoms such as visual and auditory hallucinations, delusional ideas and thought disorder in healthy volunteers (D' Souza, 2004). Δ -9-THC has also been shown to exacerbate positive and negative symptoms, perceptual alterations and learning and memory deficits in patients with schizophrenia (D'Souza et al., 2005).

However, from their examination of the evidence, Arsenault et al. (2004) conclude that cannabis use appears to be neither a sufficient nor necessary cause for psychosis. They state that it is a component cause that is part of a complex constellation of factors leading to psychosis and just how Δ -9-THC in cannabis contributes to psychotic symptoms remains a major question.

3. Why investigate the prodrome?

In 1997 Knapp et al. estimated the total cost of schizophrenia to the National Health Service (NHS) to be approximately 2.6 billion per year (5.4% of the total NHS inpatient costs). There is a vast amount of epidemiological evidence associating cannabis and schizophrenia but limited literature on how cannabis use might contribute to individuals developing the disorder. The construct of “the prodrome” is still much debated but it is agreed that there is a period of symptom development before the onset of diagnosable schizophrenia. In the Manheim schizophrenia study (Hafner et al, 1999), a large retrospective study of the early course of first episode schizophrenia, negative and cognitive-perceptive disturbances were found in 73% of patients on average 5 years before the first psychotic symptoms occurred and 6.3 years before the first hospitalization. Whether or not these changes turn out to be ‘prodromal’ (heralding a transition to psychosis) or not, they clearly present a period of ultra-high risk for subsequent psychopathology.

As the NHS improves its focus on preventative mental health treatment, the need for understanding the developmental pathways of disorders becomes greater. Research on the ‘prodrome’ or ultra high risk period can contribute to a preventative approach for mental health services in terms of both pharmacological and therapeutic intervention. Predicting transitions to psychosis is difficult but the more we can understand about common pre-psychotic experiences the better. Understanding links between the phenomenology and neurobiology of pre-psychotic experiences can facilitate predictions and the development of services to help people in the distress associated with the disorder. Early intervention is crucial if services hope to prevent the psychological and

social disruption that results from psychosis; delay in such intervention is associated with poorer outcome (Johnstone et al., 1986; Loebel et al., 1992).

It has been proposed that cannabis use leads to cognitive deficits of a similar nature to those seen in schizophrenia but of a lower magnitude (Solowij et al., 2007). From a neurobiological perspective, investigations into a drug like cannabis that causes dysregulation of dopaminergic neurotransmission might model the dysregulation reported in people with prodromal symptoms of schizophrenia. Drug models of those at risk of schizophrenia can be useful if a drug provokes features characteristic of the disorder. Drug models are especially helpful in developing new treatments and our understanding of the pathophysiology of psychosis.

4. Identifying the prodrome

Although identifying the schizophrenia prodrome is associated with substantial challenges, it is an area of study that has recently made considerable progress (White et al., 2006). The prodrome precedes the acute phase of a psychotic episode and extends from pre-morbid (“normal”) functioning to the onset of full symptoms of schizophrenia. Operationally, the prodrome is defined by duration of time, starting with the onset of decline in the baseline level of functioning and ending at the time when the criteria for a schizophrenia spectrum diagnosis is met (Yung, 1996). It is characterised by the progressive deterioration of functioning and emergence of sub-threshold psychotic symptoms. If recognised prospectively, the existence of a defined prodrome offers the opportunity for early intervention. This prodromal period can vary in time from 2-6

years (Addington and Addington, 1998; Schultze-Lutter et al., 2007) and is associated with significant levels of disability.

While the clinical hallmark of schizophrenia is psychosis (Kapur, 2003), defining the prodrome has proved difficult. Fundamentally, the prodrome is a retrospective concept – only confirmed by the subsequent development of the acute, fully developed illness. Furthermore, many of the symptoms attributed to the prodrome are highly non-specific for psychosis (Phillips et al., 2000). The most common prodromal symptoms include magical thinking, unusual perceptual experiences, social isolation, withdrawal, impaired role function, blunted affect, depressed mood, sleep disturbance, reduced concentration, irritability, anxiety and lack of initiative or energy (Yung, 2003).

Operationally, two schools of thought predominate: the ‘ultra high risk’ (UHR) approach and the Basic Symptom Approach (Olsen and Rosenbaum, 2006). Putative risk criteria for psychosis were first defined and evaluated by Yung et al. (1996, 2003). The Ultra High Risk” (UHR) criteria reflect the influence of retrospective patient reports, symptom research and genetic risk studies. They focus on attenuated positive symptoms, brief intermittent psychotic states and a genetic risk for psychosis coupled with recent significant loss of social and instrumental capacities. Studies on UHR individuals have reported first-year transition rates to frank psychosis between 34% (Yung et al., 2004) and 65% (Miller et al., 2002) for those not participating in treatment groups of preventative intervention studies.

Since then, a number of different instruments measuring the prodrome have been produced. These include the Structured Interview for Prodromal Symptoms (SIPS) from

the PRIME prodromal team at Yale university (McGlashan et al., 2001), the Comprehensive Assessment of At Risk Mental States (CAARMS) from the University of Melbourne (Yung et al., 2003), and The Schizophrenia Proneness Instrument (SPI) from the University of Cologne (Schultze-Lutter et al., 2004). In terms of validity, many of the studies of these instruments suffer from small sample sizes and low participation rates (Miller et al., 2003) and the measurement of the prodrome is still in development.

Schultze- Lutter et al's (2004) Schizophrenia Proneness Instrument (SPI) is based on the basic symptom concept. This is an integrative approach similar to the vulnerability-stress-coping model (Nuechterlein, 1992) that originates in the observation of deficits that were perceived by individuals with schizophrenia pre-psychotically, years before the first psychotic manifestation, or prior to relapses. Schultze- Lutter et al.'s basic symptoms are mild, often sub-clinical but self-experienced disturbances of drive and affect, of thought, speech, perception, proprioception and motor action as well as of vegetative functions. Klosterkötter et al. (2001) assessed German patients for the presence of "basic symptoms" using the Bonn Scale for the Assessment of Basic Symptoms (BSABS) and in an average follow-up period of 9.6 years, 49.4% of the cohort had developed schizophrenia. The prodromal symptoms that occurred in 25% of the patients who later developed acute schizophrenia included decreased ability to discriminate ideas of reference, derealisation and visual and acoustic disturbances in perception. Simon et al. (2006) extended the Ultra High Risk model (Yung et al., 2004) to determine initial prodromal states (IPS) with basic symptoms which have been shown to define more homogenous subgroups than UHR criteria alone.

In their recent study examining individuals who go on to develop schizophrenia, Schultze-Lutter et al (2007) reported twenty seven basic symptoms that were significantly more frequent at the first examination in any prodromal group when compared with the control group. These were mainly disturbances of attention, thought, perception and motor action. From their study, they conclude the existence of diverse prodromal pathways (as opposed to a singular concept).

Yung et al., (2005) have added some of Schultze-Lutter et al's Basic Symptoms to their Comprehensive Assessment of At Risk Mental States (CAARMS) for the identification of individuals likely to develop psychotic disorder. Table 1 shows the subscales that they propose identify the prodromal features of schizophrenia and the research groups who have identified these elements as "prodromal."

Table 1. Subscales proposed for the Prodrome/ Ultra High Risk for Schizophrenia

Prodrome Subscale	Reported in Prodrome/ UHR
1. Disorder of Thought Content (Assessing obsessions, delusional mood, over-valued ideas and delusions)	Yung et al., 2005: McGlashan et al 2001: Schultze- Lutter et al., 2004
2. Perceptual Abnormalities (Assessing distortions, illusions and hallucinations)	Yung et al., 2005: McGlashan et al 2001: Verdoux et al., 2003
3. Conceptual Disorganisation (Assessing subjectively experienced difficulties with forming thoughts as well as formal thought disorder)	Yung et al., 2005: McGlashan et al 2001: Schultze- Lutter et al., 2004
4. Motor Changes (Assessing subjectively experienced difficulties with movement as well as objective signs of catatonia)	Yung et al., 2005: McGlashan et al 2001: Schultze- Lutter et al., 2004; Niendam et al., 2006
5. Concentration and Attention	Yung et al., 2005: Schultze- Lutter et al., 2004; Hambrecht et al., McGlashan et al 2001: 2002; Simon et al., 2006: Hawkins et al; 2004:Hawkins et al., 2004:Gschwandtner et al., 2003
6. Disorders of Emotion and Affect (Assessing subjective sense of change in emotions and objective rating of blunting of affect)	Yung et al., 2005: McGlashan et al 2001: Schultze- Lutter et al., 2004
7. Subjectively Impaired Energy	Yung et al., 2005: McGlashan et al 2001: Simon et al., 2006 (avolition)
8. Impaired Tolerance to Normal Stress	Yung et al., 2005: McGlashan et al 2001: Schultze- Lutter et al., 2004

5. Prodromal symptoms reported as a result of cannabis use

Although no single study has systematically investigated whether heavy cannabis users report experiencing symptoms identified in the prodrome, several researchers have studied the impact of the acute administration of Δ -9-THC and of disturbances reported as a result of recreational cannabis use in one or more area of psychological functioning. Table 2 summarises these organised according to the ‘UHR symptom’ breakdown described above.

Table 2. Prodromal Symptoms reported as a result of acute administration of Δ -9-THC and recreational use of Cannabis.

Ultra High Risk Symptom	Reported in administration of acute Δ-9-THC	Reported in Recreational Cannabis users
1. Disorder of Thought Content	D’Souza et al., 2004	
2. Perceptual Abnormalities	D’Souza et al., 2004	Verdoux et al., 2003; Schiffman et al., 2005
3. Conceptual Disorganisation	D’Souza et al., 2004	
4. Motor Changes	Ramaekers et al., 2006	Varma et al., 1988;
5. Concentration and Attention	Fletcher et al., 1996 Solowij et al., 1998 D’Souza et al., 2004 Wadsworth et al., 2006	Pope et al., 1995; Solowij et al., 1995
6. Disorders of Emotion and Affect	Wadsworth et al., 2006	Lynskey et al., 2004
7. Subjectively Impaired Energy		Barkus et al., 2005
8. Impaired Tolerance to Normal Stress	D’Souza et al., 2004	Patton et al., 2002

5.1 Disorder of Thought, Perceptual Abnormalities and Conceptual

Disorganisation

There is little dispute that cannabis intoxication can lead to acute transient psychotic episodes in some individuals (Arsenault et al., 2004). D'Souza et al. (2004) reported that acute administration of Δ -9-THC produced transient positive and negative symptoms resembling those in schizophrenia. In their 3- day, double-blind, randomized and counterbalanced study, the behavioural, cognitive and endocrine effects of 0, 2.5 and 5mg of intravenous Δ -9-THC were characterized in 22 healthy individuals who had been exposed to cannabis but never diagnosed with a cannabis abuse disorder. Participants were screened for any vulnerability to schizophrenia. Δ -9-THC produced symptoms including suspiciousness, unusual thoughts, paranoia, thought disorder, thought blocking, blunted affect, reduced spontaneity, reduced interaction with the interviewer and problems with memory and attention. In a separate study, using an experience sampling method, Verdoux et al., (2003) found that in daily life, recreational cannabis use is an independent predictor of unusual perceptual experiences.

5.2 Motor Changes

The motor impact of cannabis has been investigated with particular focus on driving (Robb, 1993). There is consistent evidence that consumption of cannabis impairs motor control. Most of the studies of motor control impairment have used tasks such as maintaining a stylus within a fixed target area or remaining balanced while stationary on a platform supported by a fulcrum. Even for low doses (10 μ g/kg), hand and body

instability increases. The effect is dose related in that higher levels of consumption produce proportionally greater instability. Robb, 1993 suggests that the consumption of cannabis interferes with processing of proprioceptive feedback involved in motor control.

Varma et al. (1988) studied 26 Indian cannabis users and found they reacted significantly more slowly in perceptual-motor tasks than controls. Ramaekers et al. (2006) also reported deficits in control of motor impulsivity as a result of cannabis intoxication. Those administered higher doses showed greater difficulty inhibiting an activated or pre-cued response leading to errors of commission.

5.3 Concentration and Attention

A host of studies have identified difficulties in concentration and attention as a result of both acute Δ -9-THC and recreational cannabis use. D'Souza et al. (2004) reported transient impairments in attention in their research on acutely administering Δ -9-THC and Solowij et al. (1995) found that the ability to focus attention and filter out irrelevant information was impaired in cannabis users. Barnett et al. (1985) found a significant linear correlation between tracking errors under divided attention and THC plasma levels over 25 ng/ml among cannabis users assessed approximately 2 hours after smoking. Pope et al. (1995) tested the cognitive functioning of 64 heavy cannabis users, whom had smoked cannabis for at least 27 out of the previous 30 days. Heavy users showed significant deficits in sustaining and shifting attention.

5.4 Changes in Emotion and Affect

The negative changes in mood that are reported in the prodrome can also be found in investigations of the impact of cannabis use (Wadsworth et al., 2006). Research on the affective states of cannabis users has suggested that they are more likely than non-users to report feeling depressed (Bovasso, 2001). Beautrais et al. (1999) report that individuals with cannabis dependence (as diagnosed in DSM-IV) are at greater risk of suicide attempts. In their examination of the evidence of depression in cannabis users, Degenhardt et al. (2003) conclude that heavy cannabis use and depression are associated and evidence from longitudinal studies suggests that heavy cannabis use may increase depressive symptoms among some users. However, Degenhardt et al. (2003) state that it is still too early to rule out the hypothesis that the association is due to common social, family and contextual factors that increase risks of both heavy cannabis use and depression.

On the other hand, in a twin study, Lynskey et al. (2004) found that the twin who was cannabis dependent was more 2.5 to 2.9 times more likely to have had a major depressive disorder, suicidal ideation and attempted suicide than their non-cannabis using twin. Interestingly, this was only the case for dizygotic twins and not for monozygotic twins. This suggests that one of the factors contributing to the comorbidity of cannabis dependence and major depressive disorder may be a genetic element. Both the Degenhardt (2003) review and the Lynskey (2004) study point to vulnerability factors which will be discussed further in this review.

5.5 Decrease in Energy

A decrease in mental energy has been reported as an effect of cannabis use. The “amotivational syndrome” amongst cannabis users described by McGlothlin and West (1968) includes apathy, loss of effectiveness, a diminished ability to concentrate, to follow routines, and successfully master new material. This loss of motivation as a negative effect of cannabis was reported by Barkus et al., (2005). However this “syndrome” of apathy and lethargy has been poorly documented in uncontrolled studies in the past. It is difficult to distinguish the effects of heavy cannabis use from those of poverty and low socioeconomic status, pre-existing personality and other psychiatric disorders. Musty and Kaback (1995) attributed the amotivational symptoms they reported in a sample of heavy cannabis users to coexisting depressive symptoms and other studies have not found an association between cannabis use and lack of motivation (Foltin et al., 1990; Barnwell et al., 2006). However, in a recent online study of 2500 adult daily cannabis users, dependent users did report lower levels of motivation than non-dependent users (Looby and Earleywine, 2007).

5.6 Changes in Tolerance to Stress

D’Souza et al. (2004) found that Δ -9-THC increased levels of the stress hormone cortisol and it is not surprising that heavy cannabis users show a decreased tolerance to stress. In a seven wave cohort study involving 1601 students over six years (Patton et al., 2002), daily cannabis use in young women was associated with an over five-fold increase in the odds of reporting a state of anxiety (after adjustment for other substance misuse).

Section 5 has outlined the studies that have reported different high risk symptoms in recreational cannabis users and as a result of the acute administration of Δ -9-THC. Clearly, associations do not allow us to assume that these high risk symptoms are caused by Δ -9-THC and there may well be other factors that cause both or incidental issues around testing such as motivation and the acute effects of cannabis. Section 7 addresses vulnerability factors that have been shown to mediate these associations.

Evidence of the link between cannabis and the prodrome

The following section addresses the cognitive, neurobiological and structural evidence that supports the link between cannabis use and symptoms identified in the prodrome.

6.1 Cognitive evidence for the link between cannabis and the prodrome

Over the last 50 years empirical research has demonstrated that cognitive deficits are a core feature of schizophrenia (Heinrichs and Zakznis, 1998). Cognitive impairment in prodromal patients who have gone on to develop schizophrenia has been widely reported using evidence from baseline assessments on neuropsychological test performance (Hambrecht et al., 2002; Simon et al., 2006). The main deficits have been found in memory, attention, language and executive function. These are deficits that have also been sometimes reported in cannabis users, although the research is not consistent. Solowij et al. (2007) argue that the similarities of these deficits provide a link in the experience of those in the prodrome and heavy cannabis users and illustrates how cannabis users can also be “at risk.”

From a phenomenological perspective, it is understandable how individuals who are finding it difficult to remember, sustain attention, communicate, monitor their behaviour and thoughts and plan and organise themselves might find it harder to process their experiences. It is not difficult to imagine how these deficits may lead to confusion, misattribution and distorted thinking. The following section provides a summary of the cognitive deficits reported in prodromal individuals (6.1.1) before describing the deficits reported as a result of acute Δ -9-THC and among recreational cannabis users (6.1.2). The section concludes with the question of the duration of the cognitive deficits of

cannabis use (6.1.3). Table 3. presents a summary of studies (produced from the research criteria outlined in section 1) reporting cognitive deficits (i) in the prodrome (ii) as a result of acute and (iii) among recreational cannabis users.

Table 3. Summary of studies reporting cognitive deficits in individuals at ultra high risk or in the schizophrenia “prodrome,” following acute cannabis administration and in recreational cannabis users.

Cognitive function assessed	Prodrome/ UHR	Acute Δ-9-THC	Recreational Cannabis users
Verbal memory	Curran et al., 2002; Hawkins et al., 2004; Lenez, 2006; Niendam, 2006; Pukrop et al 2006	Fletcher et al 1996; Messinis et al., 2007	Heishman et al., 1997; Varmer et al, 1988
Working memory	Wood et al., 2003; Simon et al., 2006; Niendam et al., 2007; Gshwandtner et al., 2003	D’Souza et al., 2004; Llan et al., 2004	Schwartz et al., 1989; Pope et al., 1995: 2001
Episodic memory		Curran et al., 2002; Llan et al., 2004	
Visual Reproduction	Wood et al, 2005; Parnas et al., 2001; Niendam, 2007		
Verbal fluency	Simon et al., 2006; Pukrop et al., 2007	Curran et al., 2002	Messinis et al., 2006
Verbal expression	Schultze-Lutter et al., 2004		Block and Ghoneim, 1993

Table continued overleaf...

Cognitive function assessed	Prodrome/ UHR	Acute Δ-9-THC	Recreational Cannabis users
Attention	Hambrecht et al., 2002; Hawkins et al., 2004; Gschwandtner et al 2003	Barnett et al., 1995; Fletcher et al., 1996; Solowij et al., 1998; D'Souza et al., 2004; Wadsworth et al 2006; O'Leary et al., 2002; Pope et al., 1995	Pope et al., 1995; Pope and Yurgelun-Todd, 1996
Executive Function	Gschwandtner et al 2003; Hawkins et al., 2004; Simon et al 2006; Niendam et al., 2007	O'Leary et al., 2002; Pope et al., 1995	Bolla et al., 2002; Ramaekers et al., 2006
Processing speed	Niendam et al., 2006; Niendam et al, 2007; Pukrop et al., 2007;		Fried, Watkinson and Gray, 2005: Ghaffar & Feinstein, 2008
Psychomotor speed/ reaction times	Niendam et al., 2006; Gschwandtner et al., 2003	Chait and Pierri, 1992; Curran et al., 2002; Ramaekers et al., 2006	Varma et al., 1988

6.1.1 Cognitive deficits found in prodromal individuals

Memory - Three longitudinal studies provide evidence for memory deficits from baseline assessments comparing patients with UHR who went on to develop psychosis with UHR patients who did not within 12 months: Wood et al. (2005) observed that verbal memory

and visual reproduction impairments were specific to UHR patients who developed psychosis; Lenez et al. (2006) found significantly lower verbal memory scores in UHR patients who later developed psychosis and Whyte et al. (2006) identified greater verbal learning impairment in high-risk subjects who later became psychotic. Memory deficits were also identified by Niendam et al. (2006) in UHR individuals using the SIPS and Gschwandster et al. (2003) using the IPS. Poorer verbal learning and memory performance was also significantly associated with poorer global functioning.

Processing Speed - Niendam et al. (2006) report that deficits in cognition have been shown to occur years before the development of overt psychotic symptoms. They identified 45 individuals as ultra-high risk (UHR) for psychosis using the Structured Interview for Prodromal Syndrome (SIPS, McGlashan et al. 2001). They reported that, despite the absence of fully psychotic symptoms, participants showed significant deficits in speed of processing information. This finding has been replicated by Pukrop et al. (2007).

Attention – Hambrecht et al. (2002) at the Cologne Early Recognition Centre have found neuropsychological evidence for the prodromal symptom of reported difficulties of attention. They used the Continuous Performance Test (Cornblatt et al., 1999) with individuals with a diagnosis of schizophrenia, individuals with identified prodromal symptoms of schizophrenia and controls. Their results suggest that the deficit in attention is progressive throughout the prodromal period. Individuals with prodromal symptoms scored significantly lower than controls but those with diagnoses of schizophrenia scored the lowest. However, in an outpatient clinic for early psychosis in Switzerland, no difficulties of sustained attention were reported in some of the

individuals at high risk and this varied according to inclusion criteria (Simon et al., 2006).

Executive function - This is another domain that has been reported to be impaired in individuals at high risk (Simon et al., 2006; Pukrop et al., 2007). Niendam et al (2007) studied the everyday behavioural manifestations of executive dysfunction in individuals at UHR for psychosis. Their results indicated a high proportion (58%) of UHR show clinically significant behavioural signs of executive dysfunction according to parent report on the BRIEF (Behaviour Rating Inventory of Executive Function) (Gioia et al., 2000a). Difficulties with executive function were also found using objective measures in individuals identified to be in an “Initial Prodromal State” (IPS) (Hawkins et al., 2004; Simon et al 2006 and Gshwandtner et al., 2003 in Germany).

Language – Language deficits have also been reported in individuals at high risk (as defined by the UHR criteria). The findings of Simon et al., (2006) support the previously reported memory and executive function impairments as well as language impairments tested by letter and category fluency and verbal IQ. This has also been supported by Pukrop et al. (2007) whose findings were that individuals at greater risk showed greater impairment suggesting a progression of cognitive deficits in the prodrome before frank psychosis.

Motor Speed - Individuals in IPS and UHR for psychosis have been reported to have poorer reaction times than controls (Gshwandtner et al., 2003; Niendam et al., 2006)

Although significant cognitive differences between UHR/ IPS groups and controls have been reported, it is important to note that these were not unilateral differences and results are not consistent. Table 3 does not include studies that have not found some of the cognitive deficits identified by others. For example, Parnas et al. (2001) and Pukrop et al. (2007) found verbal memory impairments but not the spatial memory impairments that have been reported by others (Brewer et al, 2005; Niendam, 2007). Studying people who are “prodromal” or “at risk” is not easy. The significant group differences could be due to a number of alternative variables. Fundamentally, it is difficult to bring the evidence of these constructs together when research groups are using different criteria for the prodrome with different samples, continuums and transition rates. Furthermore, a significant proportion of those considered to be at risk will prove to be false-positives and another subset may progress with marked cognitive impairment in time.

6.1.2 Cognitive deficits reported following acute Δ -9-THC administration and in recreational cannabis users.

Memory - Acute neuropsychological effects (within 12–24 h) of both acutely administered Δ -9-THC and recreational cannabis use include deficits in attention, executive functioning, and short-term memory (O'Leary et al., 2002; Pope et al., 1995). One of the most consistently reported behavioural effects of Δ -9-THC is a disruption in the free recall of newly learned information. Recall of items learned before cannabis use is generally not affected, suggesting that Δ -9-THC impairs learning and the acquisition of information but not its retrieval from memory (Curran et al., 2002; D'Souza et al, 2004). Curran et al., (2002) investigated the cognitive effects of acute oral Δ -9-THC in

infrequent cannabis users and reported that oral Δ -9-THC impaired episodic memory and learning in a dose-dependent manner whilst leaving intact performance on tasks tapping perceptual priming and working memory. Llan et al. (2004) found that both episodic and working memory were impaired after subjects smoked 3.5% Δ -9-THC. Wadsworth et al. (2006) reported that heavy recreational cannabis use was associated with working memory problems and poorer episodic memory and Solowij et al. (2002) found that long-term cannabis users show impairments in memory and attention that endured beyond the period of intoxication and worsened with increasing years of regular cannabis use.

Attention – As detailed earlier (5.3) impairment in attention has been observed for several days following cannabis use (Pope et al., 1995). Attention deficits have also been observed in acutely administered Δ -9-THC (Barnett et al., 1995; Wadsworth et al 2006).

Processing speed – Processing speed has been reported to be slower in heavy cannabis users (Kelleher et al., 2004; Fried et al., 2005). Although with a small sample size, in a recent study, Ghaffar and Feinstein (2008) found that Multiple Sclerosis sufferers who smoked cannabis processed information significantly slower than their non-smoking controls.

Language - Block and Ghoneim (1993) matched heavy cannabis users and nonusers on the basis of their intellectual functioning before the onset of drug use and found

that subjects who used cannabis 7 or more times weekly for at least 2 years showed deficits in verbal expression as well as selective impairments in memory.

Executive Function – Bolla et al. (2002) reported significant deficits in executive function in chronic users of cannabis. Furthermore, in their study administering 0, 250, and 500 $\mu\text{g}/\text{kg}$ $\Delta\text{-9-THC}$ to participants, Ramaekers et al. (2006) found that these impairments in executive function were dose-related. They also found dose related impairments in motor control.

Perceptuo-Motor Function - Varma et al. (1988) tested a range of memory functions in 26 long term heavy cannabis users following 12 weeks of abstinence. Using a locally developed and validated test battery which assessed memory in 10 different domains, they found significantly poor performance on a pencil-tapping test of perceptuo-motor function in cannabis users as well as impairments in short-term memory.

Psychomotor speed – Reaction times have been showed to be delayed as a result of the acute administration of $\Delta\text{-9-THC}$ (Chait and Pierri, 1992; Curran et al., 2002; Ramaekers et al., 2006) as well as in heavy recreational users (Varma et al., 1988; Wadsworth et al., 2006).

Again, it is easy to consider the phenomenological difficulties that might be experienced as a result of difficulties with memory, attention, language, executive function and processing information. The cognitive findings show how cannabis use

can put individuals at risk of experiencing similar cognitive difficulties reported in the prodrome.

6.1.3 Duration of Cognitive Deficits of Cannabis Use

It is important to note that the duration of the deficits following cannabis use has been questioned in terms of its permanent impact on cognitive functions. The elimination half-life of Δ -9-THC has been reported to vary from 18 hours to 4.3 days (Hunt and Jones, 1980; Kelly, 1992) and D'Souza et al (2004, 2005) showed acute impairments were transient. However, in naturalistic studies of recreational use, the evidence is conflicting. Neuropsychological deficits found in heavy cannabis users have been shown to lessen a few days after cannabis use is stopped (Curran et al, 2002). Eldreth et al. (2004) used a modified version of the Stroop task to determine whether 25-day abstinent heavy cannabis users have persistent deficits in executive cognitive functioning. However, they showed no deficits in performance on the modified version of the Stroop task when compared to a non-using comparison group. On the other hand, Bolla et al., (2002) found persistent deficits in decision making, memory, executive functioning, psychomotor speed, and manual dexterity among heavy cannabis users who had been abstinent for 25 days.

Pope et al (2001) found that with abstinence of 28 days, long-term cannabis users showed no significant differences compared to non-using control groups. Lyons et al (2004) carried out a twin study with 54 monozygotic male twin pairs, discordant for regular cannabis use in which neither twin used any other illicit drug regularly. A minimum of 1 year had passed since the cannabis-using twins had last used the drug,

and a mean of almost 20 years had passed since the last time cannabis had been used regularly. Twins were administered a comprehensive neuropsychological test battery to assess general intelligence, executive functioning, attention, memory and motor skills. They found that of these, cannabis-using twins only significantly differed from their non-using co-twins on the performance of the block design subtest of the Wechsler Adult Intelligence Scale. Executive functioning, attention, memory and motor skills were not significantly different, indicating an absence of marked long-term residual effects of cannabis use on cognitive abilities. However, it is unlikely that the twins in this study recruited from the Vietnam Era Twin Registry for the study were smoking the same kind of cannabis that dominates the UK market today.

6.2 Neurobiological evidence for the link between cannabis and the prodrome

Although there has been a great deal of research focusing on the neurobiology of schizophrenia, there is relatively little on the prodrome due to the difficulty of identifying people at high risk who do go on to develop schizophrenia. However, we can learn from the neurobiological changes identified in those suffering from the disorder. The following section reports evidence for a neurobiological link between cannabis and psychosis. This derives from dysregulations in both dopaminergic (6.2.1) and endocannabinoid (endogenous cannabinoid) (6.2.2) systems in individuals suffering with schizophrenia and the effects of Δ -9-THC on those same systems. It also discusses recent findings of the impact of another cannabinoid found in cannabis: cannabidiol (6.2.3).

6.2.1 The Dopamine Hypothesis of Psychosis and Δ -9-THC Induced Dopamine Dysregulation

The Dopamine Hypothesis

For nearly three decades the dominant hypothesis about the pathophysiology of schizophrenia has been based on dysregulation of dopaminergic neurotransmission (Snyder, 1976; Carlsson, 1998). Laruelle and Abi-Dargham (1999) suggest that “Dopamine is the wind of the psychotic fire.” Although there is evidence that other neurotransmitter systems also contribute to the psychopathology of schizophrenia (Holcombe et al., 2004), the first-line treatment of positive symptoms is invariably with antipsychotics that block dopamine D2 receptors. Neuroimaging studies have shown heightened dopaminergic transmission in patients with schizophrenia; in the acute phase, psychotic patients show a higher synthesis of dopamine, heightened dopamine release in response to an impulse and a heightened level of synaptic dopamine (Kapur, 2003).

Kapur’s (2003) framework for linking the psychological and biological in psychosis posits that a central role of dopamine is to mediate the “salience” of environmental events and internal representations. Kapur proposes that a dysregulated, hyperdopaminergic state leads to an aberrant assignment of salience to elements of one’s experience. Delusions are a cognitive effort by the patient to make sense of aberrantly salient experiences while hallucinations reflect a direct experience of the aberrant salience of internal representations. Antipsychotics dampen the salience of abnormal experience and thus often help reduce positive symptoms. If the antipsychotic treatment is stopped then dopaminergic dysregulation may occur

leading to a relapse. Thus the altered perceptions identified in prodromal individuals, or individuals at high risk; captivation of attention by details of the visual field and unstable ideas of reference are thought to also be a result of dopamine dysregulation. Given early, atypical antipsychotics such as risperidone or olanzapine have been shown to ameliorate progression in individuals at risk of developing a psychotic episode (for review see Thomas and Woods, 2006).

Δ -9-THC Dopamine Dysregulation

Research on the neurobiological impact of Δ -9-THC on the brain has ranged from animal studies to acute exposure in humans. The Δ -9-THC in cannabis increases the activity of dopaminergic neurons in the ventral tegmental area-mesolimbic pathway and facilitates the release of dopamine in the brain. In-vivo SPECT studies show increased synaptic dopaminergic activity in response to cannabis consumption (Voruganti, et al., 2001). Lupica and Riegal (2005) have shown that cannabis significantly increases neuronal firing and burst firing and that Δ -9-THC increases the release of dopamine at synaptic terminal fields in the striatum and prefrontal cortex. Kapur's 'motivational salience hypothesis' of schizophrenia also explains why, under the influence of cannabis, a hyperdopaminergic state may lead to the experience of positive symptoms also experienced in schizophrenia. Since dopaminergic circuits are known to play a pivotal role in mediating the reinforcing effects of most drugs of abuse, the enhanced dopaminergic drive elicited by cannabinoids is believed to underlie the reinforcing effects of cannabis (Ameri, 1999).

6.2.2 Endogenous Cannabinoid Dysregulation in Psychosis and Δ -9-THC induced Cannabinoid Dysregulation

Endogenous Cannabinoid Dysregulation in Psychosis

In the last few decades, a major cannabinoid receptor “CB1” and the endogenous cannabinoid ligand, “anandamide,” have been discovered (Devane et al., 1988; 1992). It has been hypothesised that a dysfunction in endocannabinoid signaling may be associated with schizophrenia. Giuffrida et al. (2004) have shown that cerebrospinal fluid (CSF) from individuals suffering from schizophrenia contains significantly higher levels of anandamide than CSF from healthy volunteers. They hypothesised that endocannabinoids such as anandamide may enhance dopaminergic neurotransmission by increasing dopamine turnover. They also found that CSF anandamide levels in antipsychotic-naïve people suffering from first-episode paranoid schizophrenia are eight-fold higher than in healthy controls. However, interpretation of these results is obscured by the small number of subjects involved and the lack of systematic comparison with other mental disorders in which endocannabinoid signaling also might be dysregulated. On the other hand, anandamide has been shown to impair working memory in rats (Mallet, 1996) and, of all cognitive impairments reported in schizophrenia, the most marked are in the memory domain (Saykin et al., 1991).

Giuffrida et al., (2004) also investigated the effects of antipsychotics on CSF anandamide levels. They found that the alteration was absent in those that had been treated with antipsychotics which antagonize D2 receptors. When they compared Anandamide levels in those with schizophrenia who were not medicated, they found that

Anandamide was negatively correlated with psychotic symptoms suggesting that the elevation of anandamide may reflect a compensatory adaptation to the disease state.

The brain's own cannabinoids are a family of bioactive lipids that activate CB1 cannabinoid receptors in synapses in the brain and exert intense emotional and cognitive effects. CB1 receptor activation has been shown to stimulate dopamine transmission (Pistis et al., 2001). CB1 receptors are particularly dense in the hippocampus, cerebellum and basal ganglia and relatively dense in the cerebral cortex, amygdala and some brain stem nuclei (Chevalleyre et al., 2006). These are areas of the brain that are involved in the control of motor functions, cognition and motivation (Giuffrida et al., 2004). Cannabinoids also inhibit noradrenaline release at the sympathetic nerve terminals and centrally in the hippocampus, cortex and cerebellum. Noradrenaline is involved in the control of alertness and wakefulness.

Endocannabinoids allow cells to fine-tune their input and act as important synaptic modulators. A proposed function of CB1 receptors on synaptic terminals is that of a safety mechanism to prevent local network excitability progressing to excitotoxicity and seizures Sarne et al. (2005). Cannabinoids acutely reduce glutamate release and block hippocampal long-term potentiation (LTP), a potential substrate for learning and memory (Hoffman et al., 2007). LTP is a process by which the responsiveness of a neuron to a particular input becomes sensitized with repeated stimulation and is most prevalent in the hippocampus, an area of the brain important in memory (Ameri, 1999). Furthermore, Kim and Thayer (2001) report that cannabinoids inhibit the formation of new synapses between hippocampal neurons in culture. Functional imaging studies also

reveal that people with diagnoses of schizophrenia show reduced activation of the hippocampus in cognitive tasks like spatial navigation that are hippocampus dependent (Weinberger, 1997).

Δ -9-THC Cannabinoid Dysregulation

The main psychological effects of Δ -9-THC stem from activation of the CB1 receptor in the brain. When individuals take cannabis the synaptic modulation by the brain's endocannabinoids is disrupted, Δ -9-THC activates CB1 receptors and the cells are flooded. The effects of CB1 activation on hippocampal LTP may explain the amnesic effects of Δ -9-THC. Curran et al. (2002) describe how memory impairment is a predictable effect of Δ -9-THC given the uneven distribution of cannabinoid receptors in the brain with the highest densities in the hippocampus, basal ganglia and cerebellum. Animal studies suggest Δ -9-THC induced cell death with shrinkage of neurons and DNA fragmentation in the hippocampus (Ameri, 1999). As working memory and episodic memory rely on brain regions dense in CB1 receptors, it is unsurprising that they tend to be disrupted in acute cannabis intoxication. Δ -9-THC also increases cortisol levels via activation of the CB1 receptor. High levels of this stress hormone have been associated with schizophreniform symptomatology and memory deficits (Walder et al., 2000).

The chronic effects of cannabis suggest an adaptive process. It has been shown postmortem that chronic cannabis abusers have a downregulation of cannabinoid receptors. This was illustrated by a significantly lower density of cannabinoid receptor positive neurons than in control brains in regions of the putamen, caudate, nucleus accumbens and hippocampus (Ledent, 1999). Leweke et al. (2007) investigated the

effects of cannabis on the brain's anandamide levels. They found that low-frequency cannabis users with schizophrenia exhibited more than 10-fold higher CSF anandamide levels than did high-frequency users with schizophrenia, healthy low-frequency or high-frequency users. CSF anandamide levels and disease symptoms were negatively correlated in both user groups. Leweke et al. (2007) suggest that the results indicate that frequent cannabis exposure may down-regulate anandamide signalling in the central nervous system of patients with schizophrenia, but not of healthy individuals. Their findings suggest that alterations in endocannabinoid signaling might be an important component of the mechanism through which cannabis impacts upon mental health. Their findings also provide a further link between endocannabinoid dysregulation in schizophrenia and that resulting from cannabis use.

6.2.3 Cannabidiol

Although Δ -9-THC is the main psychoactive ingredient in cannabis it is important to emphasize that cannabis comprises over 60 cannabinoids that are unique to the plant as well as 400 different chemicals. Different strains of cannabis have varied compositions of these chemicals. Cannabidiol (CBD) is another cannabinoid in cannabis that has been identified as having neuroprotective factors (Iuvone et al., 2004) as well as anxiolytic effects (Leweke, 2007). It is a major constituent of the plant.

It has been proposed that CBD mediates the effects of Δ -9-THC and there has been evidence that CBD may block the conversion of Δ -9-THC to the more psychoactive 11-hydroxi- Δ -9-THC (Borheim et al. 1995). However, the CBD content of cannabis varies

greatly and some samples of cannabis have been reported to be devoid of CBD. Morgan and Curran (2008) analysed hair samples of 140 young participants and took measures of psychosis proneness and delusional thinking. They categorized participants by whether their hair samples revealed detectable levels of only Δ -9-THC, both Δ -9-THC + CBD or no cannabis. Their results showed higher levels of unusual experiences (an analogue of hallucinations and delusions) in individuals who had evidence of only Δ -9-THC in their hair compared to those with either both Δ -9-THC and CBD or no cannabinoids. There were also greater levels of delusions in the Δ -9-THC only group compared to individuals who showed no evidence of cannabis in their hair, with a similar trend in the Δ -9-THC and CBD group. This suggests that different strains of cannabis may manifest differing levels of psychological symptoms.

Indeed, Cannabidiol may serve as an antipsychotic medication that is not primarily based upon a dopaminergic but upon endocannabinoid mechanisms. In recent trials, CBD has been used as an antipsychotic for treatment resistant schizophrenia (Zuardi 2006; Leweke et al., 2007). Leweke and colleagues (2007) investigated the effects of CBD on 42 patients with acute schizophrenia. Some were given CBD, while others received a standard anti-psychotic drug; amisulpride. Both groups had fewer psychotic symptoms, but the CBD group also experienced fewer side-effects. Common side-effects of amisulpride include weight gain, sexual dysfunction and liver problems and it is encouraging that CBD did not produce these effects.

CBD is currently under intense investigation. Varval et al (2006) investigated whether CBD modulates the pharmacological effects of intravenously administered Δ -9-THC or

inhaled cannabis smoke on hypoactivity, antinociception (inhibition of the nociceptive processing in the nervous system), catalepsy, and hypothermia in mice, the well characterized models of cannabinoid activity. They found that intravenously administered CBD possessed very little activity on its own and, at a dose equal to a maximally effective dose of Δ -9-THC (3 mg/kg), failed to alter Δ -9-THC's effects on any measure. They concluded that as the amount of CBD found in most cannabis strains in America is considerably less than that of Δ -9-THC, CBD is likely to exert little, if any, modulatory effects in normal cannabis.

The investigations of CBD indicate that there are further interactions of cannabinoids on the brain that we have yet to understand or quantify. Although the dysregulation of cannabinoid and dopamine systems have been implicated in both the onset of psychosis and cannabis use, the neurobiological evidence is far from complete. Furthermore, the differing compositions of cannabis that is sold in the UK (specifically Δ -9-THC potency) make it hard to generalize the effects found in small samples.

6.3 Structural evidence for the link between cannabis and the prodrome

Although structural changes in the brain have been reported in the prodrome and in chronic cannabis users, the evidence remains associative rather than causal and is far from conclusive. Two MRI studies of High-Risk/Prodromal individuals (Lawrie et al., 2002; Job et al., 2003) have shown structural brain gray matter changes, particularly localized in the frontal and temporal lobes (anterior cingulate, temporal cortex, parahippocampal gyrus, frontal lobe) that are abnormal before the onset of psychotic symptoms. It may be that some of these anomalies may be progressive over time. The

anterior cingulate gyrus is responsible for a number of functions including but not limited to cross-modal sensory processing, voice and face expression identification, monitoring of conflict and error, and reward-based decision making (Pillay et al., 2004). In addition, numerous studies have shown that the anterior cingulate is involved in motor function (e.g. Backus et al., 2001).

Several studies, using different techniques (PET, SPECT, fMRI), have shown subnormal cerebral blood flow in heavy cannabis users. Lundqvist et al. (2001) measured brain blood flow levels after cessation of cannabis use (mean 1.6 days). The findings showed significantly lower mean hemispheric blood flow values and significantly lower frontal values in the cannabis subjects, compared to normal controls. In their recent review of the evidence of the structural impact of cannabis on the brain, DeLisi et al. (2008) conclude that to date, brain imaging, animal and neurocognitive studies have been inconsistent and do not clearly show any lasting adverse effects of cannabis on the structure of the brain. Apart from one or two small scale studies, none of these abnormalities has been carefully examined in pure cannabis, as opposed to polydrug, users. However, Pillay et al. (2004) found decreased cingulate activation in response to finger sequencing among heavy cannabis users, Volkow et al. (1996) report lower baseline cerebellar volume in chronic cannabis smokers and Szeszko et al. (2007) reported that cannabis use was associated with less anterior cingulate grey matter in first episode schizophrenia patients.

The anterior cingulate is an area that has been focused on in both the prodrome and cannabis research. In Eldreth et al's (2004) study of the effects of cannabis on executive

function, they used PET scans to illustrate that even after 25 days' abstinence, heavy users showed hypoactivity in the anterior cingulate cortex and the prefrontal cortex and hyperactivity in the hippocampus bilaterally when compared to the comparison group. These results suggest that cannabis users display persistent metabolic alterations in brain regions responsible for executive function. However, interpretation is difficult given that these differences may pre-date cannabis use.

The dorsolateral prefrontal cortex (DLPFC) is another area that may be effected by heavy cannabis use. Yurgelun-Todd et al. (1999) assessed chronic cannabis smokers twice with functional magnetic resonance imaging (fMRI), after 24 h and 28 days of abstinence. On a visual working memory task, control subjects showed significant activation in the DLPFC but smokers who completed 24 h of cannabis abstinence showed diminished activation in this region. The effect remained after 28 days of washout, although some increase in the DLPFC activation was noted relative to the 24-h time point. In contrast, smokers produced increased activation in the cingulate during both washout conditions, whereas controls did not. Their results suggest that even after an extended washout period, specific differential patterns of cortical activation exist in subjects with a history of heavy cannabis use. Causal links between cannabis use and brain activation are however, difficult to make in the absence of prospective research.

7. Vulnerability

The vulnerability presented by the prodrome is not as simple as neurobiological and neurocognitive abnormalities (were even these simple) and it would be naïve to ignore other vulnerability factors that have been shown to mediate the effects of Δ -9-THC. Favrat et al. (2005) have shown that individuals even vary in the sensitivity to the acute administration of Δ -9-THC where some participants developed full-blown paranoia at doses that barely affected others. The following section reviews the literature on the effects of genes, schizotypy, the impact of life events, age of first use, length of use and the dose of use on the effects of cannabis. In some of these areas the research findings have been inconsistent thus highlighting the need for further investigation.

7.1 Genotypes

Using a subgroup of the Dunedin cohort, Caspi et al. (2005) have presented evidence for a genetic influence over the vulnerability of individuals to the effects of cannabis. The catechol-O-methyltransferase (COMT) gene plays an essential role in the breakdown of dopamine in the prefrontal cortex. Caspi et al. (2005) suggested that COMT variability moderates the risk of adolescent cannabis use with at least a five-fold increased risk of developing a schizophreniform disorder if they had a particular type of VAL/VAL allele and used cannabis. However, this was only observed in a small subgroup of people within the Dunedin study and evidence for the interaction in an experimental setting was also observed in only a small subgroup of participants. 15% (8) of the 54 gene carriers used cannabis in adolescence and had psychosis, and of the 148 gene carriers who did not use cannabis, 2% had a schizophrenia-like psychosis (3 people).

Thus the number of schizophreniform individuals who used cannabis in adolescence and had the COMT variance was extremely small.

When Zammit et al. (2007) investigated COMT variance in a much larger sample (493 participants), they did not find any significant difference in the associations between the onset of schizophrenia and cannabis use in those that had the VAL/VAL allele. Nevertheless, genetic evidence should not be totally disregarded. Genetic vulnerability may be the key to identifying eventually who among cannabis users is likely to develop a psychosis. It may be not just one gene variant, but several that can increase risk. Any consideration of the deficits of cannabis use will have to include genetic variation in pathways that influence both brain neurochemistry and structure.

Genetic investigations need to be replicated but the effects of organic dysregulation of the dopamine system re-emphasize the importance of this system. It could be proposed that any factor that causes dopamine dysregulation would present as a vulnerability factor for the impact of the use of cannabis.

7.2 Schizotypy

Another vulnerability factor shown to mediate the impact of cannabis is a set of individual differences collectively termed psychosis-proneness or 'schizotypy'. These consist of a continuum of personality characteristics and sub-clinical experiences related to psychosis, often drawing on the diagnostic features of schizotypal personality disorder (SPD) and are measured by a range of personality scales and interview schedules. Schiffman et al. (2005) reported that regular cannabis users are significantly more prone

to schizotypal traits of cognitive and perceptual distortions as well as disorganization. Dumas et al. (2002) examined self-reported schizotypal traits among 232 healthy students and found that regular and past cannabis users evidenced higher schizotypal personality scores and magical ideation scores than those who had never used cannabis.

Verdoux et al. (2003) found that the effects of cannabis were modified by the individual's vulnerability to psychosis – “psychosis proneness.” This was assessed by Peters et al's., 1999 Delusions Inventory (PDI-21) and the Community Assessment of Psychic Experiences (CAPE, Stefanis et al., 2001). Participants with high vulnerability (who had experienced at least one bizarre psychotic symptom or two non-bizarre psychotic symptoms over the last month) were more likely to report perceived hostility or unusual perceptions within 3 hours of cannabis intoxication than subjects with low vulnerability. The interpretation of these results is limited due to the small scale of the study. However, a more recent study tested 142 cannabis users both when acutely intoxicated and again drug free and 140 non users at the same time point (Mason et al., submitted). This clearly showed that people in the highest quartile on trait schizotypy experienced the greatest elevation in psychotic-like symptoms following acute cannabis use.

Barkus et al. (2005) report that high scoring schizotypes are more likely to report both psychosis like experiences from smoking cannabis as well as unpleasant after-effects associated with cannabis use (“amotivational syndrome” – loss of drive, reduced attention, feeling slowed down). In a 4-year prospective study involving 2,400 people, Henquet et al. (2005) reported that the cumulative lifetime incidence of at least one

psychotic symptom was 17.4% of adolescents and young adult cannabis users at follow-up and that cannabis use increased the risk for psychotic symptoms in a dose-wise fashion. In those cannabis users with personality traits characteristic of psychotic vulnerability (i.e. paranoid, schizotypy), 23.8% had at least two psychotic symptoms on follow up compared with only 5.6% of those without these traits.

7.3 The impact of life events on individuals' vulnerability

In Moore et al.'s (2007) systematic review of the effects of cannabis approximately 50 different confounding factors were reported. The majority of these were related to family and peer relationships, adverse life events, mental health problems and other substance abuse. Van Os et al. (2002) report that urban living is another significant risk factor in the cannabis and schizophrenia association. It is hard to ignore the impact of significant adversity in mental health, not just in terms of the interpretation of every day experiences but the changes in neurobiological experience associated with distress.

7.4 Effects of age of first use

The age of first use of cannabis has been proposed to affect its impact in terms of subsequent psychopathology. Given that the age of first use of cannabis tends to be before an individual's brain is fully developed, it is not surprising that the age at which cannabis use begins has been proposed to influence its impact on the person. Cannabis users under the age of 17 are 3.44 times more at risk for developing dependence symptoms than are users over the age of 26 (Dennis et al., 2002). MRI studies have

shown that the frontal cortical connectivity is thought to still develop into the mid-twenties (Toga et al., 2006). Given that there is a concentration of dopamine-sensitive neurons in the frontal lobes, it is tempting to view this critical developmental period as one of unusual vulnerability to the neurotoxic effects of cannabis.

In the Dunedin Birth Cohort Study (Arsenault et al., 2002), cannabis initiation by the age of 18 doubled, whereas initiation by 15 quadrupled the odds of subsequent schizophreniform disorder at follow-up aged 26 years. However, in a study using Swedish conscripts, no difference in risk of according to age at first use was found (Zammit et al., 2004). As Moore et al. (2007) note, the increased risk of psychosis from a younger age observed in the Dunedin study could indicate a greater cumulative exposure to cannabis rather than a sensitive period of exposure. Clearly, further investigation is needed before any conclusions can be drawn.

7.5 Length of chronic cannabis use

Solowij et al., (1995) reported that attentional impairments were progressive with the number of years of use but unrelated to frequency of use. Messinis et al. (2007) also found that the cognitive impact of cannabis use was greater in heavy long term users than in short term users. These results suggest that a chronic use of cannabis produces both short- and long-term cognitive impairments. However, as section 6.1.3 reviews, in naturalistic studies, the duration of cognitive deficits of cannabis is still under question.

7.6 Dose response

The effects of cannabis have been found to be dose related in both recreational use and acute administration trials (Barnett et al., 1985; Pope et al., 1995; Curran et al., 2002; D'Souza et al., 2004). Bolla et al (2002) found that the cognitive deficits found in heavy cannabis users were related to the amount consumed. While acute administration of Δ -9-THC has caused transient psychotic symptoms, many of the naturalistic studies' highest exposure categories were of weekly or bi-weekly consumption of cannabis. Clearly there are much heavier users and in 2003 the IMDU reported that 21% of users use daily (Atha, 2005). It is important to consider that there is a range of use and it is difficult to generalize effects.

The Δ -9-THC content of cannabis has changed over time. In the 1960's, Δ -9-THC was isolated, identified and synthesized. "Skunk" cannabis, a cross-breed of *Cannabis sativa* and *Cannabis indica*, has become a more potent strain of cannabis, grown through selective breeding and usually hydroponics. Skunk cannabis potency ranges usually from 6% to 15% Δ -9-THC (in comparison to the 3-4% Δ -9-THC content in regular cannabis) and the average Δ -9-THC level in coffeehouses in the Netherlands is about 18–19% (Niesink et al., 2005).

According to an analysis of drug samples seized by 23 police forces for the forensic science service in recent months, skunk now accounts for 81% of the cannabis in England and Wales, compared to just 15% in 2002 (King and Hardwick, 2008). The average Δ -9-THC content in 'skunk' in the UK has risen from 7% in 1995 and between 16-19% today. In the recent police samples, the skunk examined ranged in Δ -9-THC

potency from 4% to 46% (King and Hardwick, 2008). The increase in skunk is believed to be a result of users seeking a greater “high” and the availability of home hydroponic growing under intense artificial lights. According to the EMCDDA (2007), domestically produced cannabis cultivated hydroponically rose from 11% of the UK market in 1994 to 63% in 2004. The quantity of cannabis plants seized more than doubled between 2004 and 2005, from 95,103 to 212,971 plants.

Cannabis with higher Δ -9-THC potency leads to higher Δ -9-THC serum concentrations (Mensinger et al., 2006). A Dutch double-blind, randomized, placebo-controlled, cross-over study of regular cannabis smoking males aged 18–45 years concluded that smoking cannabis with higher Δ -9-THC (reflecting the content levels of “Netherweed,” cannabis with 9–23% Δ -9-THC) leads to an increased effect (Mensinger et al., 2006). This was particularly the case among younger or inexperienced cannabis smokers, who did not adapt their smoking behaviour to the higher Δ -9-THC content. Smoking cannabis with higher Δ -9-THC concentrations was associated with a dose-related increase of physical effects (such as increase of heart rate, and decrease of blood pressure) and impairments of psychomotor speed, concentration, motor control as well as drowsiness.

Human performance studies have usually relied on low-potency cannabis (4% Δ -9-THC) for determining THC-induced impairment. In Ramaekers et al., (2006) study, they found that effect sizes for performance impairments produced by Δ -9-THC 250 μ g/kg were relatively low but generally increased by a factor of two with a dose of Δ -9-THC 500 μ g/kg. Use of higher doses of Δ -9-THC in controlled studies may offer a more reliable indication of Δ -9-THC induced impairment as compared to lower doses of Δ -9-

THC that have traditionally been used in performance studies. Clinically, there is an absence of research into the recreational use of the higher potency skunk cannabis that dominates the UK market.

8 Clinical implications

This review has illustrated some of the mechanisms by which cannabis can contribute to prodromal symptomatology. Schizophrenia is undoubtedly a devastating and debilitating mental disorder. If cannabis can cause brain abnormalities that place an individual at greater risk for developing schizophrenia-like symptoms then this is an important issue that needs to be resolved. Although this review outlines the common links between cannabis and prodromal symptoms, we are far from fully understanding the changes in the endocannabinoid system, dopamine dysregulation and structural differences that have been found in individuals with diagnoses of schizophrenia and those who use cannabis. However, it is undoubted that further research is needed to determine the biological effect that cannabis has on the brain in people who do or do not go on to develop schizophrenia.

The focus of this review has been to highlight the common cognitive and neurobiological changes found as a result of cannabis use and in individuals identified to be in the prodrome but it is important to remember that the vast majority of individuals who use cannabis do not develop psychosis. Furthermore, any fully psychotic symptoms appear to be transient after the effects of the drug have worn off. In the Dunedin sample, 95% of 18 year olds who were using cannabis did not develop

psychosis by the time they were 26 (Caspi et al., 2005). However, where the risk of psychosis is increased by 50-200% (Moore et al., 2007) in heavy users, there is a need to understand the mechanisms underlying the risk especially given that the estimated proportion of young people who have ever used cannabis in the UK is over 40% (EMCDDA, 2005).

The cognitive deficits caused by cannabis emulate some of those found in individuals at risk of psychosis and heavy users show deficits similar to prodromal symptoms. It seems as though cannabis use can put individuals in the “at risk” category but the vulnerability factors need to be investigated further. It could be that cannabis users who develop a transient psychotic episode subsequent to heavy use may have only a biochemical variant, such as low COMT activity, and thus higher dopamine synthesis that would potentiate the effects of cannabis and cause an acute psychotic reaction. With greater understanding of these vulnerability factors, public psycho-education concerning the effects of cannabis can be more effective. Murray et al.’s. (2004) research showed that up to 10% of the adult population is prone to paranoid thoughts or grandiose ideas and among those who smoke cannabis regularly, half may be tipped into psychotic delusions and end up needing treatment. Their study of 2,437 young people aged 14 to 24 found that of those who smoked cannabis regularly and had a pre-existing risk of psychosis, 50 per cent developed psychotic symptoms over the four- year follow-up period.

As a drug model for prodromal symptoms, cannabis does seem to mimic some of the cognitive and neurobiological changes reported in the prodrome and this is helpful in

considering treatment strategies. However much of the research (on both acute administration and cannabis smokers) has been carried out with cannabis that is not reflective of the current market. In light of the dose-response findings, there is a need to have a greater understanding of the impact of higher potency skunk cannabis that accounts for over three-quarters of the cannabis currently consumed in the UK.

9 Future research

The transient psychotic symptoms induced using Δ -9-THC intravenously (D'Souza et al 2004) and cognitive impairments following acute oral consumption (Curran et al., 2002) are not a reflection of the impact of cannabis consumed in the UK. In order to be able to generalise the results to normative consumption of cannabis (i.e. through inhalation), further research is needed to explore the symptoms in heavy users. The intravenous route of administration may have resulted in faster delivery and higher levels of Δ -9-THC than that typically achieved by recreational users. Indeed subjects generally reported that the Δ -9-THC effects were dissimilar to their previous experience with cannabis and participants were unable to titrate the effects by controlling dose or administration. Equally, research on the effects of cannabis with 3-5% Δ -9-THC is not reflective of the cannabis smoked today. Given the dose-response findings, it would make sense for the impact of skunk to be greater than cannabis. Whether the higher potency skunk cannabis smoked today induces more basic symptoms of the prodrome is unknown and further research is needed. Furthermore, there are areas where we can learn from previous research in limiting confounding factors. In their systematic review of research on cannabis use, Moore et al (2007) found that only roughly half of the 35 studies they included had made

adjustments for alcohol or other drug use and this needs to be considered in the future.

10 Conclusions

This review brings together research that illustrates how cannabis may contribute to different prodromal or UHR symptomatology. A major gap in the existing literature that this review has identified is that there has been no study directly assessing the full range of prodromal-like symptomatology in cannabis users. While intravenous administrations of Δ -9-THC have illustrated the psychoactive potential of cannabis, it does not provide a clinical picture. What is needed for a relevant clinical picture is research focusing on the full range of prodromal symptomatology with the cannabis that is consumed in the UK today i.e. skunk.

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Part 2

Empirical Paper

Prodromal symptoms of schizophrenia in daily skunk users.

Abstract

In the past decade meta-analyses have helped to establish a causal link between cannabis use and the onset of psychotic symptoms. Tetrahydrocannabinol (Δ -9-THC), the psychoactive component in cannabis, has been shown to induce transient psychotic experiences in healthy volunteers following acute administration. “Skunk” cannabis contains high levels of Δ -9-THC and now accounts for 81% of the UK cannabis market. However, no study has assessed the effects of this potent cannabis on recreational users. This study aimed to investigate whether heavy users of skunk show “prodromal” symptoms of schizophrenia - the symptoms of individuals at risk for developing psychosis. A total of 47 participants (27 daily skunk smokers and 20 matched controls) were assessed using the Schizophrenia Proneness Instrument, the Peters Delusions Inventory, the Dissociative Experiences Scale and the Oxford Liverpool Inventory of Feelings and Experiences. Cognitive assessments included measures of memory, fluency and superstition. Daily skunk users showed significantly more prodromal symptoms than controls and these included some of the cognitive deficits reported in individuals at high risk for developing schizophrenia. The study illustrates a profile of prodromal symptomatology in daily skunk users which appears to be differentiated from experiences under the influence of skunk. Dissociative symptoms were also observed in skunk users and these are not characteristic of the prodrome. These findings are discussed in terms of the clinical implications, the longitudinal research needed to monitor transition rate and the need for public information about potential effects of this drug which is currently consumed by over 2 million people in the UK.

Introduction

Cannabis is the most widely used, illegal drug in the world (WHO, 2007). According to an analysis of drug samples seized by 23 police forces in recent months, “skunk” cannabis now accounts for 81% of the cannabis consumed in England and Wales (King and Hardwick, 2008). In May this year, the Home Secretary, upgraded cannabis to a Class B drug mainly due to concerns about both the dominance of skunk in the UK market and the association between cannabis use and psychosis. However, there is no published research into the psychological effects of skunk. Skunk is a more potent strain of cannabis composed of the flowering tops of unfertilised female cannabis plants. It is a combination of cannabis sativa and cannabis indica that is produced by intensive indoor cultivation methods. It is called skunk because of the pungent odour it emits while growing. The main psychoactive ingredient in cannabis is delta-9-tetrahydrocannabinol (Δ -9-THC) and the average Δ -9-THC content in ‘skunk’ in the UK has risen from 7% in 1995 to between 16 and 19% today (in comparison to the 3.5% Δ -9-THC content in traditional herbal cannabis). In the recent police samples, the skunk examined ranged in Δ -9-THC potency from 4% to 46% (Hardwick and King 2008).

Cannabis with higher Δ -9-THC potency leads to higher Δ -9-THC serum concentrations (Mensinger et al., 2006). Intravenous Δ -9-THC has been shown to induce transient psychotic symptoms (D’Souza et al., 2004) and cognitive impairments have been reported following acute oral Δ -9-THC consumption (Curran et al, 2002). However, it is hard to generalize these findings to recreational cannabis consumption. Systematic reviews and meta-analyses of recreational use have suggested that there is a causal relationship between cannabis use and psychosis (Arsenault, 2004; Moore et al., 2007;

Semple et al., 2005). The most recent meta-analysis found an increased risk of any psychotic outcome to be approximately 40% in individuals who had ever used cannabis (pooled odds ratio= 1.41, 95%). This figure was elevated to a 50-200% increase in the risk for participants who used cannabis most heavily (Moore et al., 2007). Indeed, Moore et al. (2007) estimate that 14% of those currently diagnosed with schizophrenia in the UK would not have been if they had not used cannabis. The most recent British Crime Survey (Murphy and Roe, 2007) reported that 2.6 million people aged between 16 and 59 years in England and Wales reported using cannabis in 2006/07. A survey of cannabis users carried out by the Independent Drug Monitoring Unit (IDMU) in 2000 found that 21% of users smoked daily.

What is the evidence for a link between Δ -9-THC and schizophrenia?

The main psychological effects of Δ -9-THC stem from activation of the CB1 cannabinoid receptor in the brain. When individuals smoke skunk the synaptic modulation by the brain's natural cannabinoid, or "endocannabinoid," system is disrupted; Δ -9-THC activates CB1 receptors and the cells are flooded. It has been hypothesised that a dysfunction in endocannabinoid signaling may be also associated with schizophrenia. For example, Giuffrida et al. (2004) showed that cerebrospinal fluid (CSF) from individuals suffering from schizophrenia contains significantly higher levels of the endocannabinoid, anandamide than CSF from healthy volunteers. They propose that endocannabinoids such as anandamide may enhance dopaminergic neurotransmission by increasing dopamine turnover.

It has been shown that Δ -9-THC facilitates the release of dopamine in the brain (Voruganti, et al., 2001; Lupica and Riegal, 2005) and neuroimaging studies have illustrated heightened dopaminergic transmission in patients with schizophrenia. In the acute phase, psychotic patients show a higher synthesis of dopamine, heightened dopamine release in response to an impulse and a heightened level of synaptic dopamine (Kapur, 2003). Although there is evidence that other neurotransmitter systems also contribute to the psychopathology of schizophrenia (Holcombe et al., 2004), the first-line treatment of positive symptoms is invariably with antipsychotics that block dopamine D2 receptors. Thus neurobiological findings that link cannabis and schizophrenia are the endocannabinoid and dopamine dysregulation caused by Δ -9-THC which is also thought to occur in schizophrenia.

Cannabinoids also block hippocampal long-term potentiation (LTP), a potential substrate for learning and memory (Hoffman et al., 2007). LTP is a process by which the responsiveness of a neuron to a particular input becomes sensitized with repeated stimulation and is most prevalent in the hippocampus, an area of the brain important in memory (Ameri, 1999). Curran et al (2002) describe how memory impairment is a predictable effect of Δ -9-THC given the uneven distribution of cannabinoid receptors in the brain with the highest densities in the hippocampus, basal ganglia and cerebellum.

Kim and Thayer (2001) report that anandamide and other cannabimimetic drugs inhibit the formation of new synapses between hippocampal neurons in culture. Functional imaging studies also reveal that people with diagnoses of schizophrenia show reduced activation of the hippocampus in cognitive tasks like spatial navigation that are

hippocampus dependent (Weinberger, 1997) and, of all cognitive impairments reported in schizophrenia, the most marked are in the memory domain (Saykin et al., 1991). Finally, Δ -9-THC also increases cortisol levels via activation of the CB1 receptor. High levels of this stress hormone have been associated with schizophreniform symptomatology as well as memory deficits (Walder et al., 2000).

Cannabidiol

Another cause for concern regarding the prevalence of skunk in the UK is that regular cannabis resin (accounting for only 14.6% of the UK market) contains approximately 3.5% Cannabidiol (CBD) whereas skunk contains only 0.1% (Hardwick and King, 2008). CBD is another cannabinoid in cannabis that has been identified as having neuroprotective factors (Iuvone et al., 2004) as well as anxiolytic effects (Leweke, 2007). It has been proposed that CBD moderates the effects of Δ -9-THC (Morgan and Curran, 2008). In recent small-scale clinical trials, CBD has been effectively used as an antipsychotic for treatment resistant schizophrenia (Zuardi 2006; Leweke et al., 2007).

The Prodrome

The prodrome precedes the acute phase of a psychotic episode and extends from pre-morbid (“normal”) functioning to the onset of full symptoms of schizophrenia. It has been proposed that cannabis use leads to cognitive deficits of a similar nature to those seen in schizophrenia but of a lower magnitude (Solowij et al., 2007). Operationally, the prodrome is defined by duration of time, starting with the onset of decline in the baseline level of functioning and ending at the time when the criteria for a schizophrenia

spectrum diagnosis is met (Yung, 1996). It is characterised by the progressive deterioration of functioning and emergence of sub-threshold psychotic symptoms.

If recognised prospectively, the existence of a defined prodrome offers the opportunity for early intervention. Early intervention for psychosis is crucial if services hope to prevent the psychological and social disruption that results from psychosis and the delay in such intervention is associated with poorer outcome (Johnstone et al., 1986; Loebel et al., 1992). From a neurobiological perspective, investigations into a drug like cannabis that causes dysregulation of dopaminergic neurotransmission might model the dysregulation reported in people with prodromal symptoms of schizophrenia. Drug models of those at risk of schizophrenia can be useful if a drug provokes features characteristic of the disorder. They are especially helpful in developing new treatments and our understanding of the pathophysiology of psychosis.

Operationally, two schools of thought predominate: the 'ultra high risk' (UHR) approach and the Basic Symptom Approach (Olsen and Rosenbaum, 2006). Schultze-Lutter et al. (2001) developed the Schizophrenia Proneness Instrument (SPI), a semi structured questionnaire which is based on the basic symptom concept. This is an integrative approach similar to the vulnerability-stress-coping model (Nuechterlein, 1992) that originates in the observation of deficits that were perceived by individuals with schizophrenia pre-psychotically, years before the first psychotic manifestation, or prior to relapses. Schultze-Lutter et al.'s basic symptoms are mild, often sub-clinical but self-experienced disturbances of drive and affect, thought, speech, perception, proprioception and motor action as well as of vegetative functions. Klosterkötter et al. (2001) assessed

German patients for the presence of “basic symptoms” using the Bonn Scale for the Assessment of Basic Symptoms (BSABS) and in an average follow-up period of 9.6 years, 49.4% of the cohort had developed schizophrenia (according to DSM-IV criteria).

Evidence for the schizophrenia prodrome in cannabis use to date?

Although no single study has systematically investigated whether cannabis users report experiencing symptoms identified in the prodrome, several research groups have studied the impact of the acute administration of Δ -9-THC or disturbances reported as a result of recreational cannabis use on a variety of measures which can be broadly mapped onto the six dimensions of the SPI-Adult version identified by Shultze-Lutter et al. (2004). These findings are brought together in Table 1.

Table 1. Basic Symptom dimensions that have been reported as a result of the administration of acute Δ -9-THC and in recreational use of cannabis.

Basic Symptom Dimension (Schultze-Lutter et al., 2001)	Reported in administration of acute Δ-9-THC	Reported in Recreational Cannabis users
A. Affective Dynamic Disturbances	Wadsworth et al., 2006., D'Souza et al., 2004	Lynskey et al., 2004., Patton et al., 2002; Beautrais et al, 1999; Bovasso et al., 2001
B. Cognitive – Attentional Impediments	Barnett et al., 1985; Musty & Kaback., 1995; Fletcher et al., 1996; Solowij et al., 1995; D'Souza et al., 2004; Wadsworth et al., 2006	Pope et al., 1995: Solowij et al., 1995; Barkus et al., 2005
C. Cognitive Disturbances	Curran et al., 2002; D'Souza et al., 2004	Block and Ghoneim (1993)
D. Disturbances in Experiencing Self and Surrounding	Mikuriya, 1998; Dumas et al., 2002	
E. Body Perception Disturbances		
F. Perception Disturbances	D'Souza et al., 2004; Favrat et al., 2005; Mason et al., 2008	Verdoux et al., 2003; Schiffman et al., 2005; Morgan et al., 2008., Barkus & Lewis, 2008

SPIA-A: Affective Dynamic Disturbances

The Affective Dynamic Disturbances in the SPIA range from changes in mood and emotional responsiveness to impaired tolerance to stress. These are changes that have also

been reported in the acute administration of Δ -9-THC. In their 3- day, double-blind, randomized and counterbalanced study, the behavioural, cognitive and endocrine effects of 0, 2.5 and 5mg of intravenous Δ -9-THC were characterized in 22 healthy individuals who had been exposed to cannabis but never diagnosed with a cannabis abuse disorder. D'Souza et al., (2004) found that acute Δ -9-THC caused blunted affect, reduced interaction with the interviewer and increased levels of the stress hormone cortisol. Cannabis use has also been associated with depression and anxiety (Patton et al., 2002; Lynskey et al., 2004). In a seven wave cohort study involving 1,601 students over six years (Patton et al., 2002), daily cannabis use in young women was associated with an over five-fold increase in the odds of reporting a state of anxiety (after adjustment for other substance misuse).

The negative changes in mood that are reported in the prodrome have also been found in research on the mood of cannabis users (Wadsworth et al., 2006; Bovasso, 2001). In Moore et al.'s systematic review (2007), their analysis of studies investigating an association between frequent cannabis use and depression revealed an adjusted odds ratio of 1.49 (95% CI 1.15-1.95). Beautrais et al. (1999) reported that individuals with cannabis dependence (as diagnosed in DSM-IV) were at greater risk of suicide attempts. Lynskey et al. (2004) found that the twin who was cannabis dependent was more 2.5 to 2.9 times more likely to have had a major depressive disorder, suicidal ideation and attempted suicide than their non-cannabis using twin. In their examination of the evidence of depression in cannabis users, Degenhardt et al. (2003) concluded that heavy cannabis use and depression are associated and evidence from longitudinal studies suggests that heavy cannabis use may increase depressive symptoms among some users.

However, as with Moore et al. (2007), they state that it is still too early to rule out the hypothesis that the association is due to common social, family and contextual factors that increase risks of both heavy cannabis use and depression.

SPIA-B: Cognitive – Attentional Impediments

The cognitive attentional impairments in the SPIA include difficulties with attention, concentration and “thought energy.” In the SPIA, thought energy is defined as self-experience of initiating thoughts and an observable lack of goal orientation. Many studies have identified difficulties in concentration and attention as a result of both acute Δ -9-THC and recreational cannabis use. D’Souza et al. (2004) reported transient impairments in attention in their research on acutely administering Δ -9-THC and Solowij et al. (1995) found that the ability to focus attention and filter out irrelevant information was impaired in recreational cannabis users. Barnett et al. (1985) found a significant correlation between tracking errors in divided attention and Δ -9-THC plasma levels over 25 ng/ml among cannabis users assessed approximately 2 hours after smoking. Pope et al. (1995) tested the cognitive functioning of 64 heavy cannabis users, whom had smoked cannabis for at least 27 out of the previous 30 days. Heavy users showed significant deficits in sustaining and shifting attention.

In terms of ‘thought energy,’ or ‘goal directed thinking,’ an “Amotivational Syndrome” amongst cannabis users described by McGlothlin and West (1968) includes apathy and a diminished ability to concentrate but there is no specific mention of lack of thought energy. This may be a result of the semantics of the constructs being investigated but loss of motivation as a negative effect of cannabis has been reported by Musty and

Kaback (1995) and Barkus et al., (2005). However this “syndrome” of apathy and lethargy has been poorly documented in uncontrolled studies in the past and again, it is difficult to distinguish the effects of heavy cannabis use from those of poverty and low socioeconomic status, pre-existing personality factors and other psychiatric disorders.

SPIA-C: Cognitive Disturbances

The cognitive disturbances in the SPIA range from disturbances of indecision, thought interference, thought blockages, disturbance of speech and immediate recall. D’Souza et al (2004) reported that acute intravenous administration of Δ -9-THC produced symptoms including thought blocking, thought disorder, unusual thoughts, paranoia, suspiciousness, reduced spontaneity, and problems with memory. Block and Ghoneim (1993) matched heavy cannabis users and nonusers on the basis of their intellectual functioning before the onset of drug use and found that subjects who used cannabis 7 or more times weekly for at least 2 years showed deficits in verbal expression as well as selective impairments in memory. In fact, one of the most consistently reported behavioural effects of Δ -9-THC is a disruption in the free recall of newly learned information. Recall of items learned before cannabis use is generally not affected, suggesting that Δ -9-THC impairs learning and the acquisition of information but not its retrieval from memory (Curran et al., 2002; D’Souza et al, 2004). Curran et al., (2002) reported that oral Δ -9-THC impaired episodic memory and learning in a dose-dependent manner whilst leaving intact performance on tasks tapping perceptual priming and working memory.

SPIA-D: Disturbances in Experiencing Self and Surrounding

The SPIA disturbances in experiencing self and surrounding consist of decreased capacity to discriminate between different kinds of emotions, emotional reactivity, thought pressure, referential thinking and changed perception of others. Cannabis use has been shown to decrease emotional reactivity and intensity of affect and is often used to self-medicate for this reason (Mikuriya, 1998). Cannabis use has also been shown to correlate with unstable ideas of reference or 'subject-centrism' (Dumas et al., 2002)

SPIA-E: Body Perception Disturbances

The body perception disturbances dimension focuses on unusual body sensations (e.g. numbness, stiffness, migrating sensations, shrinking, enlarging sensations that are not explicable by physical illness). I was unable to find any evidence of this in the literature with relation to cannabis use or of administration of Δ -9-THC.

SPIA-F: Perception Disturbances

The disturbances of perception included in the SPIA range from sensitivity to light and sound to somatopsychic bodily depersonalisation. Using an experience sampling method, Verdoux et al., (2003) found that in daily life, recreational cannabis use is an independent predictor of unusual perceptual experiences. Schiffman et al. (2005) also found that recreational cannabis users were more prone to perceptual distortions than individuals who had never used cannabis and this has been more recently confirmed in a study by Mason et al. 2008. In acute oral administration of Δ -9-THC, D'Souza et al. (2004) and Favrat et al. (2005) found increased depersonalisation and derealisation in healthy participants.

Vulnerability Factors

A number of vulnerability factors have been suggested to mediate the effects of cannabis (for a review see Hunt, 2008) and some of these have implications for the present study. Schizotypy, age of first cannabis use, length and amount of cannabis use have all been highlighted in the literature as relevant variables.

Schizotypy

Psychosis-proneness or 'schizotypy' has been shown to mediate the effects of cannabis. Schizotypy is a continuum of personality characteristics and sub-clinical experiences related to psychosis. Verdoux et al. (2003) found that the effects of cannabis were modified by the individual's "psychosis proneness." This was assessed by Peters et al's. (1999) Delusions Inventory and the Community Assessment of Psychic Experiences (CAPE, Stefanis et al., 2001). Participants with high vulnerability (who had experienced at least one bizarre psychotic symptom or two non-bizarre psychotic symptoms over the last month) were more likely to report perceived hostility or unusual perceptions within 3 hours of cannabis intoxication than subjects with low vulnerability. These findings of the effects of schizotypy on psychotomimetic experiences as a result of cannabis use have been since replicated by Mason et al. (in press) and Barkus and Lewis (2008).

Life Experiences

In Moore et al's (2007) systematic review of the effects of cannabis approximately 50 different confounding factors were reported. The majority of these were related to family and peer relationships, adverse life events, mental health problems and other substance abuse. It is hard to ignore the impact of significant adversity on mental health, not just

in terms of the interpretation of every day experiences but the changes in neurobiological experience associated with distress.

Age of first use

The age of first use of cannabis has been proposed to affect its impact in terms of subsequent psychopathology, given that the age of first use of cannabis tends to be before an individual's brain is fully developed. According to Dennis et al. (2002), cannabis users under the age of 17 are 3.44 times more at risk for developing dependence symptoms than are users over the age of 26. In the Dunedin Birth Cohort Study (Arsenault et al, 2002), cannabis initiation by the age of 18 doubled, whereas initiation by 15 quadrupled the odds of subsequent schizophreniform disorder at follow-up aged 26 years. However, in a study using Swedish conscripts, no difference in risk of according to age at first use was found (Zammit et al., 2004). As Moore et al. (2007) note, the increased risk of psychosis from a younger age observed in the Dunedin study could indicate a greater cumulative exposure to cannabis rather than a sensitive period of exposure.

Length of use

Solowij et al. (1995) reported that attentional impairments were progressive with the number of years of use and Messinis et al. (2007) also found that the cognitive impact of cannabis use was greater in heavy long term users than in short term users. These results suggest that a chronic use of cannabis produces both short- and long-term cognitive impairments.

Amount used: The effects of cannabis have been found to be dose related in both recreational use and acute Δ -9-THC or cannabis administration trials (Barnett et al., 1985; Pope et al., 1995; Curran et al., 2002; D'Souza et al., 2004). Bolla et al (2002) found that the cognitive deficits found in heavy cannabis users were related to the amount consumed. Human performance studies have usually relied on low-potency cannabis (4% Δ -9-THC) for determining THC-induced impairment. Ramaekers et al. (2006) found that effect sizes for performance impairments produced by Δ -9-THC 250 μ g/kg were relatively low but generally increased by a factor of two with a dose of Δ -9-THC 500 μ g/kg. It is difficult to generalize acute administration results to the general population and many of the naturalistic studies' highest exposure categories were of only weekly or bi-weekly consumption of cannabis. If these effects have been reported in infrequent cannabis users, what effects would be found in daily skunk users exposed to higher concentrations of Δ -9-THC?

Present Study

While intravenous and oral administrations of Δ -9-THC have illustrated the psychotomimetic and cognitive effects of cannabis, these studies do not provide a clinical picture. The intravenous route of administration may have resulted in faster delivery and higher levels of Δ -9-THC than that typically achieved by recreational users. Indeed participants generally reported that the intravenous Δ -9-THC effects were dissimilar to their previous experience with smoked cannabis and were uneasy being unable to titrate the effects by controlling dose or speed of administration. On the other hand, research on the effects of cannabis with 3-5% Δ -9-THC is not reflective of the cannabis smoked in the UK today. As the Home Office Advisory Council for the

Misuse of Drugs have recently stated, “further research is required to assess how users react to more potent forms” (Recommendation 16, ACMD, 2008, p38).

The present study aimed to determine the extent to which daily use of high potency cannabis (skunk) is associated with elevated prodromal-like symptomatology. It was hypothesised that daily skunk users would show greater prodromal symptomatology than controls who do not use cannabis. Furthermore it was predicted that symptoms would be most marked in those who smoked the most skunk and those who had been smoking the longest.

Following previous research into the cognitive impairments of recreational cannabis use, it was predicted that daily skunk users would perform significantly poorer on cognitive tasks assessing explicit and working memory and verbal fluency. It was also hypothesized that cognitive performance would correlate negatively with skunk variables (amount, frequency and years of use).

Method

Power Calculation

There has been no previous reported research on either skunk users or on prodromal symptomatology in cannabis users. The power calculation was therefore based on results reported by Pope et al. (2003) on verbal fluency in cannabis users. The power calculations were performed using the online DSS Software (http://www.dssresearch.com/toolkit/sscalc/size_a2.asp). Group mean scores were 47.6 (± 11.3) cannabis users and 50.4 (± 11.2) controls such that 21 participants would be needed in order to achieve a power level of 0.80 with $\alpha = 0.05$. As this study was part of a larger drug/prodrome study at UCL, it was decided to use a minimum N of 20 in order to parallel other arms of the research.

Design and Participants

An independent groups design was used to investigate prodromal symptoms in daily skunk users compared with non-using controls. As the study was part of a programme investigating the impact of different drugs on mental health, I was able to share controls with Lisa Monaghan (LM) from Royal Holloway D.Clin.Psy course (Appendix A).

Given the question over whether cannabis has a differing influence over people at differing developmental ages it was important to match participants for age. Equally, years of education have been shown to be a protective factor in mental health (Faraone et al. 2002) and it was important that groups were matched for this. Groups were also matched for gender to minimize effects of sex.

Rather than both testing 30 control group participants, both LM and I tested 15 to create a control group of 30 as we were using the same test battery. This control group provided a control group for Suzanna Duffin's DClinPsy research. Only 5 of LM's controls who met the current study's age criteria were included in the analysis. The test battery was piloted independently and then with LM to check for inter-rater reliability.

Participants were assessed either in the UCL Clinical Psychopharmacology Unit or in their own homes. They were required not to take any drug before testing and were asked to give a urine sample. Participants were first given a substance use interview before a battery of questionnaires and computer tasks. Skunk smokers were also given the Severity of Dependence Scale (Gossop et al., 1995) to assess their cannabis dependence. Participants were paid £15 for their time.

The study was approved by the UCL Graduate School Ethics Committee (Appendix B). Participants were recruited through contacts, a facebook group and then snowballing. All participants gave written, witnessed, informed consent (Appendix C). The inclusion criteria were that all participants were aged between 16 and 35 years old and could speak English fluently. Participants were screened (over the telephone or in person) to exclude those with (i) any history of psychiatric diagnosis and (ii) participation in other studies using any of the same tests. Due to limited recruitment time, participants were also excluded if they failed to attend the agreed testing time twice. For the "skunk" group, participants were required to have been smoking skunk every day for at least a year and were excluded if they took any other drug more than weekly. Daily skunk smoking participants also agreed not to smoke skunk on the test day. The non-drug using controls

were then recruited to match skunk users for age, years of education and gender. Once it was established that participants were eligible for the study, they were sent an information sheet by email (Appendix D).

Assessments

Tests were selected to assess the established features of the schizophrenia prodrome.

Semi-Structured Interview

The Schizophrenia Proneness Instrument – Adult version (SPIA - Schultze-Lutter et al., 2004): This is a semi-structured interview used to assess participant's schizophrenia proneness. The SPIA is an assessment tool that has been empirically developed to identify individuals in the prodrome. It has 6 main components: (A) affective dynamic disturbances, (B) cognitive attentional impairments, (C) cognitive disturbances, (D) disturbances in experiencing self and surroundings, (E) body-perception disturbances, and (F) perception disturbances. The SPIA was used to measure change that participants noticed since they had been smoking skunk (or change in the past year for controls). Participants were specifically asked about the experiences that were not drug induced i.e. experiences when they were *not* intoxicated (Appendix E). Where participants reported these experiences, they were asked for the frequency of these experiences in order to obtain a score (e.g. "less than once a week" =1 and "daily and persistent" = 6).

Questionnaire Assessments

Oxford Liverpool Inventory of Life Experiences (OLIFE 9: - Mason et al., 1995): The short form of the OLIFE questionnaire was used to assess psychosis-proneness, principally schizotypy. Its items were deliberately chosen to make it suitable for tapping psychotic characteristics in healthy individuals. This self-report questionnaire has 30 yes/no questions that yield 4 factors: Unusual Experiences (an analogue of positive symptoms in schizophrenia including hallucinations and delusions); Cognitive Disorganisation (roughly corresponding to thought disorder); Introvertive Anhedonia (negative symptoms such as inability to derive pleasure from experiences and social withdrawal); Impulsive Non-conformity (relates to impulsivity and risk taking behaviour). Where participants report experiencing an item (e.g. “does a passing thought ever feel so real that it frightens you?”) they are given a score of 1 and these are added together to make totals of the 4 factors.

Peter's Delusion Inventory (PDI-10: Peters et al., 1999): This self-report measure was designed to assess delusional symptoms in the normal population with yes/no questions such as “Do your thoughts ever feel alien to you?” This was a 21 item questionnaire where participants also rated the degree of distress, preoccupation and conviction they had for each delusion reported on a 1-5 likert scale. Thus they received a total score (with a maximum of 21) and separate scores for totals of distress, preoccupation and conviction (each with a maximum score of 105).

Life Experiences Survey (LES - Sarason et al., 1978): This is a self-report measure that taps positive and negative life events experienced over the previous year, and the perceived stress associated with those events. The 42 items were chosen to represent life changes frequently experienced by individuals in the general population and participants had the option of adding a further 4 events if they had not been previously listed. Participants rated each life event experienced on a 7-point scale ranging from -3 (extremely negative) to +3 (extremely positive). If an event did not occur, the item was coded as 0. Every event that occurred is coded as one “life change unit” and the total of all positive and negative scores provided the LES total score. Positive and negative scores were summed separately, as was the number of items rated positive and negative.

The Beck Depression Inventory (BDI - Beck, 1978) and *Spielberger Trait Anxiety Inventory (STAI - Spielberger, 1983)* were used as measures of depression and anxiety. Although affect is measured as a factor in the SPIA, it was decided that more established questionnaire measures would be helpful to confirm levels of both depression and anxiety in participants. The BDI is a 21 item questionnaire with a maximum score of 63 (0-3 for each item). Cut offs for the BDI are >10 = Not depressed, 10-15 = Mild Depression, 15-30 = Moderate Depression, 30+ = Severe Depression.

The STAI is a 20 item questionnaire with statements such as “I am cool calm and collected” where participants can rate “almost never,” “sometimes,” “often,” or “almost always” to yield a score of 1-4.

Cognitive Assessments

Prose Recall: Version 1 of the Rivermead Behavioural Memory Test (RBMT: Wilson et al., 1985) was used as a measure of verbal memory. Participants listened to a pre-recorded short prose passage similar to a “news bulletin” on the radio. They were asked to recall the story immediately after presentation and again after a delay of 45 minutes filled by other tests. The story is divided into 21 “idea” units and recall is scored by allocating 1 point to each unit correctly recalled (or an exact synonym) and ½ a point for each partial recall of a unit or partial synonym.

Digit Span: Participants were asked to repeat strings of numbers as a measure of maintenance in working memory and then asked to repeat strings of numbers that they had heard backwards to assess manipulation as well as maintenance in working memory. When a participant failed to repeat or manipulate 2 strings, the assessment was complete. Digit Span is a subtest of the Weschler Adult Intelligence Scales (WAIS – III). For the purpose of this study, participants were given a score of 1 for each string they repeated correctly.

Verbal Fluency and Category Fluency (Benton and Hamsher, 1976): Participants were required to generate as many words as possible in 60 seconds which began with the letter F. Names of people, places were not allowed, nor were words which began with the same prefix. Category Fluency is another test used to measure participants’ speed of retrieval and level of executive function. Participants were required to generate the names of as many musical instruments as possible in 60 seconds. Each successful word

or instrument awarded the participants 1 point so that a score of 15 on category fluency meant that the participant had generated 15 musical instruments.

Spot the word (STW: Baddeley et al., 1993): This test was used to estimate participants' verbal intelligence. The spot the word consists of 60 item pairs, each of which contains one real word and one fake word and participants are required to identify the real word. Participants received one point for each successful word identification and these were then added for the total score.

Urine Samples

Each participant provided a urine sample in an EZ Split Key Cup. These allow for immediate analysis for recent use of cannabis, ketamine, cocaine, opiates, amphetamines, methamphetamines, benzodiazepines, barbiturates, methadone and tricyclic antidepressants.

Statistical analyses

All statistical analyses were performed using Statistical Package for Social Sciences (SPSS version 14.0). Group comparisons used ANOVA or t-tests where data was normally distributed or Mann Whitney for non-parametric data. Repeated measures ANOVA was used for prose recall data with immediate versus delayed as a within subjects factor. The alpha level was adjusted to 0.01 to minimize Type 1 error rate and Bonferroni statistic was used to accommodate for multiple testing. Correlations used Pearson or Spearman as was appropriate to the data.

Results

A total of 52 daily skunk smokers expressed interest. Of these: 5 failed screening due to psychiatric diagnosis, 3 failed screening due to participation in a recent similar study, 2 participants decided not to participate due to concerns about confidentiality and 6 due to worries about connections between the study and authorities (i.e. police or university examiners), 7 failed to attend their testing appointment two times. After receiving payment at the end of testing, 2 participants revealed that they did not smoke skunk daily and so were excluded. In all, 27 daily skunk smokers took part in the study (18 male, 9 female) with a mean age of 21 years old (range from 16 to 29). 20 controls who reported no use of illicit drugs were recruited (11 male, 9 female, mean age of 23 years old ranging from 16 to 33).

1. Demographics

Table 2. Group mean (s.d) demographic information for the participants.

	Daily Skunk smokers N=27	Controls N=20	F_{1,45}	P
Age	20.93 (3.83)	23.35 (5.78)	2.99	0.91 (NS)
STW	45.85 (5.76)	48.25 (5.06)	2.20	0.15 (NS)
Years of Education	14.81 (2.02)	12.70 (7.14)	2.15	0.15 (NS)

A one way ANOVA showed that there was no significant difference in age, years of education or pre-morbid IQ (Spot The Word (STW) Scores) between daily skunk smokers and controls. Of the skunk smokers, 9 were employed, 3 were unemployed and 15 were students. Of the control participants, 14 were employed, 2 unemployed and 4

were students. All were White British apart from 5 who were Asian (3 skunk, 2 controls), and of the daily skunk users 2 were Chinese and 2 were Other European.

Drug Use

All of the daily skunk users had Δ -9-THC and Δ -9-THC only in their urine and none of the controls were positive for any drug. Of the daily skunk users, the mean years of use was 5.22 (\pm 3.87) years (ranging from 1-15 years), the mean number of joints smoked per session was 2.31 (\pm 1.10) (ranging from 0.5 to 4.5) and the mean number of days to smoke an eighth of an ounce of skunk was 6.78 days (ranging from 1.5 to 30 days). The mean severity of dependence score among daily skunk users was 4.3 (\pm 2.98) which is higher than the dependence cut off score of 3 identified by Swift et al. (1998). Using this cut off, 17 (63%) of the daily skunk users were skunk dependent.

There was no significant difference in monthly alcohol consumption between the groups but daily skunk users smoked tobacco significantly more. 14 of the 20 controls had ever tried cannabis but had not used it in the previous year. Apart from skunk use, the main difference between groups in terms of current drug use was in MDMA consumption. On average, daily skunk users consumed MDMA once a month but no other drugs with such regularity. Table 3. shows the different drug use between groups.

Table 3. Group mean (s.d.) for drug use and statistical comparison.

Drug	Daily Skunk Users (N27)	Controls (N20)	Mann-Whitney U	P
Alcohol days/month	13.88 (8.25)	10.30 (7.26)	211.00	NS
Alcohol yrs regular use	6.19 (3.65)	6.83 (5.53)	269.00	NS
Alcohol units/ session	7.93 (3.86)	6.23 (4.41)	216.00	NS
Tobacco days/month	16.74 (13.54)	3.35 (9.25)	127.50	p=0.001
Tobacco yrs regular use	2.85 (3.44)	1.45 (3.23)	166.00	NS
Tobacco amount/ session	4.81 (4.76)	1.90 (5.44)	133.50	p=0.001
MDMA days/month	1.1 (1.62)	0		
MDMA yrs regular use	1.13 (1.95)	0.18 (0.67)	120.00	p<0.001
MDMA pills/ session	1.87 (1.95)	0		
Amph days/month	0.037 (0.19)	0		
Amph yrs regular use	0.15 (0.77)	0.1 (0.44)	267.00	NS
Amph amount/ session	0.13 (0.43)	0		
Cocaine days/month	0.32 (0.91)	0		
Cocaine yrs regular use	0.39 (0.84)	0		
Cocaine amount/ session	0.18 (0.33)	0		
Ketamine days/month	0.19 (0.79)	0		
Ketamine yrs regular use	0.019 (0.96)	0		
Ketamine amount/ session	0.017 (0.06)	0		

2. Schizophrenia Proneness Instrument

A one way ANOVAs of the SPIA factors violated sphericity and so each factor was subjected to non-parametric (Mann-Whitney) analysis. All 6 SPIA factors showed highly significant group differences with daily skunk smokers having higher scores than controls (Fig. 2, Table 4.). There was no significant gender difference in SPIA scores.

Fig. 1. Mean SPIA dimension scores for daily skunk users and controls (bars represent standard errors)

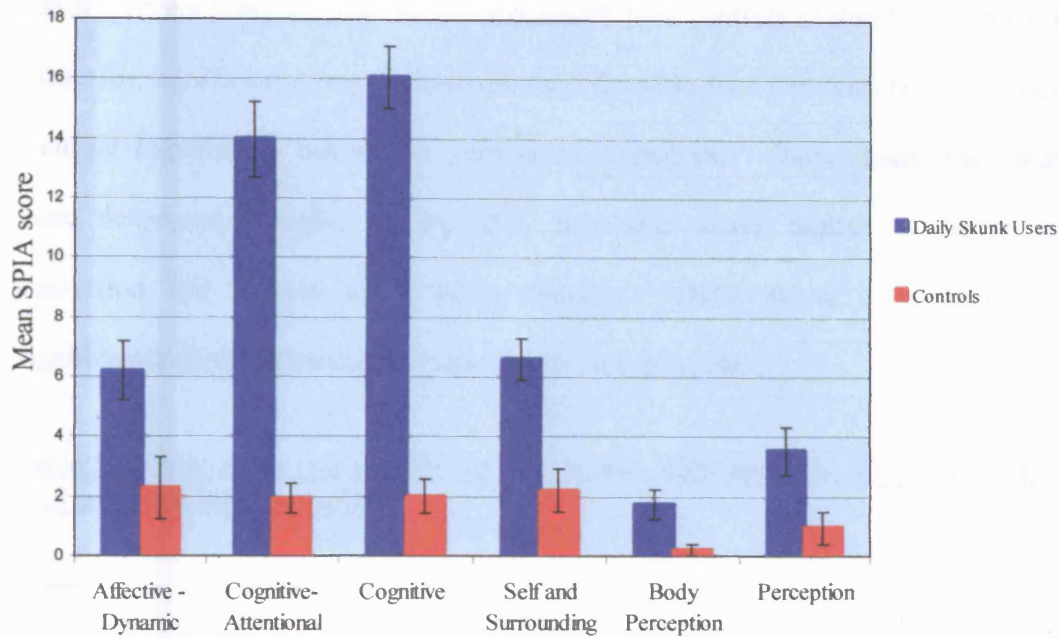


Table 4. Group Mean (s.d.) scores on SPIA factors and statistical comparison.

SPIA Factor	Group		Mann-Whitney -U	P
	Skunk	Control		
SPIA A- Affective Dynamic Disturbance	6.19 (5.11)	2.30 (4.67)	128.50	0.002
SPIA B - Cognitive Attentional Impediments	13.96 (6.63)	1.95 (2.19)	16.50	<0.001
SPIA C - Cognitive Disturbances	16.07 (5.36)	2.00 (2.53)	4.00	<0.001
SPIA D - Disturbances in experiencing self and surrounding	6.59 (3.58)	2.20 (3.24)	83.50	<0.001
SPIA E - Body Perception Disturbances	1.74 (2.60)	0.20 (0.89)	164.00	0.004
SPIA F - Perception Disturbances	3.52 (4.05)	0.95 (2.52)	30.50	<0.001

3. Questionnaire Measures

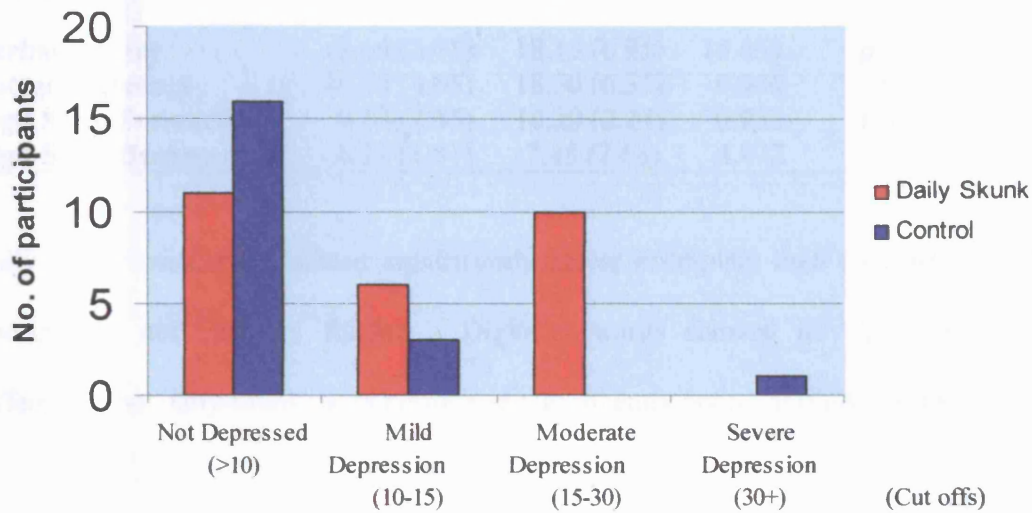
One way ANOVAs were also used for the questionnaire measures. Daily skunk users had significantly higher total schizotypy scores than controls (Table 5). Of the OLIFE subscales, significant group differences were found in Non-Conformity, Cognitions and Unusual Experiences but not in Introverted Anhedonia. Daily skunk users reported more delusional thoughts on the PDI, they also scored higher on preoccupation, conviction and distress about these thoughts. Daily skunk users also reported significantly greater dissociative experiences than controls.

Table 5. Group mean (s.d.) scores on the OLIFE, DES and PDI, STAI, BDI, BIS and LES and statistical comparison.

	Group		F (1,45)	P
	Skunk	Control		
OLIFE (Non Conformity)	4.67 (1.75)	3.10 (1.97)	8.251	0.006
OLIFE (Introverted Anhedonia)	5.07 (1.17)	4.73 (1.28)	0.762	NS
OLIFE (Cognitions)	7.04 (2.41)	3.30 (2.23)	29.452	0.001
OLIFE (Unusual Experiences)	4.85 (2.55)	2.40 (2.68)	10.150	0.003
OLIFE Total	16.26 (6.01)	8.20 (6.25)	19.93	<0.001
PDI Distress	15.04 (8.44)	7.90 (6.63)	9.80	0.003
PDI Conviction	17.78 (8.65)	11.70 (10.62)	4.67	0.036
PDI Preoccupation	14.51 (7.51)	8.10 (7.88)	8.05	0.007
PDI Total	6.19 (2.60)	3.45 (2.84)	11.76	<0.001
BDI	11.59 (7.77)	5.70 (8.18)	6.32	0.016
STAI	46.16 (4.43)	42.55 (6.64)	5.07	0.029
LES positive score	5.63 (5.64)	9.95 (6.22)	6.00	0.018
LES negative score	-5.07 (6.82)	-1.12 (4.33)	4.99	0.031
LES items rated positive	4.11 (3.95)	2.74 (2.84)	1.68	NS
LES items rated negative	2.59 (1.99)	3.21 (2.72)	0.80	NS
LES Total	-0.37 (9.28)	7.55 (6.53)	10.63	0.002

Daily skunk users had significantly higher depression scores than controls overall. 37% of the daily skunk users met criteria for moderate clinical depression and a further 22%

Fig 3. Depression in daily skunk users and controls



for mild clinical depression (Fig. 4). Skunk users also scored higher on trait anxiety than controls. There was no significant group difference in the number of positive or negative life-events that participants reported in the life events survey. However, daily skunk users rated the life events that they had experienced in the previous year more negatively than controls and the controls had significantly higher positive scores. Daily skunk smokers scored significantly higher on the Barratt Impulsiveness Scale

5. Cognitive assessments (Table 6.)

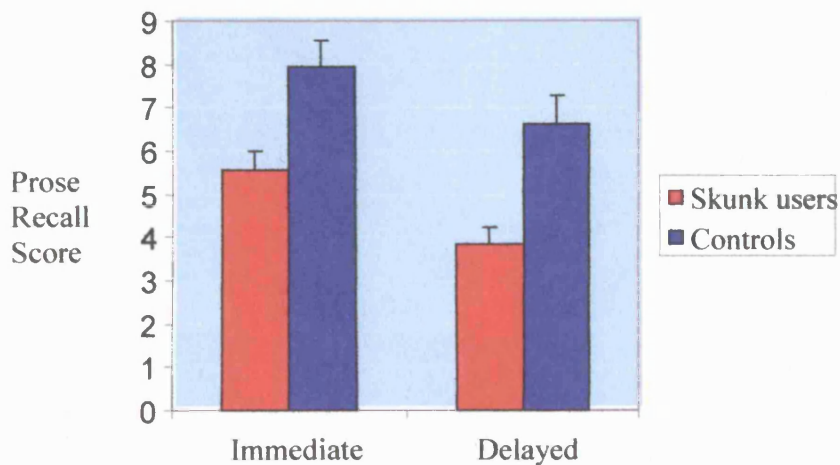
Table 6 Group Mean (s.d.) scores on Fluency and Digit Span and statistical comparisons.

	Group		F _{1,45}	P
	Skunk	Control		
Verbal fluency	12.44 (2.65)	18.15 (6.85)	15.653	p<0.001
Category fluency	16.74 (4.65)	18.30 (6.37)	0.944	NS
Digit Span Forwards	9.52 (2.45)	10.20 (2.24)	0.953	NS
Digit Span Backwards	6.11 (1.87)	7.45 (2.68)	4.072	0.05

Daily skunk smokers produced significantly fewer exemplars than controls in verbal fluency but not category fluency. Digits forwards showed no significant group differences but daily skunk users performed significantly poorer at digits backwards.

On Prose Recall, a repeated measures ANOVA showed a main effect of group ($F_{1,45} = 13.10, p=0.001$), reflecting poorer recall by daily skunk users than controls on both immediate and delayed recall (Fig 4). There was also a main effect of delay ($F_{1,45} = 64.45 p<0.001$) with both groups having better immediate than delayed recall (Fig. 4).

Fig 3: Prose recall scores by group and delay (bars represent standard error).



6. Correlations

The OLIFE and PDI correlated with SPIA total (Spearman's Rho: $r = 0.74$, $p < 0.001$, and 0.65 , $p < 0.001$, respectively). There was no significant correlation between skunk use variables (age of first use or years, quantity or frequency of use) and SPIA, delusions or schizotypy scores.

There was a negative correlation between digits backwards and years of regular skunk use ($r = -0.496$, $p = 0.009$) and a negative trend between category fluency and the number of joints smoked per session ($r = -0.46$, $p = 0.015$). Digit backwards scores correlated with SPIA-C (self report of cognitive disturbances: Spearman's Rho = 0.553 , $p = 0.01$) Negative rating of life events correlated with BDI scores ($r = -0.73$, $p < 0.001$). Among skunk users, those with higher total LES scores had higher SPIA scores ($r = -0.530$, $p = 0.004$).

Discussion

It is important to characterise the participants in this first study of daily skunk users. Their average age was 21 and they had been smoking on average for 5 years. Many (63%) met SDS criteria for dependence (and these criteria correlate highly with DSM-TR criteria for cannabis dependence, Martin et al., 2006). On average, the daily skunk users took MDMA once a month but no other drug with such regularity. The majority smoked an average of 2 spliffs in the evenings only and few found it hard to abstain for the day of the testing. Many said that they smoked to slow their thoughts, “to chill out” or because it “helps me handle stress.” Many of the students who smoked skunk seemed to have an insight into the cognitive effects and said that they would often stop smoking around exam time as they were aware of the impact that smoking skunk had on their ability to remember information.

Prodromal Findings

The findings of this study show a profile of prodromal symptoms in daily skunk users. As hypothesized, daily skunk users exhibited higher prodromal symptomatology than controls in all of the dimensions of basic symptoms. The basic symptom dimensions that were most pronounced in skunk users were cognitive disturbances and cognitive-attentional impediments. This is in line with previous research reporting cognitive impairments associated with recreational cannabis use (Solowij et al., 1998). The next greatest differences were in disturbances in experiencing self and surrounding and affective dynamic disturbances. The greater disturbances in self and surrounding in skunk users found in this study can be related to elevations in referential thinking following acute administration of Δ -9-THC reported by Dumas et al. (2002). The

affective dynamic disturbances reported in skunk users also confirms previous research (Patton et al., 2002; Lynskey et al., 2004) and is further supported by the significant differences in depression and anxiety scores. Perception disturbances were the next most affected and disturbances in body perception were the least reported, although still significantly higher in skunk users in comparison with controls.

Questionnaire measures pointed to a similar pattern of results with higher schizotypy and delusions in daily skunk users (providing support for Verdoux et al., 2003; Schiffman et al., 2005; Barkus and Lewis, 2008; Mason et al., 2008). In terms of schizotypy, daily skunk users rated more unusual experiences, cognitive disorganization and impulsive non-conformity. Interestingly, they did not differ in introverted anhedonia which may be reflective of the sample in that the majority were students who tended to smoke skunk socially in groups. Daily skunk users reported more delusional thinking and greater preoccupation and distress from these delusions. Their conviction in these delusions was also higher than controls.

It has been shown that acute cannabis smoking increases psychotic-like symptoms (Verdoux et al., 2003; Mason et al., in press) and this study shows that daily skunk users reported experiencing more psychotic like symptoms, or prodromal symptomatology. However, it is important to ask how does this “symptomatology” differentiate from acute cannabis intoxication in every day users? There is little dispute that cannabis intoxication can lead to acute transient psychotic episodes in some individuals (Arsenault et al., 2004). Yet, this study’s strength was in its use of the SPIA in that the interviewer always asked skunk using participants to differentiate between symptoms

they had experienced when “stoned” and experiences that they had had when they were not under the influence of skunk. As interviewers, SD, LM and I had to keep cueing participants back to exclude drug experiences from their ratings. However, without longitudinal data it is hard to rule out whether these group SPIA differences were pre-existing to skunk use.

Consistent with the latter suggestion, both Verdoux et al. (2003) and Mason et al. (in press) found that the psychotomimetic states following acute cannabis use were enhanced in individuals who were more psychosis prone (or schizotypal). In this study, daily skunk users with higher schizotypal traits had higher SPIA symptomatology. The significant correlation between SPIA and OLIFE scores either implies a personality element to the effects of the drug and/or an overlap in the constructs that these assessments tap. Either way, Mason et al. (in press) speculate that just as dopaminergic hyper-responsivity in schizotypal individuals has been observed (Soliman et al., 2007), cannabis-stimulated dopamine release may be the neurochemical basis of the elevation of psychotomimetic symptoms. The present study extends this possibility to include chronic as well as acute effects of cannabis use and the schizotypy findings support the continuum model of psychosis where high trait schizotypy is a vulnerability factor. This is the first time that schizotypy has been found to be associated with a clinical assessment of symptomatology.

As hypothesized, daily skunk users were also significantly more depressed and anxious than controls. Over half of the daily skunk using group met criteria for clinical depression and this is also reflected in the affective dynamic-disturbances reported on

the SPIA-A and the correlation between negative rating of life events and BDI scores amongst daily users. Negative thinking in daily skunk users may have affected the way that they answered the Life Events Survey. Although the number of negative life events was not significantly different between the two groups, the rating of these life-events was. Skunk users rated their life events more negatively and controls rated their life events more positively.

Cognitive Findings

The present results confirmed the findings of previous studies investigating the impact of recreational cannabis use on memory, executive function and fluency (Ramaekers et al., 2006; Pope et al. 2001; Fletcher and Honey, 2006). Daily skunk users performed significantly poorer on prose recall. Prose recall is a reasonable predictor of real-life memory performance (Sunderland et al. 1986) and the poorer performance by daily skunk users is indicative of impairments in explicit memory. Daily skunk smokers were impaired on digit span backwards but not forwards indicating that it is the manipulation of information in working memory that is affected by skunk but not maintenance. Although the main group difference was in skunk consumption, it is important to look at these results in light of the many other variables that have been reported to affect memory.

The lower scores of the daily skunk users on verbal fluency replicated the findings of Messinis et al. (2006), Block and Ghoneim (1993) and Pope et al. (2003) with recreational cannabis users. Interestingly, daily skunk users were significantly impaired on verbal but not category fluency. With hindsight, the category “musical instruments”

may have masked group differences given the association between cannabis use and music in this young age group.

Although there were no positive correlations of the skunk variables (years, quantity or frequency of use) with prodromal symptoms (SPIA), schizotypy, or delusions, there were associations between skunk use and cognitive measures. The more joints an individual smoked per session, the poorer they performed on category fluency and more years of regular skunk use was associated with poorer working memory (digits backwards). This suggests an accumulation of the effects of skunk and working memory. However, there was no evidence of a “critical period” of the effects of skunk in that there was no association between age of first cannabis use and either prodromal symptomatology or cognitive function.

How do cognitive impairments impact on prodromal symptomatology? If skunk causes dose-related cognitive impairments in memory and executive function, this may then contribute to how heavy daily users of skunk might interpret anomalous perceptual experiences as delusions, and other symptoms of the prodrome. From a phenomenological perspective, it is understandable how individuals who are finding it difficult to remember, sustain attention, communicate, monitor their behaviour and thoughts and plan and organise themselves might find it harder to process their experiences. It is not difficult to imagine how these deficits may lead to confusion, misattribution and distorted thinking. Memory deficits in individuals identified to be in the prodrome have been associated with poorer global functioning (Gschwandster et al., 2003). If users do not attribute perceptual anomalies to poor memory, concentration, or

visual disturbances caused by what they are smoking, they may be more likely to interpret these experiences to have meanings. Delusions are believed to be a cognitive effort to make sense of experiences. If skunk users have perceptual anomalies and other psychotomimetic experiences associated with the prodrome when they are not under the influence of the drug, this might become part of their normative experience with increasing tolerance to the effects of skunk and a hyperdopaminergic state. One could speculate that this may be a key mechanism in the link between cannabis and schizophrenia in vulnerable individuals.

Clinical Implications

The study has important clinical implications. The prodromal symptoms reported by daily users when not under the influence of skunk suggest a differentiation between acute skunk induced symptoms and early indications of a prodromal state. Daily users of skunk experience significant levels of prodromal symptomatology that is clearly separate to the acute effects of cannabis. In the past, naturalistic studies of recreational use have not distinguished between experiences when “stoned” and normal every day experiences. Given its widespread use in an age group of prime risk for psychotic disorders, the findings of skunk induced pre-psychotic state highlight substantial vulnerability in this group, and have implications for both the approach to skunk dependency and the funding of services. Nearly two-thirds of the sample were cannabis dependent (though a clinical cut-off is currently difficult) many are potentially at risk of psychotic and/ or affective disorder. Greater assessment and treatment options would seem a service priority in this area. If those cannabis dependent are in a pre-psychotic state, the NHS will need to accommodate this

service need. Cannabis dependence is now second only to heroin as the primary substance of misuse in those newly seeking treatment for addiction in Europe (EMCDDA, 2007).

While not ruling out other clinical tools, the SPIA proved sensitive in the current study and undoubtedly has clinical value in identifying and monitoring prodromal symptoms in skunk users both in addictions services and early intervention services. If individuals who are smoking daily experience psychotic-like symptoms whilst not under the acute effects of the drug, it can be distressing and clearly put them at risk for developing psychosis.

The skunk users in this study appeared to have a level of insight into the effects that skunk had on them. Performance on the digit backwards task correlated with SPIA-C (self report of cognitive disturbances) indicating (i) a level of insight in the daily skunk using participants and (ii) a degree of accuracy of their self-reports. Impairment in insight is often reported in schizophrenia. It may be that those that do not have this insight are more likely to make the transition to full psychosis. Indeed, Schulze-Lutter et al. (2007) have recently investigated the relationship between subjective and objective cognitive function in the early and late prodrome. They report that participants in an early initial prodromal state were less impaired than those with a late initial state. Although there was no formal measure of participant's insight, the correlations in skunk users' subjective and objective cognitive scores may suggest that skunk users symptoms were on the milder end of the scale.

The findings of symptoms identified to be “prodromal” in skunk users does not necessarily mean that skunk users are therefore in a developmental high risk group for developing psychosis. Many of these “symptoms” are signs and symptoms of other mental health disorders (bipolar disorder, severe depression) and it is important to put this symptomatology into context. However, many are indications of poor mental health and may well act as a vulnerability for the development of other psychopathology, indeed quite widespread levels of mild and moderate depression were indicated.

The results of this study have a number of implications at the individual level. A skunk smoker who presents with some of these prodromal symptoms will benefit from information about the association reported in this study. If these symptoms are distressing for them, they will benefit in support in ceasing their use of skunk, exploring the function of skunk for them and finding other ways to cope that do not have such potentially harmful side-effects. The results show that that individuals with cannabis dependence are likely to be suffering from depression and anxiety. As with many drugs, it may be that the acute effects of skunk allow users to avoid stress and anxiety in the short term but increase users experience of these in the long term. Furthermore, the deficits in memory and executive function found in the daily skunk users also have implications for clinical treatment of cannabis dependency. It is notable that 7 out of the 52 who expressed interest in taking part in the study repeatedly failed to attend the testing appointments. This has implications for any treatment for those with cannabis dependency who are seeking help. If they can not plan and organize themselves in order to reach outpatient appointments, they may benefit from home treatment initially for any successful engagement.

Future Research

This research has illustrated a broad profile of prodromal symptoms in individuals who use skunk every day but we do not know what percentage of these users may actually develop schizophrenia. A follow-up study would help us map this pathway and allow us to see if a change in SPIA prodromal symptomatology follows any change in skunk use over time. It would also allow us to learn if the impairments in working memory, episodic memory and fluency improve in those who reduce or cease their skunk use.

The duration of cognitive effects after cannabis users stop smoking is still under debate. Pope et al (2001) found that with abstinence of 28 days, long-term cannabis users showed no significant differences in cognitive tasks compared with non-using control groups. However, Lyons et al. (2004) and Bolla et al. (2002) found persistent cognitive deficits in decision making, memory, executive functioning, psychomotor speed and manual dexterity among heavy cannabis users who had been abstinent for 25 days. It is likely that participants were smoking less potent cannabis less frequently in these studies and a follow up skunk study would be more relevant to what is consumed today.

At present, it is difficult to generalize from this small sample of predominantly white British students. Replications with a more ethnically diverse sample would be useful. Furthermore, this study has brought up some phenomenological questions about skunk use which it would be helpful to address qualitatively. What motivates individuals to start using and maintains their use? Do users become tolerant to the effects? The level of insight that the skunk users in this study appeared to have may suggest a titration of

the level of psychotomimetic experiences that individuals are able to cope with. What determines the titration of their skunk use and how does their use change over time? The answers to these questions will have implications for both treatment and public education campaigns.

Limitations

There are a number of limitations to this study. Firstly, some of the individuals who may have been most negatively affected by their skunk use did not take part in the study because (i) they were paranoid that I was an undercover police officer or (ii) they were unable to organize themselves to get to the department. Paranoia and impairments in executive function are both commonly reported in psychosis. Secondly, much of the data from this study relied on self-report. Although correlations between objective and subjective measures give support to the responses, under-reporting is common in substance misuse. Thirdly, the urine analysis provided an indication of recent use but did not allow us to quantify how much or what was in individual's systems. I did not have a measure of the relative cannabinoid content of spliffs smoked which recent evidence (Morgan and Curran, 2008) has shown to have an impact on the psychotic-like effects of cannabis. Furthermore, "Skunk" has become a generic term for higher potency cannabis and there are many strains of varying potency. The study did not include a measure of the potency of the cannabis that each skunk user was using. Fourthly, as researchers, we were not blind as to which group participants were in. We had hypothesized and expected to see prodromal symptomatology in the skunk users and this may have biased our use of the SPIA. Fifthly, although the SPIA interview question

sheet was piloted by us as researchers together, there was no formal inter-rater reliability in using the SPIA.

Finally, despite the strength of the findings, it is difficult to discount other potential differences between skunk users and controls that may influence their reporting of prodromal symptomatology. Although participants had to have not been given a psychiatric diagnosis to be included in this study, this does not exclude the possibility that some of the skunk users may have had a pre-existing mental health difficulty. This is a fundamental issue in a cross-sectional research design. As stated before, Moore et al. (2007) identified over 50 confounding factors in their review of the effects of cannabis on psychotic symptomatology and we did not have the time or resources to accommodate for these in this study.

Conclusions

This is the first study to investigate the effects of skunk. It has been carried out at a time when political anxiety about the effects of skunk is high and it is important to consider the findings of this study in context. Although daily skunk users did show more symptoms of the schizophrenia prodrome than controls, clearly this does not mean that they will go on to develop schizophrenia. Further research is needed to investigate this. Most cannabis users do not develop psychosis. There is a dearth of public information on the composition of skunk and the known effects of cannabis. The public need to be made aware that the minimal CBD content of skunk reduces the anxiolytic potential (that users in this study reported seeking) of the drug at the cost of more psychoactive and neurotoxic levels of Δ -9-THC. The cognitive impairments that were most

pronounced in skunk users (deficits in working and episodic memory and verbal fluency) need to be shared with the public so that skunk users are aware of the potential impact of the drug upon their function and educational achievement.

This study supports the ACMD's (2008) Recommendation 6 that a well resourced public education campaign alerting young people to the dangers of cannabis use needs to be developed. Further investigation into a drug that can cause prodromal symptomatology in users is undoubtedly needed. If 81% of 2.6 million people in the UK are using it and 21% are using it daily, the potential implications for health costs are enormous. Longitudinal studies following the effects of skunk would help us understand the long term issues presented by this drug, and put us in a position to advise the public.

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Part 3

Critical Appraisal

Introduction

The following section provides a critical appraisal of the research, reflections on the recent reclassification of cannabis, future directions for skunk research and a personal reflection on the research.

Critical appraisal of the research

Before I started this research I had never heard of “the prodrome” or thought about observable pre-psychotic phenomena. I had recently read Mary Boyle’s book on schizophrenia (Schizophrenia: a scientific delusion) and I was far from convinced about the construct of schizophrenia let alone the concept of the prodrome. However, I appreciate the need for medical constructs for treatment development and I am keen to focus on preventative, early intervention, approaches to mental health. From meeting people who smoke skunk every day, it was clear that their presentations were distinctly different from “the norm” and I was curious to investigate this further.

Cannabis and schizophrenia

The association between cannabis use and schizophrenia has been investigated for decades and only recent meta-analyses have indicated that the relationship is probably causal. My review helped me to understand the neurobiological and cognitive reasons why this may be the case. Using the SPIA to investigate changes since skunk users began smoking the drug allowed us to begin to attribute prodromal symptomatology to skunk use. As controls were asked for changes in the past year, it allowed a control for

“normative” change. This was particularly noticeable in the adolescent control participants who reported more changes in the previous year.

The prodrome as a concept

The notion of a developmental period of time before an individual develops frank psychosis is undoubtedly helpful in understanding schizophrenia and the early intervention, treatment and management of mental health. However, the prodrome is a vague construct with multiple pathways which are difficult to reduce to core criteria. Furthermore, the transition rates for the SPIA reported by Klosterkötter et al. (2001) were 49.4% and others have ranged from 34% (Yung et al., 2004), to 65% (Miller et al., 2002). This leaves a large percentage of those showing prodromal symptoms who do not go on to develop diagnosable schizophrenia.

As a measure of prodromal symptomatology, the SPIA is one of the more sensitive instruments in comparison to other measures such as the Structured Interview of Prodromal Symptoms (McGlashan et al., 2001), the Comprehensive Assessment of At Risk Mental States (Yung et al., 2003) or the Initial Prodromal States (Simon et al., 2006). It is important to be mindful that the prodrome is a relatively new construct that is still developing. The SPIA does not include perceptual abnormalities such as distortions, illusions and hallucinations which perhaps are closer to the development of frank psychosis and the level of insight in skunk users in this study may indicate that if they are prodromal they are more likely to be in the early initial prodromal state (Schulze-Lutter et al., 2007). It would be helpful to compare the different instruments

with the skunk population to get an idea of their sensitivity (assuming that the prodome is a developmental period of time).

Participant Payment

Paying participants may have influenced this research in different ways. Firstly, those that were motivated by the financial incentive of £15 were more likely to be students and it subsequently had an impact on the sample. Secondly, payment may have had an impact on how much and what participants *reported* smoking. I was offering to pay individuals £15 if they had been smoking skunk every day for a year. Although I had urine analysis to check that they were smoking cannabis regularly, I had no way of determining (i) if this was skunk or (ii) if it was daily as the half life of cannabis in urine is prolonged. This became clear when two subjects at the end of two hours of testing revised the amount they reported smoking to 12 days per month. They knew that to be eligible for the research and the £15, participants needed to be smoking skunk daily. It was only in discussion with them at the end of the session that they admitted that they were not smoking daily and I had to exclude them from the analyses.

Exploratory Superstition Task

This study included the “Supertask” to investigate superstition and showed its potential usefulness as an objective measure. Skunk users saw patterns in the reinforced stimuli when reinforcement contingencies were totally randomised. The task was easy to use and participants enjoyed doing it. Although it assesses whether individuals saw patterns,

it may have been helpful to control for individuals' level of suggestibility as asking, "did you find any patterns?" may be a leading question.

Reclassification of cannabis

When the home secretary recently reclassified the class of cannabis, she ignored the expert advice sought by the Advisory Council on the Misuse of Drugs (ACMD, 2008). She was motivated by concerns about the prevalence of skunk in the UK market and the association of cannabis use with schizophrenia. However, she did this without the benefit of any research into the impact of skunk. In my view, this was a message to voters and not to cannabis users. Research by the Independent Drug Monitoring Unit (IDMU, 2007) has shown that many cannabis users do not i) understand the classification system or ii) know what classification cannabis is. The added cost of reclassification in terms of regulating drug traffic, sentences and fines would be far better invested in services and public education campaigns. In fact, the British Crime Survey showed that use declined between 20-25% in the past 5 years and cannabis was downgraded to a class C drug in 2004, (Murphy and Roe, 2007).

This study shows prodromal symptomatology in daily skunk users and I have concerns that the findings could be taken out of context and sensationalized without consideration of transition rates and follow-up studies. It is often the sensationalizing of research by the press that raises political pressure to make quick decisions like the one that Patricia Hewitt made in May 2008. The downgrading of cannabis in 2004 followed a press campaign to decriminalize the drug. Now, the attention of the press has moved to the "danger" of skunk and it has been reclassified. It is important to recognize that

reclassification does not affect use because cannabis use did not go up when it was downgraded to Class C.

It is also important to put the impact of skunk on prodromal symptomatology in context. Countless variables have been proposed to influence the development of schizophreniform disorder and these are likely to mediate the influence of skunk. There are a number of other variables that would be helpful to include. For example, in their comparative study of prodromal symptoms, Hao-Yang and Yong-Guan (2001) reported that the most common prodromal symptom was social isolation and it would be interesting to see what influence social support has on prodromal symptomatology in skunk users. Equally, according to Sundquist et al. (2004), 34.6% cases of schizophrenia would be prevented if people were not born and brought up in cities, compared to 5.4% of cases that would be prevented if people did not have parents or siblings who suffered from the illness.

Skunk: the future

A follow-up study would allow us to learn what happens to this group of daily skunk users in terms of prodromal symptomatology over time and how this compares to the transition rates reported by Klosterkotter et al. (2001). It would be interesting to know if the process of taking part in the research has an impact on their smoking behaviour. All of the skunk users wanted to be informed of the outcome of the study (and many were eager for feedback on their own results). For those who smoke less or cease smoking, does their prodromal symptomatology/ cognitive impairment get better?

Skunk research would benefit from a large qualitative investigation into what influences people to begin smoking and what maintains their smoking behaviour. Investigation into the function of skunk use would help us explore the reasons behind its use. Eight out of the 30 skunk using group said that they smoked it “to calm me down” or to “slow down my thinking” whether these were “anxious thoughts” or “lots of thoughts.” If it is self-medication that people are seeking from skunk, there may be alternative remedies that have less dangerous potential and this would aid both treatment and public education campaigns.

The frequency of skunk use has decreased in the past decade. In 1995, 54.9% of users were smoking cannabis daily whereas in 2003, only 21% of users reported using daily (Atha, 2005). It would be helpful to understand qualitatively why users think this is. Some said that they “could not find regular traditional cannabis anymore so they had to smoke skunk.” Has the potency of cannabis lowered people’s frequency of use, do people titrate to a level they are comfortable with, and how does this change over time in terms of tolerance?

Further research into the physiological and neurobiological effects of skunk on the brain is also needed. Different combinations of CBD and Δ -9-THC in variations of cannabis may have different effects. There is a huge variety in the potency of different strains of skunk cannabis in the UK. In recent police seizures, the skunk examined ranged in Δ -9-THC potency from 4% to 46% (Hardwick and King, 2008). I had no way of measuring what participants were smoking in terms of CBD or Δ -9-THC content. The development of a cheap street version of gas chromatography would allow users to

measure CBD and Δ -9-THC content of the cannabis they purchase and might give users more control over what they are smoking.

Personal reflection on the research

Motivation

I have always been interested in the effects of cannabis. When I was 19, a friend of mine who had smoked a vast amount of cannabis at a party accelerated his car into a tree. He survived to explain that he thought he could see a portal to another world and he knew that in order to get there he needed to be going as fast as possible. He will never play football again. On my clinical placements, I met clients who had also had cannabis induced psychoses and this further fuelled my curiosity.

Experience of Research

When I started this research I was apprehensive. My previous experience of research had involved an undergraduate BSc and a few audits. I was not confident about any statistical analyses it may involve and I saw the process of research on the course as a necessary hurdle that I would just have to face. I had always been more interested in the clinical side of training. It is only now when the research is coming to a close that I realize how much I have learned and how much I have gained from the experience. I now understand the process of carrying out research and this has given me confidence. This is undoubtedly the longest piece of work I have ever undertaken. It has been a daunting process and getting started was difficult. I spent far too long collecting papers for my literature review (it seemed easier to read other people's work than to start

typing) and I hadn't appreciated that I could have easily written my methods section while I was recruiting. In hindsight, I realize that I had no real comprehension of the process of carrying out research like this. I hadn't appreciated the stages of planning, recruiting, inputting, analyzing, thinking and reflecting and perhaps if I had understood these from the beginning it would have felt less overwhelming. For example, I hadn't realized how long it would take to run the superstition task macros and hadn't budgeted time for this. I'm sure that in comparison with many of my colleagues (who have already done PhD research) I was naïve in this way. Perhaps it just felt like a big jump from my BSc research 8 years ago.

My previous experience of using statistical theory and techniques was dry and not particularly exciting (another course hurdle). Until I owned my own data set, I didn't know how enjoyable uncovering the results could be. Now I feel confident in using SPSS and I have enjoyed owning my data and exploring it. Previously I would have preferred to look for a post without a research component when I qualify whereas now it is one of the core criteria of any post that I apply for. I enjoy putting together and interpreting the results of my work and the satisfaction of finding quantitative evidence for my experience.

Practicalities

Despite previous literature highlighting difficulties in memory and executive function found in cannabis users, I had not fathomed the practicalities of this in terms of coordinating skunk smokers to arrive at the department for testing. It took a number of DNAs and late nights in the department to realize that a strategy was required. I learned

that I needed to call to confirm the time and place that we had arranged more than once and I also sent emails with maps showing Goodge Street station and the UCL area. I then called people on the day to remind them and met them at the Goodge Street station and walk them to the department. The skunk users also took much longer to test. They had more to say on the SPIA and their processing speed seemed slower (although I did not get a chance to test this). Fortunately, the skunk users as a population generally were relaxed and pleasant to test.

Researcher Role vs Clinician

A number of participants were interested in the changes that they had noticed since they had been smoking skunk and were motivated to take part in the research in seeking reassurance that they were OK. In their eyes, they were coming to see a trainee psychologist who'd tell them whether or not they were "OK." Where individuals were showing basic symptoms, it was difficult to know how much to encourage them to see their GP. For most, these symptoms were not distressing but where they were, I did encourage participants to visit their GPs. Some wanted to discuss this in detail and the boundaries between role as a researcher and as a clinician were hard to maintain when my instinct was to contain and support them in seeking professional help.

It was clear that the enterprise of answering questions about their skunk use and about the impact that this was having was a space for reflection that perhaps they had not had before. Many wanted specific feedback on their performance on the assessments which as a researcher I was unable to give. All wanted to know the outcome of the study and I have arranged to email a synopsis of the findings to everyone. In terms of an agency of

change, the process of reporting the negative effects of their skunk use was having a noticeable impact on participants and most were keen to discuss these in terms of thinking about decreasing or ceasing their use. As has been shown in the correlations between subjective and objective measures, most of the skunk users recognized the impact the drug was having on them. As already mentioned, many took breaks from smoking when they had exams or important events when they wanted their memories to function.

This made me question my role as a researcher. If skunk was having a negative impact on participants, did I have a responsibility to inform them and where did the boundary of my role lie? This raised an ethical issue for research as a whole for me. The participants did not sign up for clinical assessment; they offered to take part in research. While I was able to inform individuals that their scores were high and strongly advise them to see their GPs, it felt strange not having the clinical responsibility that I have become accustomed to on placement.

Being part of a team

My experience of this research as part of a team at UCL has been a very positive one. Although Lisa Monaghan, Suzanna Duffin and I were investigating different drugs, our battery of tests were the same. This provided a support that I do not think I can quantify. As researchers, Suzanna, Lisa and I were able to sound out ideas, approach methodological issues and the difficult practicalities of testing together. Furthermore, we were able to support each other through lonely testing evenings in the department. It was not just as a team that we had support. I found huge confidence in the Clinical

Psychopharmacology Unit (Professor Val Curran, Dr Celia Morgan and Dr Oliver Mason) and despite my limited research background, I felt enabled and supported. I never imagined that I would finish the course feeling capable of setting up independent research and now surprise myself in how interested I am in doing so.

Dissemination

From the literature review to the empirical investigation, this research has addressed the mechanisms linking cannabis use and prodromal symptomatology and investigated these in skunk users. This first investigation into the impact of skunk suggests prodromal symptoms and cognitive deficits in daily users. Undoubtedly, further investigation is needed but the confirmation of cognitive deficits and the finding of prodromal symptoms reported in skunk users motivate me to try to publish and disseminate the results. I feel a responsibility in contributing to the existing knowledge base and welcome constructive criticism which will allow this knowledge to grow. I feel that in this case, with knowledge comes responsibility and I would like to be involved in thinking and managing public education campaigns – particularly to schools and in areas where children are most vulnerable. This way, on the basis of evidence, people can make informed decisions about using skunk, be aware of the potential negative impacts and of ways to seek help.

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Appendix A - Joint Thesis

Joint Thesis

This thesis was completed as part of a joint project to investigate the chronic effects of ketamine, cocaine and cannabis on prodromal symptomatology and cognitive dysfunction. Three separate theses were completed as a result of the joint project. They were entitled:

- 1) Prodromal symptoms in daily skunk users.
(Suzanna Hunt, Trainee Clinical Psychologist, UCL)
- 2) Do ketamine users show psychotic symptomatology and cognitive dysfunction associated with the pre-psychotic state of the psychoses?
(Suzanna Duffin, Trainee Clinical Psychologist, UCL)
- 3) Chronic Cocaine use and prodromal symptoms of schizophrenia
(Lisa Monaghan, Trainee Clinical Psychologist, Royal Holloway)

All trainees completed the design of their individual theses together, as some participants were shared. Below is an outline of the contribution of each individual member to the joint project:

- 1) Suzanna Hunt: Completed the semi-structured interview protocol for the SPI-A alongside Suzanna Duffin. Piloted full assessment battery with 1 skunk user and 2 controls. Collected data as outlined in her methodology for 27 daily skunk users and 15 controls (reporting no illicit drug use). Data for 5 additional control participants was gained from control data gathered by Lisa Monaghan.
- 2) Suzanna Duffin: Completed the semi-structured interview protocol for the SPI-A alongside Suzanna Hunt, and created the scoring sheet for the SPI-A. Collected data as outlined in my methodology from 21 frequent and 20 infrequent ketamine users. Data for 20 matched control participants was selected from control data gathered by Suzanna Hunt and Lisa Monaghan.
- 3) Lisa Monaghan: Piloted the SPI-A with recreational drug users. Collected data as outlined in her methodology for 30 cocaine users and 15 controls (reporting no illicit drug use). Data for 15 additional control participants was gained from control data gathered by Suzanna Hunt.

Appendix B - Ethical Approval

SPECIAL NOTE

**THIS ITEM IS BOUND IN SUCH A
MANNER AND WHILE EVERY
EFFORT HAS BEEN MADE TO
REPRODUCE THE CENTRES, FORCE
WOULD RESULT IN DAMAGE**



Amendment Approval Request Form

1	ID Number: 0052 / 001	Name and Address of Principal Investigator: Professor H Valerie Curran
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2	Project Title: The determinants and psychological consequences of ketamine use
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3	Information about the amendment: (a) Is the amendment purely administrative? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A (b) Has the Participant Information Sheet/Consent Form been changed as a result of the amendment? If yes, please enclose a copy. <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
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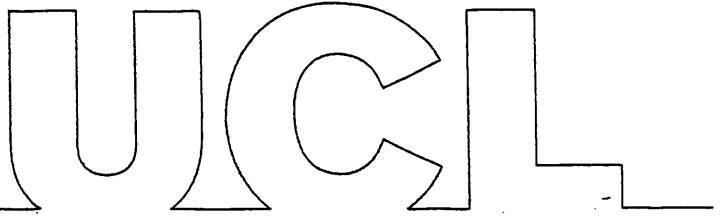
4	Summarise the issues contained in the amendment: The amendment is for a spin-off study from the main project which has suggested that some ketamine users exhibit 'prodromal' (psychosis-proneness) symptoms. To investigate this formally, we will be administering the Schizophrenia Proneness Inventory, which is a semi-structured interview measure that examines a range of experiences phenomenologically related to schizophrenia. We will also be adding some straightforward tasks that tap cognitive changes in schizophrenia (superstition, context modulation, and memory). We will compare ketamine users with 2 groups of other drug users by splitting the group of polydrug users in the main study into those who use cannabis and those who use stimulant drugs. The rationale for this comparison is that i) cannabis use is a known trigger of psychosis-like symptoms and ii) drugs that are primarily dopamine-releasers (like stimulants) can also induce psychotic symptoms. There will be four postgraduate students (Doctorate in Clinical Psychology) carrying out this study: Suzanna Duffin, Suzanna Hunt and Lisa Monaghan. To assess the additional participants, we request an extension of the ethical approval of the project until December 2008.
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5	Please give any other information you feel may be necessary:
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Signature of Principal Investigator:	Date of Submission: 16 February 2007
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FOR OFFICE USE ONLY: Amendments to the proposed protocol have been ... <i>approved</i> ... by the Research Ethics Committee.	
Chair's Signature: _____	Date: <i>12/3/07</i>

Appendix C - Consent Form



Consent Form

CONFIDENTIAL

The determinants and psychological consequences of ketamine use

Investigators: Dr. Celia Morgan, Suzanna Duffen, Suzanna Hunt, Lisa Monaghan, Leslie Muetzelfeldt, Prof. H. Valerie Curran

Please complete the following:

delete as necessary

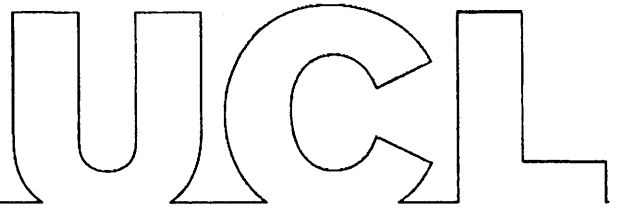
1. Have you read the information sheet ? YES / NO
2. Have you had an opportunity to ask questions and discuss this study ? YES / NO
3. Have you received satisfactory answers to all your questions ? YES / NO
4. Have you received enough information about this study ? YES / NO
5. Which investigator have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

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

Name (please print)

Investigator.....

Appendix D - Information Sheet



VOLUNTEER INFORMATION SHEET

The determinants and psychological consequences of cannabis use

Investigators: Suzanna Hunt, Suzanna Duffin, Lisa Monaghan, Leslie Muetzelfeldt, Dr. Celia Morgan, Prof. H. Valerie Curran

Purpose of the study:

To determine the long term effects of recreational skunk use

INFORMATION LEAFLET FOR VOLUNTEERS

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

WHAT IS THE PURPOSE OF THE STUDY?

We are interested in the effects of recreational drug use on mental functioning and mood. We also wish to examine whether mental functioning and mood changes as use of skunk and other drugs changes over time.

SOME BACKGROUND TO THE RESEARCH

Many drugs have long term effects; for instance people who drink lots of alcohol often find their memories are not as good as they were. This can often be affected by factors such as the length of time they have been drinking and the quantity that they drink. The present study aims to find out what the long-term effects of using recreational drugs, in particular skunk, may be, by examining how any changes in cognitive functioning are related to changes in drug use.

WHAT WILL BE STUDIED?

We will be looking at memory, problem solving and concentration as well as mood and mental state in people who take skunk, people who take other drugs but not skunk and people who do not take any recreational drugs.

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

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

If you agree to participate, on the testing day you will come to the Psychopharmacology Laboratories at UCL or if agreed, the experimenter may come to your home. The experimenter will then record some information about your current drug use and patterns of use, including giving a hair and urine sample, and you will take part in an interview about your mood and mental state. Altogether this will last for approximately half an hour. You will then complete some computer-based cognitive tasks, which will last for approximately 1 hour, with space for a break if you should need one. You will then be paid for participation.

CONFIDENTIALITY

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

If you require further information please ask Suzanna Hunt

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

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

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

Appendix E – SPIA Interview Schedule

SCHIZOPHRENIA PRONENESS INSTRUMENT – ADULT VERSION (SPI-A) INTERVIEW SCHEDULE

I would like to ask you a number of questions about some of your experiences since you started smoking skunk. I need to emphasise that I am not asking you about experiences you may have had **WHILST** you were on the drug or whilst you were coming down from the drug, **BUT** rather I'm interested in your everyday experiences.

A) Affective-dynamic disturbances

A1: Impaired tolerance to certain stressors

GENERAL QUESTION

- Do you think your ability to tolerate stress has decreased since you started smoking skunk? So specifically I am asking about stress that involves unusual or new things, social everyday situations (like having a chat or watching TV), and working under time pressure?

IF YES

OK – I'm going to ask you a few more specific questions about this now

GO TO A1.1

IF NO

move to A2

A1.1 Impaired tolerance for unusual, unexpected or specific novel demands

- Can you handle new, unusual or suddenly occurring tasks as well as before you started smoking skunk? Things like a specific demand at work or a visit to the local authorities, or moving or having a holiday?
- Do you feel like you can't handle it when something unusual or unplanned happens, so a situation like this would be too exhausting or too much?
- Do unusual or unplanned things happening cause feelings like being nervous, tense, restless, or dizzy, or problems with sleeping?

Rating: Frequency I

If needed: Effects on performance behaviour (VI)

A1.2 Impaired tolerance for certain social everyday situations (which are socially neutral)

- Can you still tolerate being around others or having conversations with others since you started smoking skunk?
- Can you still do things like go to the shops, go on public transport, or go to public events as comfortably as you did before you started smoking skunk?
- Do any of these situations cause feelings like nervousness, tenseness, restlessness, heart beating, sweating, pain or concentration difficulties?
- Do you sometimes feel like watching or hearing things like the radio or TV is just too much for your senses, like its exhausting or you can't handle it?

Rating: Frequency I

If needed: Effects on performance behaviour (VI)

A1.3 Reduced ability to work under pressure of time or rapidly changing different demands, therefore start to avoid such situations or be more rigid in their behaviour

(NOT A.8.4 which is more to do with a cognitive deficit in not being able to divide attention)

- Are you as able to deal with having several different things to do at once and working under time pressure, as you were before you started smoking skunk?
- Does having multiple tasks to do, or being in time pressured situations make you more nervous and agitated now? Do you find you have problems with concentration during such situations, or you experience nervousness, heart racing, restlessness, sweating or pain?
- Do you have to avoid being rushed since starting to take skunk?

Rating: Frequency I

If needed: Effects on performance behaviour (VI)

A2 Change in mood both positive and negative (usually low or emotionless mood – always unrelated to external events) AND emotional responsiveness

NOT brief or transient change; NOT A3 which is to do with activities and interests losing their positive impact on client

- Has your GENERAL mood changed overall since you started smoking skunk – for example has it become more negative and low?
- Can you be as happy, laugh and enjoy things as much as you used to?
- Do you think your feelings have become less intense since you started smoking skunk?
- Do you think you have become less emotionally involved in things since you started smoking skunk? Is this generally the case or just with certain things?

Rating: Frequency I

If needed: Subjective burden (IV), Effects on quality of life (VI), Areas of life (VIII)

A3 Decrease in positive emotional responsiveness towards others. (decreased feelings of love, affection, sympathy, pity and/or interest towards other persons or previously important activities/hobbies. DO NOT score this item if decrease in responsiveness & hobbies, etc is a coping behaviour to a decreased stress tolerance with respect to everyday situations)

- Are you still as interested and emotionally involved in things you like to do - your hobbies etc. – as you were before you started smoking skunk?
- Do you still feel the same affection and/or interest for your relatives and friends as before you started smoking skunk?

Rating: Frequency I

If needed: Subjective burden (IV), Effects on behaviour (VI)

B) Cognitive-Attentional impediments

OK – I'm now going to ask you about your thinking and attention abilities since you started smoking skunk.

B1 Inability to divide attention

(difficulty splitting attention between stimuli which require different senses; problems *switching* attention not scored here)

- Can you do two things at the same time as easily as before you started smoking skunk? So for example, can you write notes *whilst* you talk to someone on the phone, or can you do the cooking AND talk to someone at the same time?
- Do you have to just do one thing at a time to make sure it gets done properly?

Rating: Frequency II

If needed: Subjective burden (IV), Effects on B&P (VI)

B2 Feeling overly distracted by stimuli

(one's attention is raised *randomly* by external stimuli you don't want to attend to); NOT difficulties intentionally splitting attention – this is scored in B1 or any sort of cognitive interference that occurs without the presence of an external stimulus (C2 & D3)

- Do you think that since you started smoking skunk, everything around you catches your attention, even if you don't want it to?
- Is your *thinking* interrupted, aimless or disturbed by being too aware of other things? For example, have you ever found that you can't focus on something because other things around you have *randomly* taken your attention away?

Rating: Frequency II

If needed: Subjective burden (IV), Effects on B&P (VI)

B3 Difficulties concentrating

(NOT because of any other cog disturbance such as intruding thoughts (C2) obsessive/ perseveration of thoughts (O1), thought pressure (D3), thought blocking

(C3), disturbance of comprehension of visual or auditory material (C4), attention disturbances (B1, B2, O7) language problems; could be because of memory disturbances – score this in C.1.8./9 too)

- Concentration problems are when you find it difficult to keep your mind on a task for several minutes, like watching TV or reading, or making a cup of tea. Thinking about that, do you think you have had more difficulties concentrating since you started smoking skunk?
- Do you know the reasons for your concentration problems – for example, are they because of your thoughts racing or are they triggered by work, or difficulties understanding what others are saying to you?
- When you are concentrating on something, do thoughts about other things come into your mind? Are your thoughts suddenly gone or do you simply lose the train of thoughts? Is it always things like that which cause your difficulties concentrating?
- Can your concentration problems occur at any time or just when you feel quite stressed?

Rating: Frequency I

If needed: Subjective burden (IV), Coping (V), Effects on B&P (VI)

B4 Difficulties to hold things in mind for less than half an hour

- Have you noticed you have more difficulties keeping things in mind, even for half an hour, since you started smoking skunk? For example, after you have read something or watched something on TV, can you still remember the main content half an hour after?

Rating: Frequency II

If needed: Subjective burden (IV), Coping (V), Effects on B&P (VI)

Do not ask B5 if criteria B3 scored (NOTE: if C4 or C5 are scored, then score for B5 is invalid – see paper for explanation why)

B5 'Slowed-down' thinking

(general complaint that thinking has become slower and harder; which might occur AS A RESULT of other cognitive disturbances)

- Do you sometimes feel that your thinking has become slower, harder or more sluggish since you started to take skunk?
- For example, is every answer in this interview a real effort?

Rating: Frequency II

If needed: Subjective burden (IV), Coping (V), Effects on B&P (VI)

B6 Lack of 'thought energy' or goal-directed thoughts

(NOT loss of performance of automatically performed skills - O11)

- Do you think you sometimes lack the strength or energy to think or speak, since you started smoking skunk?
- Do you sometimes have difficulties developing your own ideas or planning things, such as cooking?

Rating: Frequency II

If needed: Subjective burden (IV), Coping (V), Effects on B&P (VI)

C) Cognitive disturbances

OK - I'd now like to ask you some questions about your thinking and your decision making abilities since you started to take skunk.

C1 Increased indecisiveness with regard to insignificant choices between equal alternatives

(different to loss of spontaneity and carefree responding - B3)

- Is it more difficult to make decisions since you started smoking skunk, even about the most unimportant things, such as which washing powder to go for?

Rating: Frequency II

If needed: Subjective burden (IV), Effects on behaviour (VI), Areas of life (VIII)

C2 Thought interference

(when *random* thoughts, unrelated to current thoughts or external events disturb the person's train of thought); NOT obsessive perseveration of thought (C.1.2), thought blocking (C3), or distraction of attention by external stimuli (B2)

- Since you started smoking skunk, do you sometimes find it difficult to take part in a conversation or concentrate on a book or TV, because unimportant and unrelated thoughts enter your mind?
- Do you sometimes have difficulties participating in a conversation, because your thoughts drift away to other things that have nothing to do with what's being discussed since you started smoking skunk?

Rating: Frequency II

If needed: Subjective burden (IV), Effects on performance (VI)

C3 Thought blockages

(5 subtypes: sudden disappearance of old thought without replacement by new one / sudden disappearance of old thought *with* replacement by new one / slow and gradual disappearance of old thought without new thought afterwards / slow and

gradual disappearance of old thought, as new intrude at same time / loss of thread, train of thoughts

- Since you started smoking skunk, do you sometimes lose your train of thought, or do your thoughts suddenly disappear as if they were cut short?
- Do your thoughts suddenly stop sometimes, as if they are being blocked or as if the thought gradually fades?
- Does another thought take the place of the old one?

Rating: Frequency II

If needed: Subjective burden (IV), Coping with it by increasing effort (V), Effects on performance (VI)

C4 Disturbance of receptive speech

(When reading or listening to others, the person has difficulties or is unable to comprehend and recognise the meaning of words, word sequences or sentences, e.g. in conversations, movies, TV or radio) DO NOT score when due to concentration difficulties or when occurrence is only during very high demand tasks such as a scientific lecture.

- Do you sometimes have difficulties *understanding* conversations, or when reading simple books or articles, since starting skunk?
- Since you started to take skunk, is it sometimes difficult to understand simple words or sentences – is it like you are reading or hearing something in a foreign, but well-known language: so you recognise the word but have to think about its meaning?

Rating: Frequency II

If needed: Subjective burden (IV), Effects on performance, avoidance (VI)

C5 Disturbance of expressive speech

(problems producing adequate words – word fluency and precision slowed down, difficulty finding correct words, sometimes words used which are associated but not correct); NOT a difficulty expressing feelings verbally and non-verbally.

- Do you speak as fluently and precisely as before you started smoking skunk? For example, is it sometimes difficult to find the right words or build the right sentences?

- Have you begun to use the same words and phrases again and again to avoid these difficulties?

Rating: Frequency II

If needed: Subjective burden (IV), Effects on performance, speaking (VI)

C6 Disturbance of immediate recall

(complaints about not being able to remember things for even a very short time - 5 to 40 sec)

- Do you sometimes have difficulties remembering things immediately since you started smoking skunk? For example, are the questions I'm asking hard to remember straight after I've asked them?
- Do you sometimes have difficulties to follow a conversation, because you quickly forget what was just said?

Rating: Frequency II

If needed: Subjective burden (IV), Coping (V) , Effects on performance (VI)

D) Disturbances in experiencing self and surrounding

I'm now going to ask you some questions now about your emotions and your beliefs about yourself.

D1 Decreased capacity to discriminate between different kinds of emotions

(all feelings often experienced as monotone or tainted with a dysphoric quality, even ,positive' ones). NOT change in mood and emotional responsiveness (A2) or a decrease of positive feeling toward others/ previously enjoyed activities (A3)

- Are you always able to tell the difference between unpleasant and pleasant, negative and positive feelings clearly and easily? How does this compare to before you started smoking skunk?
- Have all emotions become somehow unpleasant since you started skunk?

Rating: Frequency II

If needed: Subjective burden (IV)

D2 Increased emotional reactivity in response to routine social interactions that affect the patient or his/her significant others (emphasis on social interaction not everyday events like sad music, TV or books BUT on emotional reactivity to self and significant others which may have not been so strong previously AND the participant is aware they are over-reacting); NOT as the result of a specific trigger like thought perseveration (O1)

- Do the actions or comments of others, or discussions and arguments, get you more worked up now than before you started smoking skunk?
- Do you have the feeling that you are more sensitive now – that almost everything gets under your skin?

Rating: Frequency I

If needed: Subjective burden (IV), Effects on B&P (VI)

D3 Thought pressure

(great number of random, different thoughts/ images enter the mind and disappear again in quick sequences without the person being able to suppress or guide them) NOT thought interference (C1), nor though perseveration where many thoughts/ images come from shared theme (O1)

- Do you sometimes have the feeling that you are not able to control your thoughts, in comparison to the time before you started smoking skunk - Do your thoughts just run wild, impossible to control?
- Do you sometimes jump from one subject to another so much that your single thoughts feel unrelated to each other, since you started smoking skunk?

Rating: Frequency II

If needed: Subjective burden (IV), Effects on B&P (VI)

D4 Unstable ideas of reference, 'subject-centrism'

(individual feels they are the focus of attention but has no clear reason for this and overcomes this quickly NOT ideas of reference related to depressive, social anxiety or paranoid beliefs)

- Do you sometimes feel that things going on around you have a special meaning for you, even though you know at the same time that this is improbable or impossible? How does this compare to before you started smoking skunk?
- Do you sometimes feel as if random things were meant especially for you, e.g. comments on the radio or TV? What does it take for you to realise that this is just a sudden idea and not true? How long does this idea last?

Rating: Frequency II

If needed: Severity (III), Subjective burden (IV), Areas of life (VIII)

D5 Changed perception of the face or body of others

(face or body of others is seen as strange and peculiar, e.g. colour of skin, eyes or hair - may lead to impaired ability to recognise facial expressions)

- Do the faces or bodies of other people sometimes appear different or distorted since you started smoking skunk?

Rating: **Frequency II**

If needed: **Severity (III), Subjective burden (IV), Effects on B&P (VI)**

E) Body perception disturbances

General question:

Have you ever had unusual or peculiar body sensations, unlike those you normally experience or are familiar with? Can you describe them? Have you seen a doctor about it, and if so, what did they say?

IF YES: **E1**

IF NO: **Go to F**

E1 Unusual bodily sensations of numbness and stiffness

(resemble paraesthesias incl. numbness and stiffness, wandering sensations of stiffness, which can be transient or chronic. NOT real motor blockages (O10; where person can not move), NOR slowing down of movements UNLESS slowing down is accompanied by sensations of stiffness, NOR the feeling that the body, or parts of it do not belong to oneself (F6)

- Have you sometimes experienced unusual, numb or stiff feelings in your arms or legs or in another part of your body, since you started smoking skunk?
- When you experience this stiffness / numbness, do you feel as if you are paralysed and cant move, or are you actually moving slower? (qu to rule out O10 etc)

Rating: **Frequency II**

If needed: **Severity (III), Subjective Burden (IV), Effects on performance (VI),
Consulting a doctor (VII)**

E2 Unusual bodily sensations of pain in a distinct area

(painful, often long-lasting sensations with a piercing, tearing or shooting quality, which cant be neurologically explained. Often occur at certain times of day, like sudden attack; often accompanied by affective disturbances; depth location is also often difficult. NOT Intense feelings of being electrified (E4)

- Do you sometimes have a peculiar pain, like a piercing, tearing or shooting feeling, since you started smoking skunk? Where is it located; how deep is it?
- Is this pain different from pains you had before you started smoking skunk?

Rating: Frequency II

If needed: Severity (III), Subjective Burden (IV), Effects on performance (VI), Consulting a doctor (VII)

E3 Migrating bodily sensations wandering through the body (fluctuating, wandering sensations around body, which can increase to sometimes painful / attack-like severity); NOT a more static sensation (E5)

- Do you sometimes have irritating and uncomfortable body sensations that move through your body, and can even become painful since you started smoking skunk? If you do, what route do they take?
- Is this moving sensation different from sensations or pains you had before you started smoking skunk?

Rating: Frequency II

If needed: Severity (III), Subjective Burden (IV), Effects on performance (VI), Consulting a doctor (VII)

E4 Electric bodily sensations, feelings of being electrified

(feeling like being given an electric shock, which are not related to external influences. If described as painful, only score here NOT E2. If the electric sensations whirl, wander or circle around the body, score at E3 too)

- Since starting to take skunk, do you sometimes experience a feeling that is like being given an electric shock?

Rating: Frequency II

If needed: Severity (III), Quality of being new/different (IV), Subjective burden, (VI), Effects on performance (VI), Consulting a doctor, (VII)

E5 Bodily sensations of movement, pulling or pressure inside the body or on its surface

(sensations perceived as if something is actually moving inside the body, organs or on the skin - itching, vibrating, shaking, knocking, trembling, quivering, twitching, crawling, digging, tearing, stroking); NOT just a sensations swirling, circling around body (E3)

- Since you started smoking skunk, do you sometimes have the feeling as if something is moving inside your body, or on your skin?
- How would you describe this feeling? Is it like a twitching, jumping, vibrating, knocking or trembling?

Rating: Frequency II

If needed: Severity (III), Subjective Burden (IV), Effects on performance (VI), Consulting a doctor (VII)

E6 Sensations of the body or parts of it extending, diminishing, shrinking, enlarging, growing or constricting

(can affect whole body or just parts, and generally 'attack-like'. Often accompanied by affective changes, which can escalate to panic depending on the 'reality' of the sensations); NOT sensations of body being heavy, light or empty, falling or sinking, NOR depersonalisation.

- Do you sometimes feel as if your whole body or parts of it is going to shrink or grow or change in some way?

Rating: Frequency II

If needed: Severity (III), Subjective Burden (IV), Effects on performance (VI), Consulting a doctor (VII)

F) Perception disturbances

I'm going to ask you a few more questions about your vision and hearing now.

F1 Hypersensitivity to light or certain optic stimuli

(NOT scored if these experiences occur as a result of a migraine, epileptic aura or another known physical illness)

- Have you become much more sensitive to sunlight, or felt things were brighter than usual, since you started smoking skunk?
- Have you consulted a doctor about this? If so, what did they say?

Rating: Frequency II

If needed: Subjective burden (IV), Coping (V), Effects on B&P (VI)

F2 Photopsia

(are simple moving or fixed white, bright or coloured hallucinations in form of flashes, stars, flames, circles or very strong, blinding light. ONLY SCORE when it causes SUBJECTIVE complaints and is NOT related by the individual to the outside world but to themselves)

- Do you sometimes see flashes of light or other very bright figures like stars, dots or flames in your eyes? Have you always had this, or has it developed since you started smoking skunk?
- Have you consulted a doctor about this? If so, what did they say?

Rating: Frequency II

If needed: Subjective burden (IV), Effects on B&P (VI)

F3 Micropsia, Macropsia

- Do objects ever appear bigger or smaller than they really are, or distorted in any way?
- Have you always had this, or has this developed since you started smoking skunk?

Rating: Frequency II

If needed: Severity (III), Subjective burden (IV), Effects on B&P (VI)

F4 Hypersensitivity to sounds or noise

(sounds of unchanged intensity or quality are experienced as too loud, distracting or annoying; NOT changed intensity, quality of sound, F5)

- Are you much more sensitive to sounds and noise in comparison to before you started smoking skunk?
- Have you consulted a doctor about this? If so, what did they say?

Rating: Frequency II

If needed: Subjective burden (IV), Effects on B&P (VI)

F5 Changes in the perceived intensity or quality of acoustic stimuli

(Do not score a sole hypersensitivity to sounds without any qualitative changes in auditory perceptions (F4) or derealisation – which also requires visual perceptual distortions (O8) here)

- Do you sometimes have strange problems with hearing? Can you describe them?
- Do you sometimes have sudden and short-lived difficulties with your hearing such as sounds seeming muffled or less loud or short periods of deafness?
- Have you always had these experiences, or have they developed since you started smoking skunk?
- Have you consulted a doctor about this? If so, what did they say?

Rating: Frequency II

If needed: Severity (III), Subjective burden (IV), Effects on B&P (VI)

F6 Somatopsychic bodily depersonalisation

The body or parts of it are perceived as not belonging to oneself anymore, as isolated or separated from each other or not existing at all OR body is perceived as falling apart/ body parts seem no longer to be connected, although all parts still belong to the person affected. (NOT depersonalisation nor visual perceptions of changes in the person's face or expression which cause the individual to repeatedly check themselves in the mirror)

- Do you sometimes feel as if parts of your body have been separated from the rest of your body or do not exist anymore?
- Are you sometimes unable to feel your body or parts of it?
- Do you sometimes have a feeling as if your body could fall apart like a jigsaw?

- Have you always had this, or is it an experience that has developed since starting to take skunk?

Rating: **Frequency II**

If needed: **Severity (III), Subjective burden (IV), Effects on B&P (VI),
Consulting a doctor (VII)**

O) Optional Extras:

O1 Thought perseveration

(usually re: events, conversations, mundane things that have happened a few hours earlier, maybe even the day before; thoughts all following the same theme. NOT a depressive rumination about a negative future, NOR thought interference (C2) where unimportant thought/image interferes with functioning *without* being constantly repeated, NOR thought pressure (D3) where there is a succession of unrelated thoughts)

- Do you sometimes have to think about past unimportant conversations or events, when you want to think about something else?
- Does this ever take the form of images in your mind's eye?

Rating: **Frequency II**

If needed: **Subjective Burden (IV), Coping (V), Effects on B&P (VI)**

O2 Decreased ability to discriminate between ideas and perception, pure fantasy and true memories

- Are you sometimes unsure whether you actually see or hear something, or if you just imagined it?
- Do you sometimes become confused whether you have actually done certain things in the past or just imagined them? Do you ever ask others to make sure?
- Have you always had these experiences, or have they developed since you started smoking skunk?

Rating: **Frequency II**

If needed: **Subjective Burden (IV), Coping (V), Effects on B&P (VI)**

O7 Captivation of attention by details of the visual field

(NOT 'feeling overly distracted by stimuli' (B2) where attention is easily distracted by *all* kind of things going on in the environment, so that s/he has difficulties to focus on one thing, here, the attention is fixed on one thing and the rest of the environment is not paid any attention anymore)

- Since you starting smoking skunk, have you ever noticed that specific aspects of the environment you are looking at really stand out in a striking way, and seem somehow isolated from the rest?
- Do you ever have to stare at these details, without actually wanting to?

Rating: Frequency II

If needed: Subjective Burden (IV), Coping (V), Effects on performance, behaviour, avoidance (VI)

O8 Derealisation

- Since starting to take skunk, do you sometimes experience your surroundings as changed, unreal or strange? As if the world around you isn't quite real? (subtype 1)
- Have there been times when you have experienced a high, euphoric mood during which your surroundings, the landscape, animals or people seemed different, somehow great, impressive and moving? (subtype 2)

Rating: Frequency II

If needed: Severity (III), Subjective Burden (IV)

O10 Motor Blockages

(Impediment or complete blockage of intended motor actions that appear attack-like, all of a sudden, and vanish quickly)

- Are you sometimes, especially in the morning, suddenly unable to speak or move although you are fully awake?

Rating: Frequency II

If needed: Subjective Burden (IV), Coping (V), Effects on B&P (VI)

AND FINALLY....

Are there any other changes to how your mind works I may have missed? or any feelings or behaviours that you think have changed since you started smoking skunk?

How often has this affected you?

How much does it affect you?

Frequency

Looking at this scale and smoking into account everything you have just told me, how frequently do you believe this has occurred in the last week?

Severity (III)

Taking into account everything you have told me how severe has this been?

Subjective Burden (IV)

Smoking into account everything you have just told me, how burdened do you feel by this?

Coping (V)

Smoking into account everything you have just told me, do you believe you are currently able to cope with difficulties with this..... or do you think that the difficulties are not bad enough to have to “cope” with them?

Effects on Behaviour & Performance (VI)

Do you currently avoid certain places, situations, people or activities because of this.....?

Include information the participant has told you previously about their behaviour and functioning to judge this answer.

Effects on quality of life (VI)

Smoking into account everything you have just told me, how hasx..... affected your quality of life?

Consultation with a doctor (VII)

Have you considered consulting a doctor about these experiences? If so, how many appointments have you had, and how many doctors have you seen?

Areas of life (VIII)

Smoking into account everything you have just told me, how many areas of your life do you believex..... has affected in the last week?