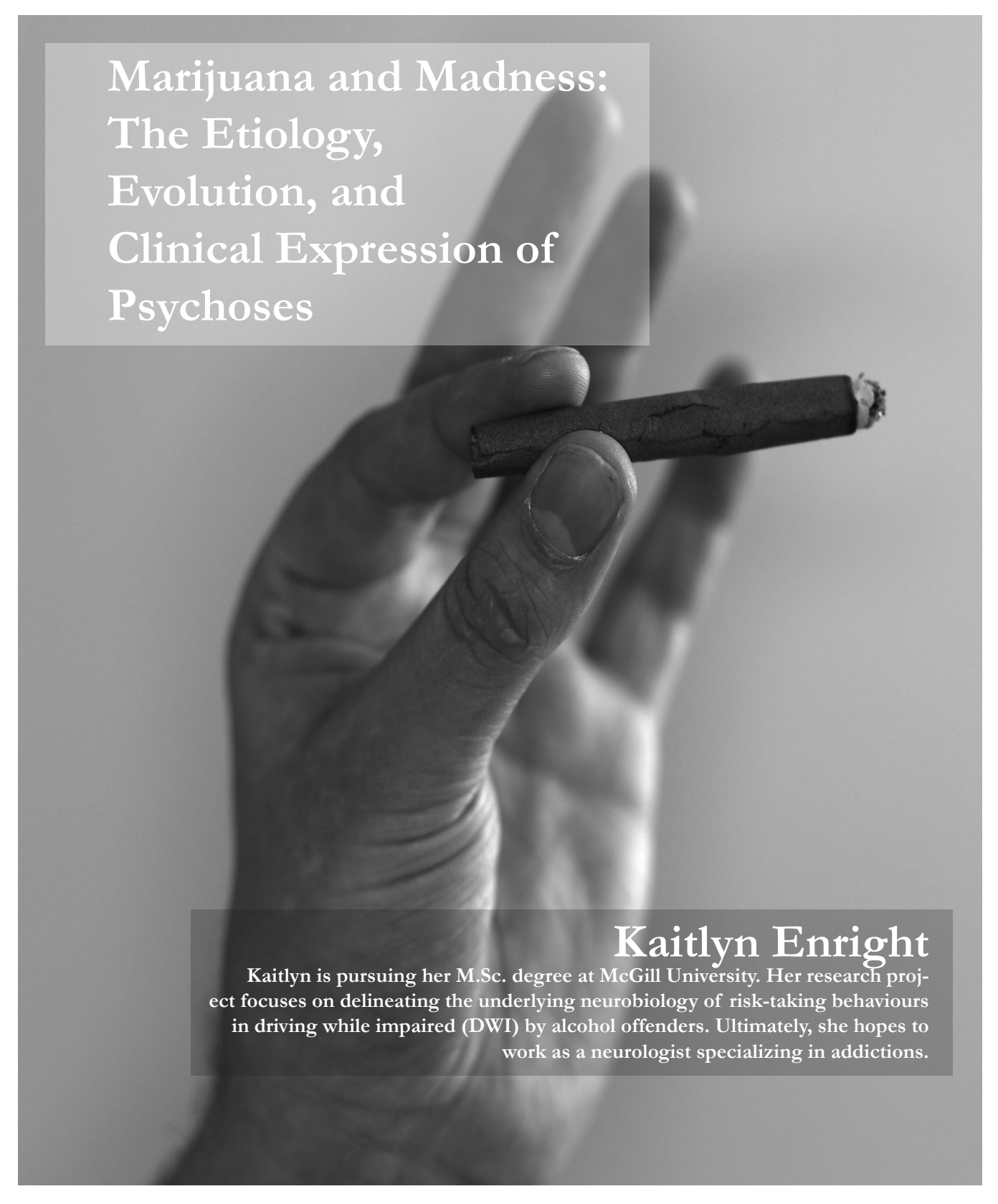
Marijuana and Madness: The Etiology, Evolution, and Clinical Expression of Psychoses



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Kaitlyn is pursuing her M.Sc. degree at McGill University. Her research project focuses on delineating the underlying neurobiology of risk-taking behaviours in driving while impaired (DWI) by alcohol offenders. Ultimately, she hopes to work as a neurologist specializing in addictions.

Background

Epidemiological Data

Throughout the world, cannabis is the most widely consumed illicit drug (EMCDDA, 2008). Dramatic increases in cannabis consumption have been observed in the last 30 years, possibly due to increased social acceptance and legalization in some areas (UNODC, 2012). There has also been a substantial decline in the initial age of use, with overall use remaining primarily linked to youth between the ages of 15 and 25. In 2012, the yearly prevalence of cannabis use among the general population was approximately 5% (UNODC, 2012). However, rates among people with psychiatric disorders, such as schizophrenia, remain consistently 5-10 times higher than the normal population, and the reason for this is unknown (Degenhardt, Hall & Linskey, 2003).

Developed countries are the main consumers of cannabis (see Figure 1). According to the Canadian Addiction Survey (2004), almost half the population (44.5%) has used cannabis in their lifetime and the rate in Quebec (46.4), is slightly higher than the national average. Assuming that prevalence rates will not change significantly over the next few decades, demographic trends suggest that the total number of cannabis users could, in accordance with population growth, increase significantly. Given its prevalence, there is little wonder why cannabis has become so controversial, dividing opinion

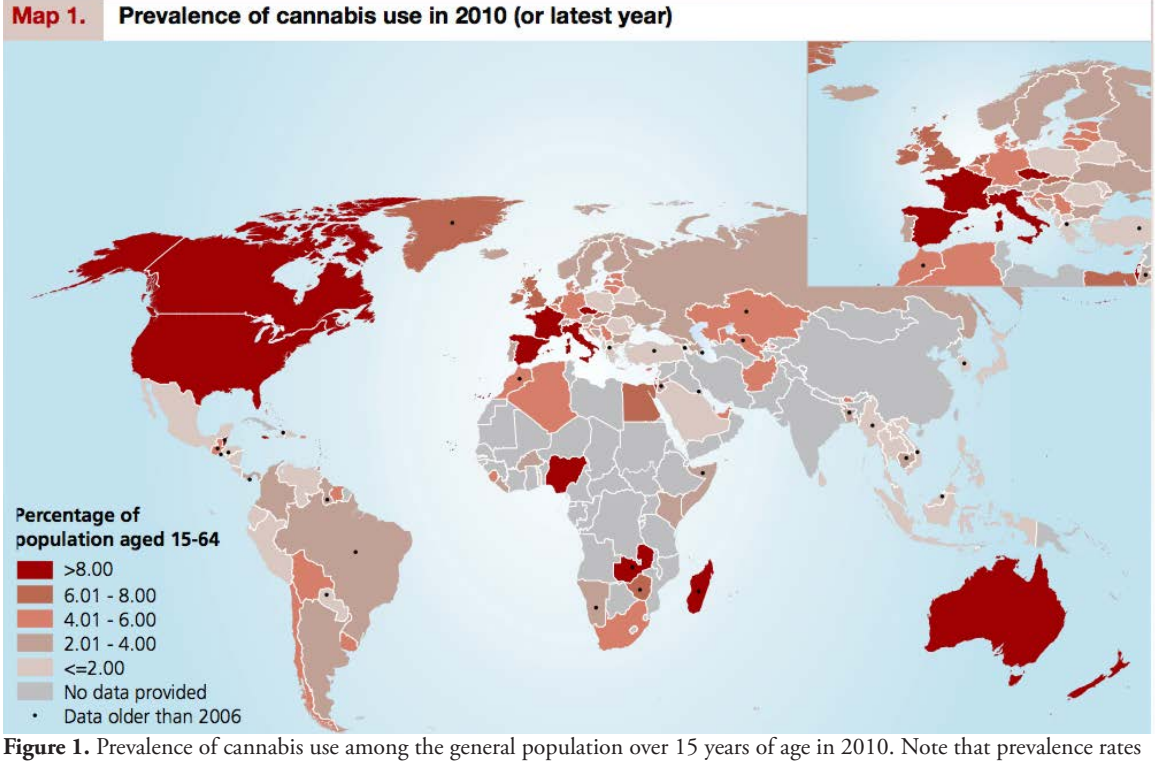

Figure 1. Prevalence of cannabis use among the general population over 15 years of age in 2010. Note that prevalence rates are high in North America (i.e., >8% of the population) (UNODC, 2012).

among policymakers, researchers, law enforcers, and consumers alike (UNODC, 2012).

Characteristics of Cannabis

The main psychoactive ingredient in cannabis is delta-9-tetrahydrocannabinol (THC) (Curan et al., 2002; Luzi, Morrison, Powell & Murray, 2008; Hell et al., 2012). Cannabinoid compounds bind to CB_1 cannabinoid receptors found mainly in the central nervous system, and CB_2 receptors found mainly in the peripheral nervous system (Hell et al., 2012). However, cannabis' primary mechanism of action is to act as an agonist at CB_1 receptor sites, and it is the resulting dopamine release in the nucleaus accumbens and ventral tegmental area that is attributed to the psychotogenic properties of cannabis. It is important to note that dopamine release within these structures is not only involved in the rewarding effects (i.e., euphoria) associated with psychotropic drugs (Hell et al., 2012), but that each of these aforementioned regions has been implicated in the pathophysiology of schizophrenia (Luzi et al., 2008).

Pathophysiology of schizophrenia

The pathophysiology of schizophrenia is incompletely understood. The "dopamine hypothesis of schizophrenia" suggests that a dysfunctional dopamine system causes hypodopaminergia in the frontal regions of the brain, and an excess of dopamine in striatal areas. These processes are proposed to be involved in psychosis, as the hypodopaminergia supposedly results in negative symptoms, such as a blunted affect, and the hyperdopaminergia translates into positive symptoms, such as delusions, which are commonly associated with schizophrenia (Howes & Kupar, 2009). However, many other neurotransmitters have been implicated in the pathophysiology of schizophrenia, such as glutamate (Goff, 2000) and serotonin (Aghajanian & Merek, 2000). There also seems to be a strong genetic component to the disorder, as it has a high heritability (Kukshal, Thelma, Nimgaonkar & Deshpande, 2012).

Neuropsychological and Behavioral Effects of Cannabinoids

Acute effects

Cannabis, or more specifically THC, affects a wide range of central nervous system domains. Its acute effects have been recognized for thousands of years (Goff, 2000), and recent studies have confirmed that cannabis has analgesic and antiepileptic properties, can decrease short-term memory and cognition, and increase relaxation and appetite (Curran et al., 2002; Kuepper et al., 2011; Andréasson, Allebeck, Engström & Rydberg, 1987). Most of these responses occur in a dose-dependent manner (Curran et al., 2002). Of course, as is the general case in psychiatry, the symptomatic expression is never universally specific, but only typical.

In rare circumstances, a substance-induced psychosis may follow cannabis intake. The expressions appear shortly after consumption, and are similar to the symptoms of schizophrenia, including hallucinations and/or delusions. Fortunately, prognosis is favorable as remission is achievable through abstinence, and usually does not require medical intervention (Henquet, Murray, Linszen & Van, 2005). High doses of cannabis, length of exposure, multiple substance use, use at an early age, certain personality traits, and vulnerability to major mental illnesses, all seem to be contributing factors that increase the likelihood of experiencing a

substance-induced psychosis (Kuepper et al., 2011). However, cannabis can trigger brief psychotic episodes in inexperienced consumers with no pre-existing vulnerability to psychoses (Andréasson et al., 1987).

Chronic effects

Early reports of an association between cannabis and schizophrenia became the topic of heated debates amongst the scientific community. After all, if the prevalence of cannabis use has dramatically increased in recent years, then we would expect to see a similar associated increase in the prevalence of schizophrenia. As medical costs associated with schizophrenia rise above 10 million dollars annually in the United States, an increase in its prevalence would have adverse effects on the economy (Henquet et al., 2005). Also, given that the age of first-time use has decreased, youth would be particularly susceptible to the harmful effects of cannabis, and the subsequent risk of psychoses, as it has been shown to have a negative effect on the brain's maturational processes during critical developmental stages (Kuepper et al., 2011). In response to this potential public health crisis, researchers began investigating whether this reported association between cannabis and schizophrenia was true.

Study Review

In 1987, a longitudinal study involving over 45,570 Swedish conscripts demonstrated a convincing association between cannabis and psychosis. It revealed a dose-response relationship between early cannabis use and later development of schizophrenia. The results of this 15-year follow-up indicated a two-fold increase in the relative risk of developing schizophrenia among consumers of cannabis compared to non-users (Andréasson et al., 1987). A later meta-analysis (Henquet et al., 2005) would also confirm this odds ratio. The risk of developing schizophrenia increased exponentially among "heavy users", defined as using on 50+ occasions (Andréasson et al., 1987) (see Figure 2). While intriguing, further investigations into this area of research did not significantly advance until after the second millennium, and thus, the causal link between cannabis and schizophrenia remained unanswered.

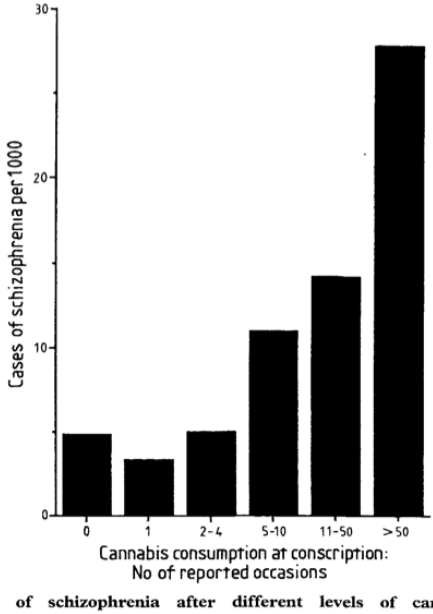

Figure 2. Association between rates of schizophrenia and different levels of cannabis use. Note the dose-response association between the number of occasions of cannabis use and cases of schizophrenia (Andréasson et al., 1987).

Viewpoint #1: Does psychosis induce cannabis use?

The "reverse causality hypothesis" proposes that individuals with a vulnerability to schizophrenia may be predisposed to using cannabis

as a means of "self-medicating" their distress (Henquet et al., 2005). Many studies have provided data that is inconsistent with this hypothesis. For example, a cohort study found that the association between cannabis use and psychoses was not influenced by distress invoked by experiences, making the self-medication hypotheses unlikely (Kuepper, 2011) (see Table 1). Also, a 10-year follow-up study showed that psychotic episode at a first follow-up did not predict cannabis use in a subsequent follow-up; therefore, their data do not provide evidence in support of the self-medication hypothesis. Also in this study, the association between cannabis use and psychotic episode was independent of many confounding variables, such as age, sex, socioeconomic status, use of other drugs, urban/rural environment, childhood trauma, and other psychiatric illness. Therefore, the association is unlikely to be the result of common cofactors, and a residual confounding explanation does not provide sufficient analytical capability (Kuepper, 2011). These studies help to address the issue of reverse causality by clarifying the temporal association between cannabis use and psychoses. It is also a common observation that while cannabis users are overrepresented in the schizophrenic population, not all schizophrenics use cannabis (Degenhardt, Hall & Linskey, 2003).

Viewpoint #2: Does cannabis use cause psychosis?

The "causality hypothesis" proposes that consuming cannabis causes psychotic symptoms in users. However, population statistics argue against this hypothesis. For example, in the aforementioned Swedish study, only 3% of the heavy cannabis users went on to develop schizophrenia, suggesting that cannabis might exert its causal role only in vulnerable individuals (Andréasson et al., 1987). Also, statistical applications of the causal model suggest that at the population level, complete elimination of cannabis would not result in a significant reduction in the prevalence of schizophrenia (i.e., < 8%) (Arsenault, Cannon, Witton & Murray, 2004). This is in accordance with observations from the World Health Organization (2000) that prevalence rates of schizophrenia remain constant throughout time, and among differing cultures and geographical regions, despite fluctuations in cannabis use. Therefore, while in rare cases cannabis may cause transient, schizophrenic-like symptoms in the general population, data indicate that cannabis use does not necessary *cause* psychosis. Rather, it may increase the risk of earlier and more frequent relapses, and worsen the overall course of the illness, in those with a pre-existing vulnerability (see Figure 3). This association between psychosis liability and

	Effect of cannabis life-time frequency use on continuous psychosis dimension, expressed as the regression coefficient from multiple regression equations			
	*Hallucinations** B† *(P-value)*	*Paranoia* B† *(P-value)*	*Grandiosity** B† *(P-value)*	*First-rank* B† *(P-value)*
No distress group	1.30 (0.000)	0.45 (0.000)	0.41 (0.000)	0.21 (0.000)
Distress group	0.78 (0.000)	0.11 (0.000)	0.31 (0.001)	0.14 (0.000)

Table 1. Self-medication hypothesis. Effects of cannabis as a function of distress associated with psychotic experiences (Stefanis et al., 2004).

cannabis use has been demonstrated in many studies (Henquet et al., 2005; Degenhardt et al., 2007; Griffith-Lendering et al., 2013).

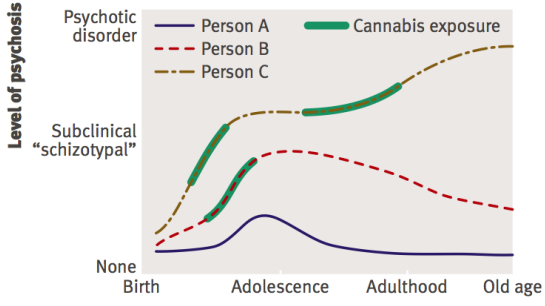

Figure 3. A proposed cannabis-psychosis persistence model. Person A has normal developmental expression of subthreshold psychotic experiences that are mild and transient. Person B has similar expression but longer persistence because of additional environmental exposure (here, cannabis). Person C has prolonged persistence and subsequent transition to clinical psychotic disorder because of repeated environmental exposure - that is, repeated cannabis use (Kuepper et al., 2011).

Causality: The accumulating evidence

According to Henquet and colleagues (2005), causality is plausible if studies meet the following criteria: (i) they report an association between the exposure and the outcome consistently, (ii) show dose-response relationships between the exposure and the outcome, (iii) show that the exposure precedes the outcome, and (iv) show that there is a plausible biological mechanism linking the exposure and the outcome. With the exception of criterion (iv), previous studies have fulfilled criteria (i-iii) for causality. Therefore, there is increasing evidence that the association between cannabis use and psychoses is indeed a causal relationship. However, given that not all cannabis users develop schizophrenia, and not all schizophrenics consume cannabis, it would seem that cannabis is neither a necessary nor a sufficient cause of schizophrenia. Nonetheless, since evidence supports that an association exists, then perhaps cannabis is a component cause of schizophrenia. That is, its influence on psychoses risk may be dependent on another factor(s) (Luzi et al., 2008).

Biological Plausibility – The Mechanism That Explains This Association

In the absence of known causes of schizophrenia, and as evidence indicates that cannabis may be a component of the sufficient cause of the illness, studies have begun investigating the possible biological mechanism(s) underlying this association (Canadian Addiction Survey, 2004), in an attempt to meet the (iv) criterion of causality. One combining factor that has been previously suggested is genetic liability to schizophrenia (Curran et al., 2002). A preliminary study investigating this possibility directly through gene mapping, revealed an association between certain gene alleles and more severe psychotic outcomes following cannabis use (Henquet et al., 2006). However, these finding have not been replicated and their validity has been questioned (Zammit et al., 2011). However, a study by Caspi and colleagues (2005) supports the genetic vulnerability hypothesis as they found an interaction between a polymorphism in the catechol-O-methyltransferase gene and exposure to cannabis. Specifically, they found a five-fold increase in the likelihood of developing schizophrenia among cannabis users with the Val allele for the COMT gene (see Figure 4). Unfortunately, studies investigating direct measures of a gene by environment interaction are in their preliminary stages, and there are many complicated issues associated with gene mapping. For example, it is unlikely that the disor-

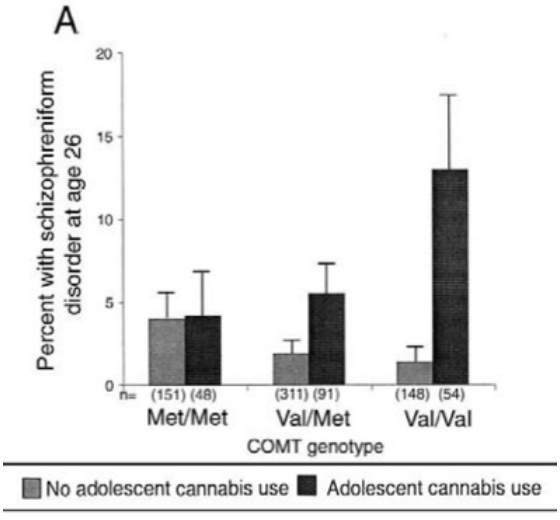

Figure 4. The influence of adolescent-onset cannabis use on adult psychosis is moderated by variations in the COMT gene (Caspi et al., 2005). Shown is the percentage of individuals meeting diagnostic criteria for schizophreniform disorder at age 26.

der can be attributed to a single gene or mutation. Therefore, in the meantime, more tenable experimental designs which investigate indirect measures of a gene by environment interaction should be proposed. Especially considering the social and economic costs of schizophrenia, studies investigating the possible factor(s) associated with strengthening cannabis' influence on psychoses risk are warranted.

Objectives

Investigate whether an underlying mechanism of a gene by environment interaction explains the association between early cannabis use and later development of psychoses. If our predictions are confirmed, this research could point to original approaches for detection and individualized intervention of high-risk individuals.

Hypotheses

A double-blind, placebo-controlled crossover design will be used to explore the following hypotheses: *Hypothesis 1)* schizophrenic patients, and their first-degree relatives, will show a significantly greater sensitivity to the cognitive impairments of cannabis, compared to control subjects; and *Hypothesis 2)* schizophrenic patients, and their first-degree relatives, will show significantly greater psychotic symptoms in response to cannabis, in comparison to controls.

Methods

Measures

Cognitive assessment and analyses of current psychotic experiences will be assessed by a series of self-administered questionnaires.

Procedures

The entire protocol consists of two seperate visits to the lab, seperated by one week. At each visit, participants receive either THC intravenous injections (1.5mg/70kg), or a saline solution, in randomized order. The infusion rate will be set to 20 minutes.

Expected Results

Thirty minutes after the completion of THC administration (T2), which represents the height of intoxication, both schizophrenics *and* first-degree relatives of schizophrenics are expected to show significant cognitive impairments and significant increase in psychotic symptoms, in comparison to control subjects. Compared to their first-degree relatives, schizophrenics will demonstrate an increased vulnerability to the cognitive impairments and psychotic symptoms at of cannabis.

Anticipated Conclusions

If we find that first-degree relatives of schizophrenic patients are significantly impaired by the cognitive and psychotic effects of cannabis, compared to controls, then this would provide evidence supporting a gene-environment interaction underlying the relationship between cannabis use and psychoses. Furthermore, the repeated finding that schizophrenic patients are significantly more vulnerable to the cognitive and psychotic effects of cannabis, compared to controls, will confirm the reliability of previous studies. Lastly, the finding that schizophrenic patients are still significantly more impaired than their first-degree relatives, would indicate the possibility that a protective mechanism exists in a non-clinical population.

Implications

This study provides an indirect means of investigating the influence of genetic risk on the causal association between cannabis use and psychoses. Our results will identify whether genetic risk to psychosis is an objective biological marker capable of delineating a high-risk subgroup from within the heterogeneous cannabis-using population. If this is shown, such a group may be targeted in early identification and intervention programs.

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