CHAPTER FOURTEEN

Cannabis, Cannabinoids, and the Association with Psychosis

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1. INTRODUCTION

An association between cannabis and psychosis has long been suspected. The increasing rates of cannabis use, the use of cannabis for medical purposes, the increasing potency of cannabis, the earlier age of onset of cannabis use by adolescents, the greater availability of synthetic cannabinoids, and recent advances in our understanding of the role of endogenous cannabinoids in the brain have both, renewed and reinvigorated interest in the link between cannabis use and psychosis.

In this chapter, we review the literature pertaining to the association between cannabinoids and psychosis. At the outset, it is important to highlight a few distinctions. Firstly, the distinction between 'psychotic symptoms' and a 'psychotic disorder' is an important one. Psychotic symptoms refer to alterations in perception, hallucinations, delusions and disorganized thinking and speech. In experimental studies with cannabinoids, these symptoms are transient and abate spontaneously. A psychotic disorder, such as schizophrenia, is characterized by, not only positive psychotic symptoms but also negative symptoms (such as amotivation, social withdrawal and blunted affect) and cognitive deficits (such as impairments in attention, memory, working memory and executive functioning). Furthermore, these symptoms are persistent and result in significant socio-occupational dysfunction. Secondly, a distinction must be made between 'cannabinoids' and 'cannabis'. Much of the experimental evidence is derived from studies that use Δ^9-tetrahydrahydrocannabinol (Δ^9-THC), the main psychoactive ingredient of cannabis. Cannabis, however contains more than 70 different cannabinoids apart from Δ^9-THC , including cannabidiol (CBD) and cannabinol (CBN). Therefore, cannabis is more than just Δ^9-THC. Synthetic cannabinoids are compounds derived from analogues of cannabinoid receptor (CB-1R) agonists and bind to CB-1R with greater affinity, but are not known to be found in cannabis. Synthetic cannabinoids are hence not cannabis, and are more than just Δ^9-THC.

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2.1. TRANSIENT BEHAVIORAL AND COGNITIVE EFFECTS OF CANNABINOIDS: NONEXPERIMENTAL EVIDENCE

2.1.1. Anecdotal Reports of Cannabis Effects and Surveys of Cannabis Users

Cannabis use was suggested as a cause of "moral degeneracy" probably as early as the Eleventh century A.D. as is illustrated in the story of Hasan ibn al-Sabbah. His fanatical group of followers, referred to as the "Hashishiyans", (a term from which the English word "assassin" is derived), allegedly earned the moniker because of their use of "hashish" (*Cannabis indica*) (Nahas, 1982). The earliest report of an association between cannabis and altered behavior can be traced back to 1235A.D. when Ibn Beitar, an Arabian physician, made the link between insanity and the consumption of "hashish" (Warnock, 1903). In the Nineteenth century, the French psychiatrist Jacques-Joseph Moreau a member of the famous Parisian Club des Hashischins, a club dedicated to the exploration of drug-induced experiences, was the first to describe the psychotomimetic effects of hashish in a systematic manner. In his 1845 book, Hashish and Mental Illness, he reported that hashish intoxication could precipitate "acute psychotic reactions, generally lasting but a few hours, but occasionally as long as weeks" (Moreau, 1973). Since then, there have been numerous anecdotal reports describing psychotic symptoms in the context of cannabis intoxication (Brook, 1984; Chopra and Smith, 1974; D'Souza, 2007; Grossman, 1969; Keeler and Moore, 1974; Marshall, 1897; Moreau, 1973; Smith, 1968; Spencer, 1971; Talbott and Teague, 1969; Thacore, 1973). The symptoms commonly reported include depersonalization, derealization, paranoia, ideas of reference, flight of ideas, pressured thought, disorganized thinking, persecutory delusions, grandiose delusions, auditory and visual hallucinations, and impairments in attention and memory in an otherwise clear consciousness. The subjective experience with cannabis however varies to a great degree and depends on various extrinsic and intrinsic factors, including personality traits, such as schizotypy (Barkus et al., 2006), individual set of beliefs/expectations and the setting in which cannabis is used (Adamec et al., 1976). While rich in detail, individual accounts are fraught with some confounds and are difficult to generalize.

Some of the limitations of anecdotal accounts can be addressed in population-based surveys. The Indian Hemp Drugs Commission Report (1894), an exceptionally detailed report comprising some seven volumes and 3,281 pages, documents that cannabis use may have been responsible for psychotic reactions in 222 of 2344 cases (i.e. 9.5%) admitted in asylums in India. More recent studies suggest that between 20% and 50% of individuals report paranoia, persecutory ideas, and hallucinations while under the influence of cannabis (Green et al., 2003; Reilly et al., 1998).

2.1.2. Effects of Medicinal Cannabinoids

Treatment with synthetic cannabinoids has also been linked to transient psychotic symptoms with. Dronabinol (Δ^9-THC), nabilone (9-trans-ketocannabinoid) and levonantradol

have been used to manage pain syndromes, chemotherapy-induced nausea and spasticity from multiple sclerosis. Patients being treated with these synthetic cannabinoids have reported to experience transient psychotic symptoms, such as "loss of control", thought disturbances, feelings of unreality, apprehension, fear and paranoia, anxiety and panic, dissociation, depersonalization, dysphoria, difficulty concentrating, hallucinations, perceptual alterations, amnesia and anxiety (Citron et al., 1985; Cronin et al., 1981; Diasio et al., 1981; Heim et al., 1984; Heim et al., 1981; Jain et al., 1981; Kenny and Wilkinson, 1982; Laszlo et al., 1981; Leweke et al., 1999; 1998; Sheidler et al., 1984; Stambaugh et al., 1984; Stuart-Harris et al., 1983; Volkow et al., 1991; Wesnes et al., 2009). The severity of these symptoms appears to be dose-dependent and dependent on the affinity of the compound for the CB-1R receptor. In fact, Levonantradol, which has 30 times higher affinity for the CB-1R receptor than Δ^9-THC and was being developed as an analgesic agent had to be abandoned from further drug development because of the high incidence of intolerable behavioral side effects.

In two systematic reviews of randomized clinical trials that examined the efficacy of synthetics cannabinoids for chemotherapy-induced nausea and vomiting, the use of these synthetic cannabinoids led to hallucinations in 6% of patients, paranoia in 5% of patients, and was responsible for nearly 30% of dropouts, primarily because of intolerable behavioral effects. (Machado Rocha et al., 2008; Tramer et al., 2001). Importantly, in these trials, hallucinations and paranoia were seen exclusively with cannabinoids, and not with other antiemetic agents. These effects appear to increase both with increasing potency, dose and with repeated dosing.

2.1.3. Synthetic Cannabinoids (Spice, K2)

The phenomenon of "Spice" provides another very recent source of nonexperimental evidence linking cannabinoids to psychosis. "Spice" refers to synthetic cannabinoids that have been sprayed onto a herbal substrate of dried leaves, flowers and stems from a number of plants. These products are marketed under a number of suggestive names, like "Spice", K2, Yucatan Fire, Skunk, Moon Rocks, and others. For convenience, we heretofore refer to these products as "Spice". It is sold for $10–50 in attractive and colorful packages, weighing about 3 gm, via the internet, headshops, and gas stations. "Spice" does not contain tobacco or phytocannabinoids (such as Δ^9-THC or CBD). Instead it contains one or more synthetic cannabinoids from the Pfizer (CP) group (CP-47,497 and CP-47,497-C8), the aminoalkylindole group (JWH-018, JWH-073, JWH-081, JWH-122, JWH-210 JWH-250) the HU group (HU-211) or the benzoylindole group (RCS-4) (Auwarter et al., 2009; Dresen et al., 2010; Lapoint et al., 2011; RTL, 2012; Schneir et al., 2011; Uchiyama et al., 2011; Uchiyama et al., 2009; Uchiyama et al., 2010). These compounds are high affinity, full agonists of brain cannabinoid receptors and are between 10–200 times more potent than THC. While the product labels list a number of herbs (e.g. alfalfa, blue violet, nettle leaf, etc.) often, these cannot be detected or are not relevant to the effects of "Spice". Similarly, the absence of cannabinoid-2 receptor

(CB2R) agonists, which are generally not psychoactive, in "Spice" suggests that it is sold for its psychoactive effects. Even though "Spice" is advertised as "natural herbs" or "harmless incense," "not for human consumption" or "for aromatherapy only," it is typically smoked. This labeling places the burden of responsibility on the user.

"Spice", has become the second most frequently used illicit substance after herbal cannabis in the U.S. (NIDA, 2011). The promise of a stronger high than cannabis, easy access, affordability, a perception that the products are legal, a perception that the products are safe "like marijuana", and the difficulty in detecting these compounds in standard urine toxicology tests have likely contributed to "Spice"'s growing popularity and use. The use of "Spice" is increasing amongst youth in the US. In the most recent Monitoring the Future survey, 11% of high school seniors nationwide admitted using "Spice" in the previous year, compared to 36% who admitted using cannabis in the past year (NIDA, 2011). "Spice" is typically smoked using a pipe resulting in rapid (10–20 minutes) onset of effects (Every-Palmer, 2011; Vandrey et al., 2012).

2.1.3.1. The Acute Effects of "Spice"

There are no published controlled data on the effects of "Spice". The synthetic cannabinoids present in "Spice" have not undergone the rigorous testing to which most other drugs are subjected. Most of the information about "Spice" effects consists of retrospective case reports from ER visits (Lapoint et al., 2011; Muller et al., 2010a; Schneir et al., 2011) and Poison Control Centers (AAPCC, 2011), media and law-enforcement reports of catastrophic events associated with "Spice" use (Businessweek, 2011; CBS, 2011; CNN, 2011; News, 2011; NPR, 2011; Post, 2011) and survey data (Every-Palmer, 2011; Hu et al., 2011; Vandrey et al., 2012). Reported effects reported to Poison Control Centers include agitation, drowsiness, and hallucinations (62% of calls). Emergency room reports from the US document more severe effects including anxiety, agitation, disorientation, hallucinations, and paranoia (Benford and Caplan, 2011; Lapoint et al., 2011; Mir et al., 2011; Schneir et al., 2011; Vearrier and Osterhoudt, 2010). Users in an internet survey most commonly endorsed feeling the following effects "most of the time" or "every time" they used "Spice": hallucinated (3%), felt paranoid (11%), produced a dream-like state (26%) (Vandrey et al., 2012).

Psychotic relapses may occur following the use of "Spice" in patients with preexisting psychotic disorders (Every-Palmer, 2010, 2011; Muller et al., 2010a). Müller (Muller et al., 2010b) reported a 25-year-old man with a family history of schizophrenia and a personal history of psychotic episodes precipitated by cannabis use. The patient had been stable for 2 years until he smoked "Spice" 3 times over the course of a month. He was hospitalized for exhibiting anxiety, paranoid delusions, and hallucinations. Every-Palmer described five forensic patients with sudden agitation, disorganization, and delusions after using "Spice" containing JWH-018 and/or CP47,497 (Every-Palmer, 2010). Interestingly, only one of the five patients displayed insight into the possible psychotogenic

nature of "Spice" (Every-Palmer, 2010). Every-Palmer conducted a follow-up survey of 15 inpatients with Serious Mental Illness in a forensic psychiatric facility (Every-Palmer, 2011). Patients exhibited psychotic symptoms and anxiety after smoking "Spice"; however, few reported tolerance (23%) and none reported withdrawal symptoms.

The adverse clinical events reported in case reports with the use of "Spice" involve altered consciousness, confusion, anxiety, irritability, agitation, paranoia, hallucinations, and psychosis (Every-Palmer, 2010; Hurst et al., 2011; Muller et al., 2010b; Schneir et al., 2011;Vearrier and Osterhoudt, 2010). Psychotic symptoms are reported in patients with no previous history of psychotic symptoms. However, the majority of case reports to date discuss people 25 years or younger (youngest cases reported age 16 (Cohen et al., 2012; Mir et al., 2011)). Therefore it is possible that "Spice" exacerbated a preexisting prodrome syndrome. Case reports and cross-sectional surveys are only able to show correlation and cannot elucidate causation.

The sparse literature on "Spice" effects reviewed above has a number of limitations, including selection bias, a reliance on the accuracy of written record or subject recall, the uncontrolled nature of the evidence, the inadequate characterization of cases, the lack of standardized assessments, the confounding effects of other drugs used concomitantly with "Spice", variable dose and routes of administration, and variable set and setting. Cases reported by the media and law enforcement may represent extremes that might not be generalizable. The temporal profile, range, and intensity of "Spice" effects, and whether the effects are dose-related and biphasic, are not known. Furthermore, the relationship between dose, effects, and blood/urine levels of the parent compound and metabolites is not known.

Analysis of the content of "Spice" suggest that adverse events following consumption of synthetic cannabinoid preparations are unlikely to be due to impurities or residue from the manufacturing process, but rather to effects of the active drug or interactions with other psychoactive chemicals from herbs blended into products marketed as cannabis alternatives (Ginsburg et al., 2012).

2.1.3.2. The Changing Composition of "Spice"

One unique aspect of the "Spice" phenomenon is that the constituents of "Spice" are changing over time. This might be related to manufacturers staying one step ahead of legislation. The first generation of "Spice" contained CP-47,497-C8, JWH-018 and JWH-073. As first observed in the UK (Dargan et al., 2011), Germany (Lindigkeit et al., 2009), and Japan (Kikura-Hanajiri et al., 2011), as these compounds were banned, they were replaced by structurally similar and pharmacologically active compounds that skirted the regulations. In March 2011, the U.S. Drug Enforcement Agency (DEA) placed JWH-018, JWH-073, JWH-200, CP-47,497, and (C8)-CP47,497 present in "Spice", on the Schedule 1 list under 21 U.S.C. 811(h) of the Controlled Substances Act (21 CFR Part 1308) (NIDA, 2011). The banned compounds have been replaced

in the U.S. by structurally related ones including JWH-081, JWH-250, JWH-122, and JWH-210 (Today, 2011). Furthermore, some "Spice" samples are explicitly labeled not to contain banned cannabinoids.

While the specific combination of synthetic cannabinoids in "Spice" may change over time, the primary site and mechanism of action of its components remains unchanged. However, unlike Δ9-THC—the principal active constituent of cannabis, which is a low efficacy, partial agonist at CB-1RRs—the cannabinoids in "Spice" are high potency, high efficacy, high affinity, full agonists at CB-1RR. (Atwood et al., 2010; Atwood et al., 2011; Huffman and Padgett, 2005; Huffman et al., 2005; Lindigkeit et al., 2009; Marriott and Huffman, 2008). This may explain the higher rates of adverse events associated with "Spice" use relative to cannabis use. Furthermore, people who do not appreciate the differences between cannabis and these high potency, full agonist synthetic cannabinoids may be lulled into a false sense of security and therefore, be more likely to use "Spice" and experience adverse events.

2.2. TRANSIENT BEHAVIORAL AND COGNITIVE EFFECTS OF CANNABINOIDS: EXPERIMENTAL EVIDENCE

2.2.1 Gendral Studies

Studies conducted in a scientific manner provide an opportunity to control variables such as dose and setting, and to objectively measure positive symptoms, negative symptoms, cognitive and psychophysiological effects. In one of the earliest semi-experimental studies, Siler et al. (1933) examined soldiers in the Panama after they were given cannabis and reported that it led to "mild intoxication" but not psychotic symptoms (Siler et al., 1933). The cannabis was of a strain that was grown in the Isthmus of the Panama, and the content of Δ^9-THC may have been variable. One of the earliest studies using a method of standardization is contained in the so-called "Mayor's Report" or "LaGuardia Committee Report" of 1944. The mayor of New York City, Mayor Fiorello LaGuardia was concerned about the widespread use of cannabis and appointed a Committee on Marihuana in 1939 in order to assess the nature and extent of physiological and psychological effects of cannabis on humans. The clinical portion of the study was conducted in 72 inmates from penitentiaries in New York who were given about 2–5 ml of cannabis concentrate (equivalent to 30–75 mg oral tetrahydrocannabinol and 830 mg smoked tertahydrocannabinol). Nine (12.5%) of the subjects developed psychotic reactions. The symptoms resolved within 34 h in 6 subjects, persisted for days to months in 2 subjects, while one subject who was given numerous, large doses of cannabis concentrate, went on to develop a persistent psychotic illness similar to schizophrenia. Cannabis was also found to produce significant dose-related impairments in memory, problem-solving ability, hand steadiness and balance (Mayor's Committee on Marijuana, 1944). Although the study has serious limitations in terms of the mental health status of the subjects given that they were prison inmates and

that they had been exposed to various other drugs over their lifetime, the study drew attention to the negative consequences of cannabis use. Ames (1958) examined the effects of unassayed oral doses of cannabis extract in 10 medically trained individuals. Subjects were given between 240420 mg of cannabis extract (50 to 70 mg Δ^9-THC) and their subjective experiences were documented. Despite interindividual variations in experiences, the most frequently reported psychotic symptoms were perceptual changes, fragmented thinking, dissociation between thoughts and action, visual illusions and hallucinations, derealization and depersonalization. Some subjects experienced paranoia, which took on delusional proportions. The experiences ranged from a conviction that there were hidden recorders in the room, to fears that the individual was going to be hypnotized or subjected to electroconvulsive therapy. One subject refused to answer questions altogether for fear of being certified as insane. Other similar quasi-experimental studies of cannabis have reported a range of dose-related psychotic symptoms with cannabis (Isbell et al., 1967; Isbell and Jasinski, 1969; Renault et al., 1974; Siler, 1933; Williams et al., 1946).

The first controlled double-blind study was conducted in 1968 in the Behavioral Pharmacology Laboratory of Boston University. Weil et al (1968) administered cannabis extract containing 0.9% Δ^9-THC in a double blind manner and did not observe any psychotic effects. They however, reported that experienced users were more susceptible to perceptual effects compared to naïve users, suggesting that there may be some form of "pharmacological sensitization" with continued use (Weil et al., 1968). This was further tested by Jones and Stone, (1970) who examined the effects of smoked and oral cannabis extract (0.5 g containing 0.9% Δ^9-THC) in 10 heavy cannabis users, but found that they had lesser effects suggestive of "tolerance" (Jones and Stone, 1970). They also noticed significant differences between the oral and smoked routes. Melges et al, 1970 administered oral Δ^9-THC in three doses (20 mg, 40 mg, 60 mg) in a randomized, double-blind placebo-controlled study in 8 healthy individuals (Melges et al., 1970). Subjects were noticed to experience significant difficulty integrating their thoughts and manifested loose-associations and a lack of goal-directedness, apart from deficits in short-term memory. Renault et al wondered whether the route of administration made a difference to the effects observed. They developed a system to deliver cannabis smoke assayed to contain 1.5% Δ^9-THC (Renault et al., 1971) and subsequently used their apparatus to examine the effects of cannabis smoke in humans (Renault et al., 1974). Psychosis was observed in one of the 7 subjects who participated in a 10 day, multiple dosing paradigm (Renault et al., 1974). The method was however not foolproof and an unmeasurable amount of Δ^9-THC was lost in the process of combustion and delivery. Kaufmann et al, (2010) examined the effects of oral cannabis extract on a sample consisting of only female subjects. Cannabis, but not diazepam, increased scores on the Brief Psychiatric Rating Scale (BPRS) a scale that is commonly used to measure symptoms in schizophrenia. One of the subjects experienced "severe" psychotic symptoms that lasted for several hours (Kaufmann et al., 2010). Another aspect that has come to light is that different cannabinoids may have different neurophysiological and behavioral effects,

although these studies await replication. Fusar-Poli et al (2009) used oral doses of Δ^9-THC (10 mg) and cannabidiol (CBD) (600 mg), the other main psychoactive ingredient of cannabis in a functional magnetic resonance (fMRI) paradigm that examined brain responses to emotional expression of faces (Fusar-Poli et al., 2009). Δ^9-THC was found to result in increased psychotic symptoms and increased skin conductance responses while processing fearful faces. CBD, on the other hand led to a reduction in anxiety and a decrease in skin conductance response. Δ^9-THC and CBD were also found to have opposite effects on blood oxygen-level dependent (BOLD) responses in tasks of verbal recall, response-inhibition, processing fearful facial expressions, auditory processing and visual processing (Bhattacharyya et al., 2010). The relatively small sample size, the route of drug administration and lack of assessment of drug availability and the fact that the authors' selected areas where activation was in opposite directions post hoc, are significant limitations of this study.

Other studies have used the intravenous route to examine the psychotomimetic properties of Δ^9-THC in order to ensure standardization of drug-delivery and adequate plasma levels, both in healthy subjects (D'Souza et al., 2004) (D'Souza et al., 2008b) (Morrison et al., 2009) (Morrison et al., 2011) and in patients with schizophrenia (D'Souza et al., 2005). D'Souza et al. (2004), administered intravenous Δ^9-THC in two doses (2.5 mg, and 5 mg), in a double blind, randomized, placebo-controlled study in healthy adults ($n = 22$). Subjects were screened to rule out significant psychiatric disorder or family history of Axis I disorders (D'Souza et al., 2004). The study found that Δ^9-THC produced transient positive psychotic symptoms (Figure 1) including

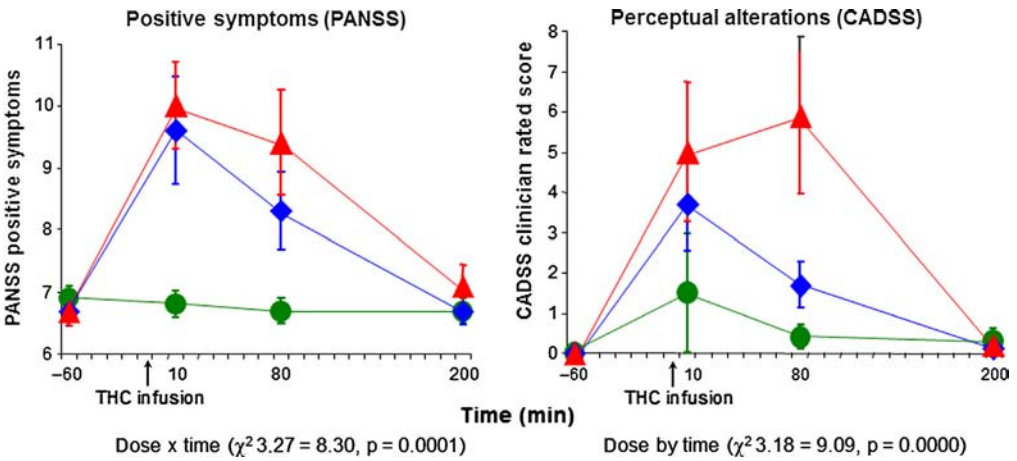

Figure 1 Δ^9-THC induces transient psychotomimetic effects in healthy individuals. The figure shows the effects of Δ^9-THC on the seven-item positive symptom subscales of the Positive and Negative Syndrome Scale (PANSS) (left panel) and on the eight-item clinician-rated subscale of the Clinician Administered Dissociative Symptoms Scale (CADSS) (right panel). (Green line = placebo, Red line = 2.5 mg Δ^9-THC, Blue line = 5 mg Δ^9-THC.)

perceptual alterations, negative symptoms, mood symptoms such as euphoria and anxiety, and cognitive deficits, especially in attention, working memory and verbal recall, without altering general orientation. In a similar study in healthy individuals, using almost identical methods, Morrison et al (2009), showed that intravenous Δ^9-THC (2.5 mg) produced similar effects on positive psychotic symptoms, mood, and cognition.

We provide a brief summary of the effects observed with cannabis, Δ^9-THC and other synthetic cannabinoids below. It is interesting to note that these compounds produce the full range of positive psychotic symptoms, negative symptoms and cognitive deficits seen in schizophrenia.

2.2.2. Positive Symptoms

Cannabis, Δ^9-THC and other cannabinoids induce a range of transient, positive psychotic symptoms which are qualitatively similar to that seen in schizophrenia. These symptoms include suspiciousness, paranoid and grandiose delusions, conceptual disorganization, fragmented thinking, and perceptual alterations. Additionally, Δ^9-THC results in depersonalization, derealization, distorted sensory perceptions, altered body perception, and feelings of unreality. Time perception abnormalities are known to occur in schizophrenia, but have received little attention (Andreasen et al., 1999; Carroll et al., 2009; Davalos et al., 2003; Tysk, 1983). Cannabinoids have been shown to alter time perception in both preclinical (Conrad et al., 1972; Han and Robinson, 2001; McClure and McMillan, 1997; Schulze et al., 1988) and clinical studies (Hicks et al., 1984; Mathew et al., 1998; McDonald et al., 2003; Sewell and D'Souza, April 3rd, 2011; Stone et al., 2010; Tinklenberg et al., 1972). Cannabinoids have also been found to disrupt performance on the binocular depth inversion task, a potential surrogate marker for psychosis seen in patients with acute paranoid schizophrenic or schizophreniform psychosis (Koethe et al., 2006). This effect has been observed with cannabis resin (Emrich et al., 1991), nabilone (a synthetic analogue of Δ^9-THC) (Leweke et al., 2000), dronabinol (a synthetic analogue of THC) (Koethe et al., 2006), and in chronic cannabis users (Semple et al., 2003).

2.2.3. Negative Symptoms

Δ^9-THC also produces a range of effects similar to the negative symptoms of schizophrenia, including blunted affect, emotional withdrawal, psychomotor retardation, lack of spontaneity and reduced rapport. It is difficult to tease out whether these "negative symptoms" were primary or were a consequence of the sedating and cataleptic effects of cannabinoids observed in animal studies. It is also unclear if the negative symptoms were an external manifestation of internal preoccupation with positive psychotic experiences. Furthermore, acute pharmacological studies may be limited in their capacity to "model" negative symptoms.

2.2.4. Cognitive Deficits

Cannabis, Δ^9-THC and other synthetic cannabinoids also produce transient, dose-related cognitive impairments, especially in the domains of verbal learning, short-term memory, working memory, executive function, abstract ability, decision making, and attention (Hart et al., 2001; Heishman et al., 1990; Hooker and Jones, 1987; Leweke et al., 1998; Marks and MacAvoy, 1989; Miller et al., 1977; Ranganathan and D'Souza, 2006). These effects are not limited to humans and are also seen in rodents and nonhuman primates (reviewed in Lichtman et al., 2002; Wilson and Nicoll, 2002). Interestingly, the profile of impairment observed in different cognitive domains is similar to that observed in schizophrenia (Heinrichs and Zakzanis, 1998). The cognitive impairment produced by Δ^9-THC is most pronounced in the domain of verbal learning and memory (Ranganathan and D'Souza, 2006), which is also one of the domains of significant impairment in schizophrenia (Heinrichs and Zakzanis, 1998). Figure 2 illustrates the effects of Δ^9-THC on the Hopkins Verbal Learning Test (HVLT) in healthy subjects (D'Souza et al., 2005). Δ^9-THC produced robust dose-dependent impairments on both, immediate and delayed (30-minute) verbal recall. Δ^9-THC also increased the number of "false positives" and "intrusions" on the HVLT. Similar findings have been recently reported by Henquet et al., (Henquet et al., 2006) and Morrison et al (Morrison et al., 2009).

The acute effects of cannabinoids are likely modulated by genetic and personality factors. This would explain why only a small minority of people experience the

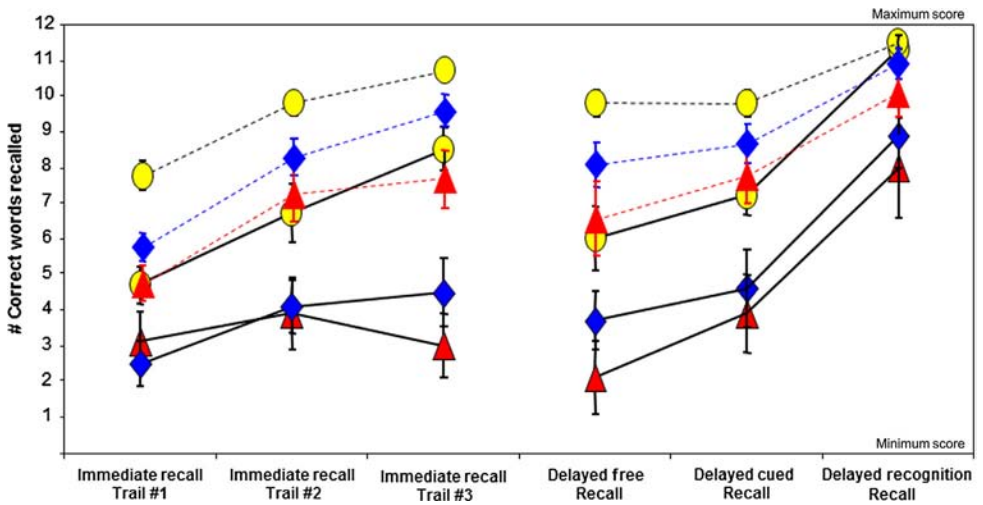

Figure 2 Δ^9-THC impairs verbal memory. The figure shows the effects of Δ^9-THC on verbal learning and recall (means ± SEM) as measured by the Hopkins Verbal Learning Test in healthy subjects (dashed lines) and patients with schizophrenia (solid lines). (Green line = placebo, Red line = 2.5 mg Δ^9-THC, Blue line = 5 mg Δ^9-THC.)

psychotomimetic effects of cannabinoids. Henquet et al (2006) examined the effects of the interaction of Catechol-O-methyl transferase (COMT) polymorphism and a trait index of psychosis liability on smoked Δ^9-THC (0.3 mg/kg) on cognitive performance and psychosis in 30 healthy individuals (Henquet et al., 2006). They found that individuals with the Val/Val polymorphism and high scores on psychosis liability had higher Δ^9-THC-induced psychotic symptoms.

2.3. EFFECTS OF CANNABINOIDS ON SCHIZOPHRENIA PATIENTS

The three drugs most commonly misused by schizophrenia patients are tobacco, alcohol, and cannabis (Margolese et al., 2004; McCreadie, 2002). Of illicit drugs, cannabis is the most frequently used (Bersani et al., 2002; Buhler et al., 2002; Cuffel et al., 1993; Farrell et al., 1998; Fowler et al., 1998; Green et al., 2005; Hambrecht and Hafner, 1996; Jablensky et al., 2000; Kessler et al., 1995; Linszen et al., 1994; McCreadie, 2002; Mueser et al., 1992). A recent meta-analysis showed that about 25% of schizophrenia patients in clinical samples have been diagnosed with cannabis abuse or dependence (Koskinen et al., 2009); in contrast, the rate of cannabis abuse and dependence in the general population has been estimated to be 1.13% and 0.32%, respectively (Compton et al., 2004). Information about the acute effects of cannabis and cannabinoids on schizophrenia patients comes from subjective reports, retrospective self-assessments, longitudinal and observational studies, and experimental studies.

2.3.1. Nonexperimental

2.3.1.1. Retrospective Self-assessments

Drug users' stated beliefs about the effects that they experience from drugs are often inaccurate but nevertheless frequently drive drug-taking behavior (Dixon et al., 1991). Behavior is often based on attitudes that spring from beliefs; moreover, beliefs that are based on personal experience have a stronger influence in the formation of attitudes than information gained in other ways, and better predict later behavior. Thus, what cannabis-using schizophrenia patients believe are the effects that cannabis has on them can be a crucial determinant in their use of cannabis, including whether they continue to use or relapse.

Many qualitative studies have been conducted in North America, Australia, and the United Kingdom investigating self-reported reasons for drug use in patients with psychotic disorders. Some protocols ask open-ended questions (Baigent et al., 1995; Fowler et al., 1998); in others patients select reasons for use from predetermined lists (Addington

and Duchak, 1997; Dixon et al., 1991; Test et al., 1989; Warner et al., 1994). These studies reveal three main beliefs that motivate use of cannabis:

1. Cannabis use causes relaxation and enhances positive mood (Dixon et al., 1991; Fowler et al., 1998).
2. Cannabis use decreases negative emotions (such as depression) (Addington and Duchak, 1997; Baker et al., 2002; Dixon et al., 1991; Fowler et al., 1998; Gearon et al., 2001; Goswami et al., 2004; Green et al., 2004c; Schofield et al., 2006; Spencer et al., 2002).
3. Cannabis use enhances social occasions and makes it easier to cope with people (Fowler et al., 1998; Test et al., 1989).

Cannabis is also reported to reverse neuroleptic effects. In one study, half of 45 participants reported that they were using drugs (including cannabis) or alcohol to cope with or reduce auditory hallucinations feelings of suspiciousness or paranoia, and two out of five were using drugs when they were experiencing medication side effects (Gregg et al., 2009). However, a recent review of 14 studies specifically addressing self-reported reasons for cannabis use in patients with psychotic disorders concluded that the three reasons listed above were the most cited, with only a minority reporting that cannabis use relieved medication side effects or symptoms of psychosis such as hallucinations and suspiciousness (Dekker et al., 2009). Patients with psychosis appear more likely to use cannabis for mood elevation than for relaxation; less likely to use out of habit or for social reasons, and more likely to use in order to cope with boredom or other negative affective states (Green et al., 2004a).

Despite these expectations, however, the actual subjective effects reported by patients following cannabis use are often negative. Although patients initially report feeling "inspired, relaxed, energized, or active" following cannabis use, they also frequently describe an exacerbation of positive psychotic symptoms and increases in dysphoria and aggression following the initial positive effects (Knudsen and Vilmar, 1984). Some patients report cannabis to be unpleasant and to cause adverse psychic effects (Negrete et al., 1986). Severe exacerbations of psychosis and functional deterioration sometimes follow periods of moderate cannabis use (Treffert, 1978), and more than 50% of subjects in one study reported that cannabis increased their positive symptoms (Addington and Duchak, 1997). Although some schizophrenia patients experience reductions in anxiety, depression and negative symptoms, others report increased suspiciousness, derealization, and variable effects on hallucinations (Arndt et al., 1992; Dixon et al., 1990; Hekimian and Gershon, 1968; Peralta and Cuesta, 1992; Weil, 1970). Recently diagnosed schizophrenia patients have also reported increased visual and auditory hallucinations and confusion after cannabis use, as well as longer-term social problems, depression, and less control over thoughts (Peters et al., 2009a).

It is possible that from the patients' viewpoint cannabis use is beneficial because it decreases their preoccupation with psychotic symptoms, even as it increases objectively measured symptoms. Alternatively, while cannabis may increase psychotic symptoms,

it may also reduce symptom-related distress so that schizophrenia patients experience the overall effects of cannabis as beneficial. However, retrospective self-report data are subject to distortion. Individuals who misuse drugs typically use denial and rationalization to justify their use. In addition, cannabis alters perception and has amnestic effects that may influence the interpretation of events and therefore interfere with the accurate recall of drug effects. Longitudinal studies that follow cohorts of schizophrenia patients over time and observational studies that assess cognitive and behavioral functioning are better able to measure objective data such as hospital admissions or changes in cognition.

2.3.1.2. Longitudinal and Observational Studies

Most longitudinal studies find that the more cannabis schizophrenia patients use, the more problems they have (Andreasson et al., 1987; Linszen et al., 1994; Rais et al., 2008; Yucel et al., 2008). Cannabis use interferes with the therapeutic alliance (Dixon, 1999; Wilk et al., 2006), is associated with less access to nonpharmacological interventions (Regier et al., 1990; Wilk et al., 2006), and increased chance of prematurely early discharge from the hospital (Brunette et al., 1997), and an increased need for interventions and longer hospitalizations (Kivlahan et al., 1991). Cannabis-using schizophrenia patients have worse psychopathology and higher relapse rates (Johns, 2001; Linszen et al., 1994; Swartz et al., 2008), as well as an increased need for interventions and longer hospitalizations (Kivlahan et al., 1991). A recent prospective cohort study of 145 male schizophrenia patients followed for 12 months found that those who used cannabis were more frequently hospitalized than noncannabis-using patients although they did not differ with respect to psychopathology (van Dijk et al., 2012).

Although most studies concur that cannabis use has a negative effect of cannabis use on the course of schizophrenia, some studies find positive or equivocal effects as well. One study found no baseline differences in psychopathology between cannabis users and nonusers (Zisook et al., 1992). In the CATIE cohort, cannabis use was even associated with equal or higher psychosocial functioning compared to abstinent patients (Swartz et al., 2006). One group of cannabis-using schizophrenia patients had better cross-sectional scores on affective measurements compared with their noncannabis-using counterparts (Peralta and Cuesta, 1992), and a subgroup of schizophrenia subjects that used cannabis less than once daily in a Dutch cohort reported similar positive effects of cannabis on anxiety and depressive symptoms (Linszen et al., 1994). Other authors have also reported less anxiety and fewer depressive symptoms in schizophrenic patients using cannabis (Johns, 2001). Cannabis-using schizophrenia patients have lower negative-symptom scores (Peralta and Cuesta, 1992), and cannabis-using adolescents with first-episode psychosis have lower negative symptom scores and a better prognosis that those who do not use cannabis (Baeza et al., 2009).

The literature on the effect of cannabis use on cognitive functioning in patients with schizophrenia is also mixed. While acutely, cannabinoids appear to worsen cognitive test

performance in schizophrenia patients, cross-sectional studies suggest that schizophrenia patients who abuse cannabis have better cognitive performance (Joyal et al., 2003; Løberg and Hugdahl, 2009; Potvin et al., 2005; Ringen et al., 2010; Scholes and Martin-Iverson, 2010; Stirling et al., 2005). A cross-sectional study of nearly a thousand schizophrenia patients compared with nearly a thousand sibling and over 500 controls in a battery of cognitive tasks found poorer performance on immediate verbal learning, processing speed, and working memory in the current cannabis users, but better performance on acquired knowledge, facial affect recognition, and face recognition identity in lifetime users (Meijer et al., 2011). More recently, DeRosse et al (2010) showed that patients with schizophrenia who also abused cannabis had better performance on measures of processing speed, verbal fluency and verbal learning and memory that patients with schizophrenia who did not use cannabis (DeRosse et al., 2010). The study was subsequently critiqued for inadequate methods of analysis (Suckling, 2011). However, a review of 23 studies on cannabis, schizophrenia, and cognition by Løberg and Hugdahl, (2009) also found that 14 studies reported *better* cognition in the cannabis-using groups (Løberg and Hugdahl, 2009).

Furthermore, two recent meta-analysis, one with 8 studies on the effects of cannabis on neurocognitive functioning in schizophrenia with a total sample size of 942 (Rabin et al., 2011), and the other with 10 studies (total sample size = 572) (Yucel et al., 2012) concluded that patients with schizophrenia who use cannabis (Rabin et al., 2011) and patients with first-episode psychosis who use cannabis (Yucel et al., 2012) have better neurocognitive performance. The studies are cross-sectional in design and hence cannot ascribe causality to the association between cannabis use and better neurocognitive functioning. While it is possible that cannabis use improves cognition, it is more likely that cannabis using patients have higher baseline neurocognitive functioning which would be essential in order for them to be able to procure and use an illegal substance, while at the same time avoid the legal system. Hence, although there is a deterioration in cognitive performance with the pathological processes associated with schizophrenia, the performance could appear to be better when examined in cross-sectional studies. This notion is also supported by the fact that the improved cognitive performance is not specific to cannabis but is also seen in patients with schizophrenia who abuse other illicit substances (Potvin et al., 2008).

It is difficult to attribute consequences solely to cannabis in naturalistic studies, because cannabis is often used in combination with nicotine, alcohol, and other illicit drugs. Moreover, positive and negative effects of cannabis are likely to be dose-related, and dose-response relationships are all but impossible to assess in naturalistic studies because of uncertainty over dose and potency of the cannabis. Some of these limitations have been addressed in experimental studies.

2.3.2. Experimental Studies

Only three studies have directly recorded the effects of Δ^9-THC or cannabis administration to schizophrenia patients in order to study acute effects on psychosis outcomes,

cognition, and side effects. In the first study, in 1934, Lindeman and Malamud administered unassayed doses of hashish to a group of schizophrenia patients, who experienced an exacerbation of their symptoms (Lindemann and Malamud, 1934).

The second study, seven decades later, was a randomized, double-blind, placebo-controlled study that examined whether schizophrenia patients were more vulnerable than healthy controls to the cognitive and propsychotic effects of Δ^9-THC (D'Souza et al., 2005). Thirteen stable antipsychotic-medicated schizophrenia patients and 22 healthy controls were given 0 mg, 2.5 mg, and 5 mg Δ^9-THC intravenously in a three-day, double-blind, randomized, counterbalanced study, with test days were separated by at least a week (more than three times the elimination half-life of Δ^9-THC) in order to minimize carryover effects. Subjects were abstinent from caffeine, alcohol, and illicit drugs for two weeks before testing until study completion, confirmed through urinary testing. A three-point or greater increase on the Positive and Negative Syndrome Scale (PANSS)(Kay et al., 1986) positive symptom subscale was considered a clinically significant response; the PANSS was administered several times after Δ^9-THC or placebo administration. Acute Δ^9-THC effects on neuropsychological functioning were also tested using a verbal fluency test (Corkin et al., 1964), the Hopkins Verbal Learning Test (Brandt, 1991) for learning and immediate and delayed recall, and a continuous performance test (Gordon, 1986) to measure attention. Motor side effects were measured using the Abnormal Involuntary Movement Scale (AIMS) for dyskinesias, the Barnes Akathisia Scale for akathisia, and the Simpson Angus Scale (SAS) for parkinsonism.

There were similarities between the schizophrenia patients and healthy controls, as well as differences. Plasma Δ^9-THC and 11-nor-Δ^9-carboxy-THC (metabolite) levels were the same in both patient and control groups. Δ^9-THC transiently increased positive symptoms in both schizophrenia patients and matched healthy controls. These effects were dose-related, occurred 10 to 20 minutes after Δ^9-THC administration, and resolved within four hours. Eighty percent of the schizophrenia patients but only 35% of control subjects had a clinically significant increase in psychosis in response to 2.5 mg Δ^9-THC, and 75% of schizophrenia patients but only 50% of control subjects had a suprathreshold response to 5 mg (Figure 3). Δ^9-THC acutely impaired immediate recall, delayed free recall, and delayed cued recall in a dose-dependent fashion, as well as increasing omission errors in the attention task. Schizophrenia patients were more sensitive to the cognitive effects of cannabis, particularly impairment of memory and attention (Figure 2), although there were no significant group-by-dose interactive effects. Δ^9-THC had no effects on verbal fluency, nor did it make subjects more calm and relaxed. There was no interaction between group, dose, and time, nor was there a difference between groups in Δ^9-THC's effects on other measures, such as feeling high (VAS) or perceptual alterations (on the Clinician-Administered Dissociative States Scale). Δ^9-THC increased total scores on the AIMS (dyskinesia) as well as on the SAS (rigidity).

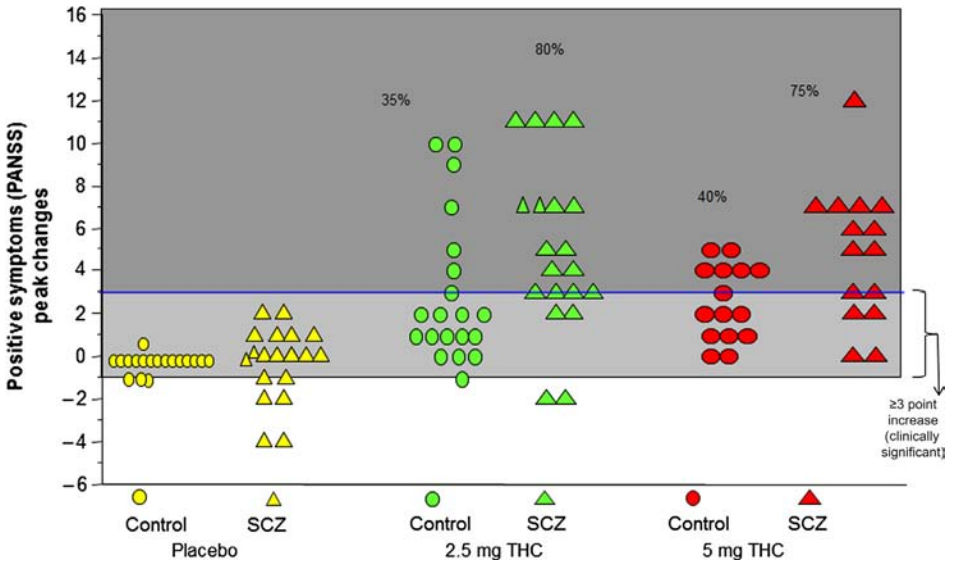

Figure 3 Enhanced sensitivity to the psychotomimetic effects of Δ^9-THC in schizophrenia. The figure shows the peak increase in on the positive symptom subscale of the Positive and Negative Symptoms Scale (PANNS) (group means ± 1 SD) in healthy subjects (controls) and in patients with schizophrenia.

The third study was a *momentary assessment study* that investigated the complicated dynamics of cannabis use and its varied effects in psychotic patients in the context of daily life by using the Experience Sampling Method (ESM) (Henquet et al., 2006). The study tracked the acute effects of cannabis on mood and psychotic symptoms in the daily life of 80 cannabis users; 42 psychotic patients and 38 healthy controls. In ESM, subjects received a digital wristwatch and a recording booklet. Twelve times a day on six consecutive days, the watch beeped randomly about once every 90 minutes, signaling the subjects to complete Likert scales on affect, thoughts, symptom severity, and activity at the moment of the beep. This systematic observation of recreational cannabis use in daily life revealed that not only was the frequency of cannabis use significantly higher in patients than in controls, but that neither positive nor negative affect predicted cannabis use at the next sampling point, indicating that there was no evidence for "self-medication". Similarly, no associations were found between delusions or hallucinations and subsequent cannabis use. Cannabis acutely induced hallucinatory experiences in patients but not healthy controls, and decreases in negative affect were observed after cannabis use in patients but not in controls, indicating that patients were more sensitive to the positive mood-enhancing effects of cannabis as well as the negative propsychotic effects. Patients were also became more sociable with cannabis, whereas no such effect was observed in the control group. *Post hoc* analysis suggested that cannabis may have immediate positive effects on mood, followed by decreases in

mood and increases in hallucinations several hours later. The authors concluded that this delay between immediate reward and negative consequences might explain why schizophrenia patients continue to use cannabis.

In summary, cannabis is one of the drugs most commonly misused by schizophrenia patients. Information about the acute effects of cannabis and cannabinoids on schizophrenia patients comes mostly from subjective reports, retrospective self-assessments, longitudinal studies, with few experimental studies. Subjectively, schizophrenia patients are motivated to smoke cannabis because they feel that it causes relaxation and enhances positive mood, decreases negative emotions (such as depression) and enhances social occasions and makes it easier to cope with people, with some also reporting relief of medication side effects or psychotic symptoms such as hallucinations and suspiciousness. The actual subjective effects reported by patients following cannabis use are often negative, however.

Most longitudinal studies find that the more cannabis schizophrenia patients use, the more problems they have, although some do find positive or equivocal effects as well. Only two modern studies have directly recorded the effects of Δ^9-THC or cannabis administration to schizophrenia patients. Schizophrenia patients are more sensitive to the cognitive effects of cannabis, particularly impairment of memory and attention, and it did not make patients more calm and relaxed. Cannabis may have immediate positive effects on mood, followed by decreases in mood and increases in hallucinations several hours later. This delay between immediate reward and negative consequences might explain why schizophrenia patients continue to use cannabis. It is also possible that from the patients' viewpoint, cannabis use is beneficial because it decreases their preoccupation with psychotic symptoms (making them more bearable) and elevates their mood, even considering the cost of increased symptoms.

2.4. EFFECTS OF CANNABINOIDS ON BRAIN STRUCTURE AND FUNCTION

2.4.1. Effects of Cannabinoids on Brain Structure

The effects of chronic exposure to cannabinoids on brain structure have been studied in animals and humans. In general, chronic administration of cannabinoids to rats and nonhuman primate produces dose-dependent neurotoxic changes in areas with a high density of CB-1RRs. However, it should be noted that few of these studies replicate the pattern of cannabis exposure typical in humans. Brian regions showing evidence of neurotoxic effects include the hippocampus, amygdala, and cortex (Chan et al., 1998; Downer et al., 2007; Harper et al., 1977; Heath et al., 1980; Landfield et al., 1988; Lawston et al., 2000; Scallet, 1991; Scallet et al., 1987). For example, treatment of hippocampal slices and neuronal cultures with Δ^9-THC resulted in shrinkage of neuronal cell bodies and nuclei, breakages in DNA strands and apoptosis (Chan et al., 1998). In a study that used a pattern of chronic Δ^9-THC administration to rats (5 times weekly

for 8 months, i.e approximately 30% of the life-span) similar to cannabis exposure in humans, Landfield et al (1988) noted significant morphological changes in the hippocampus which included decreased neuronal density and increased glial cell reactivity (Landfield et al., 1988). Hippocampus specific toxic changes were also noticed with chronic administration of the synthetic cannabinoid WIN 55,212-2 administered twice daily for 21 days (Lawston et al., 2000).

Studies that have examined the effect of cannabis use on brain structure in humans have yielded contradictory results with some studies suggesting changes in specific brain regions while others showing no changes. In one of the earliest case-series of 10 chronic cannabis abusers, Campbell et al (1971) found significant cerebral atrophy and ventricular enlargement among abusers when compared with control subjects (Campbell et al., 1971). However, the technique of pneumoencephalography and the choice of controls are limitations of that study. Subsequent studies using computerized tomography failed to detect significant structural abnormalities (Co et al., 1977; Hannerz and Hindmarsh, 1983; Kuehnle et al., 1977).

More recent studies using magnetic resonance imaging (MRI) have reported mixed results. While several studies did not find any changes (Block et al., 2000; Jager et al., 2007; Medina et al., 2007a; Tzilos et al., 2005), others reported global changes in both gray and white matter density (Wilson et al., 2000), focal changes in the hippocampal and parahippocampal areas (Matochik et al., 2005; Medina et al., 2007c), cerebellum (Cousijn et al., 2012; Solowij et al., 2011) and alterations in cortical gyrification (Mata et al., 2010). The mixed findings are likely due to the variability in cannabis exposure in the samples studied. Thus, while studies with lower frequency and/or amount of cannabis exposure show no change (Block et al., 2000; Jager et al., 2007; Medina et al., 2007a; Tzilos et al., 2005) or an increase (Medina et al., 2007b) in hippocampal and parahippocampal volumes, studies of samples with heavier cannabis exposure show reductions (Matochik et al., 2005).

Studies that have investigated the effect of cannabis use on structural brain abnormalities in patients with psychotic disorders (Table 1) have also yielded mixed results. The lack of consistent findings in these studies may be because of intrinsic differences in the samples, differences in the amount of cannabis exposure (current vs lifetime history), concomitant use of other drug (ranging from cannabis only to polydrug users), duration of illness and the effects of antipsychotic medication. Taken together, it appears that if exposure to cannabis alters brain structure, the effects are small. Furthermore, whether these structural changes have any functional consequences is not clear.

2.4.2. Effects of Cannabinoids on Brain Function (Psychophysiology)

Psychophysiological measures may be particularly informative in elucidating the mechanisms mediating the link between cannabinoids and psychosis. EEG is one of the few available methodologies that can directly measure neural events (postsynaptic potentials) with high temporal precision in humans (Luck et al., 2010). Psychophysiological indices using event-related potentials (ERPs) have been shown to one of the most consistently

Table 1 Cannabis Effects on Brain Structure in Schizophrenia

Study	Method	Participants	Results
Cahn et al. (2004)	MRI	27 S + C, 20 S − CB (naïve)	No difference in total brain, GM, WM or caudate nucleus volumes
Szeszko et al. (2007)	MRI	20 S + C, 31 S − C, 56HC	Anterior cingulate GM volume: S + C < S − C, HC
Potvin et al. (2007)	MRI	12 S + SM; 5 SC + 2; 2 S+ EtOH; 5 S + EtOH; 11 S − C, 15 HC	Ventral striatal GM density: S + SM > 2
Rais et al. (2008)	MRI	19 S + C; 32 S − C; 51 HC	Over five years: Loss of GM volume: S + C > S − C > HC; LV enlargement: S + C > S − C, HC; TV enlargement: S + C > S − C, HC
Bangalore et al. (2008)	MRI	Untreated first episode psychosis: 15 S + C; 24 S − C	Right posterior cingulate GM density: S + C > S − C
Wobrock et al. (2009)	MRI	20 S + SM (primarily C); 21 S − SM	No change in volume of amygdala, hippocampus, superior temporal gyrus and cingulate cortex.
Peters et al. (2009b)	DTI	24 S + C (onset < 17 y); 11 S − C	FA in frontal WM, uncinate fasciculus and anterior internal capsule: S + C > S − C
Dekker et al.	DTI	10 S + C (onset < 15 years); 8 S + C (≥17 years); 8 S − C	FA density in splenium: S − C < S + C (<15 years); WM demsity in splenium, right occipital lobe and left temporal lobe: S − C < S + C (<15 years)
Solowij et al. (2011)	MRI	17 S (47% S + C)31 HC (48% SM)	Cerebeller WM reduction in CB using healthy subjects as well as S + C
James et al. (2011)	MRIDTI	16 S + C, 16 S − C28 HC	GM density in temporal fusiform gyrus, parahhippocampal gyrus, ventral striatum, right middle temporal gyrus, insular cortex, precuneus, right paracingulate gyrus, dorsolateral prefrontal cortex, left postcentral gyrus, lateral occipital cortex and cerebellum: S + C < S − C. FA IN brain stem, internal capsule, corona radiata, superior and inferior longitudinal fasciculus: S + C < S − C

S + C = patients with psychotic illness and cannabis use; S − C = patients with psychotic illness without cannabis use; GM = gray matter; WM = white matter; HC = healthy controls; SM = substance misuse (abuse or dependence); EtOH = alcohol; LV = lateral ventricle; TV = third ventricle; DTI = diffusion tensor imaging; FA = fractional anisotropy.

replicated psychophysiological abnormalities in schizophrenia, and have yielded some of the largest effect sizes in the neurobiological study of schizophrenia (Heinrichs, 2004; Turetsky et al., 2007). ERPs are averaged electroencephalographic (EEG) responses time-locked to particular stimuli or events (Figure 4).

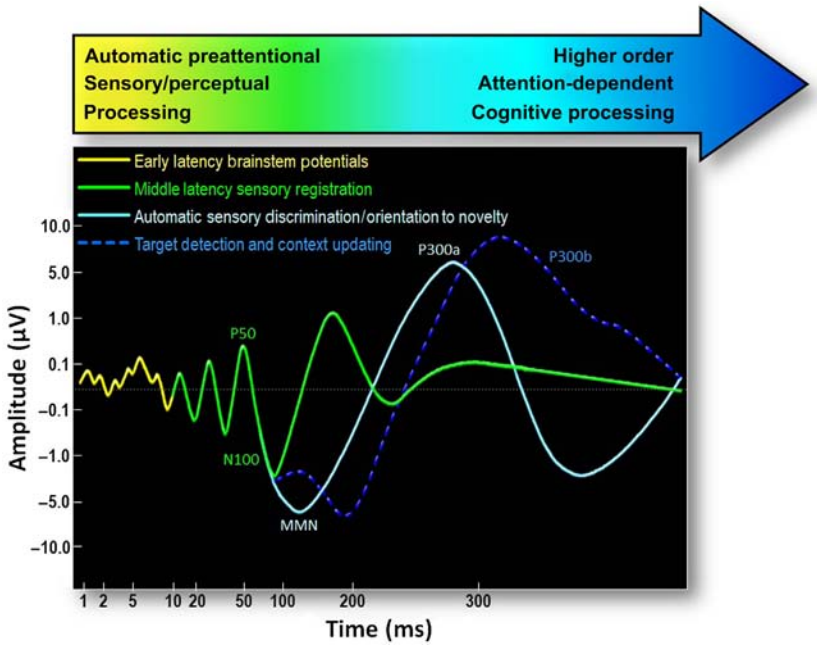

Figure 4 Schematic depiction of event-related potentials. Illustration demonstrating prototypical event-related potentials (ERPs) thought to be sensitive to both cannabinoids and schizophrenia. Time is shown using a logarithmic scale. Stages of information processing from automatic preattentional to higher order attentional processes are shown from left to right, respectively. *Adapted from Picton et al. (1974) and Rissling et al. (2010).*

As described by Solowij and Michie (2007), ERPs from several paradigms have been shown to exhibit parallel disruptions in both psychotic disorders and following the administration of exogenous cannabinoids. These paradigms include auditory sensory gating (P50) and the P300 (Solowij and Michie, 2007). A brief review of recent studies utilizing these psychophysiological outcomes in relation to psychosis and cannabinoids follows. Moreover, descriptions of several other putative biomarkers are included, namely mismatch negativity (MMN) and the N100 response. For a historical review of EEG studies on cannabis prior to 1990, see Struve and Straumanis (1990) (Struve and Straumanis, 1990). See Figure 4 for a schematic representation of ERPs thought to altered both in relation to cannabinoids and schizophrenia.

2.4.2.1. Auditory Sensory Gating (P50)

The P50 is a positive voltage, midlatency (~50 ms), preattentive ERP component elicited by discrete auditory stimuli (e.g. brief white noise clicks). In the P50 sensory gating or "dual-click" procedure, the amplitude of the P50 to a second paired click (S2) is reduced relative to the P50 amplitude to the first click (S1; 500 ms interstimulus

interval). While the P50 to S1 is related to the capacity of the central nervous system to register salient stimuli, the attenuation of the P50 amplitude to S2 (compared to S1) is associated with the automatic suppression or inhibitory gating of redundant and irrelevant stimuli. P50 suppression deficits in schizophrenia were first observed in the early 1980s (for recent reviews, see Braff and Light, 2004; Patterson et al., 2008; Potter et al., 2006; Thaker, 2008; Turetsky et al., 2007), and have also been demonstrated in clinically unaffected relatives, and individuals with schizotypal personality disorder (Cadenhead et al., 2000; de Wilde et al., 2007). Recent meta-analyses of over 20 sensory gating studies in schizophrenia have resulted in large effect sizes (Bramon et al., 2004; de Wilde et al., 2007; Patterson et al., 2008). Clinically, alterations in sensory gating may represent an inability to filter out redundant and irrelevant sensory information, thus leading to perceptual overload, which could contribute to positive symptomatology (Boutros et al., 1999; Thaker, 2008).

The brain regions thought to mediate auditory sensory gating include the hippocampus, the temporoparietal region, and the prefrontal cortex (Grunwald et al., 2003; Luntz-Leybman et al., 1992). Interestingly, in both humans and nonhuman primates, it has been shown that each of these areas have a high density of CB-1RRs (Eggan and Lewis, 2007). This fact, along with reports that THC intoxication can induce severe perceptual distortions (D'Souza et al., 2004), suggests that cannabinoids may contribute to psychosis by altering sensory gating. While no studies to date have examined the effects of acute cannabinoids on sensory gating, preclinical studies in rats suggest that cannabinoid agonists (CP-55940 and WIN 55,212-2) disrupt sensory gating in animal analogs of this paradigm (N40) (Dissanayake et al., 2008; Zachariou et al., 2008).

In contrast to the lack of any data on the acute effects of cannabinoids on P50 gating in humans several preliminary studies have demonstrated disruptions in P50 suppression in chronic cannabis users abstinent for at least 24 h (Patrick et al., 1999; Patrick and Struve, 2000). Furthermore, Edwards et al. (2009) assessed heavy cannabis users after 24 h of abstinence and replicated the findings of abnormal P50 gating in the cannabis group (larger S2/S1 amplitude ratios), which was positively correlated with the estimated number of joints smoked in the previous 6 months (Edwards et al., 2009). Finally, Rentzsch et al. (2007) assessed sensory gating in schizophrenia patients and healthy controls with and without comorbid cannabis abuse. It was demonstrated that cannabis-using controls (assessed after 28 days of abstinence) had significant P50 gating deficits, which correlated with the number of years of cannabis consumption (Rentzsch et al., 2007). However, cannabis using schizophrenia patients did not differ from cannabis-free schizophrenia patients, suggesting normalization and protection via antipsychotic medication. In sum, a common information processing deficit could link psychosis and cannabinoids at the level of inhibitory sensory gating, possibly through disruptions in GABAergic modulation of inhibitory neural circuits.

2.4.2.2. Target Detection (P300)

One of the most consistent psychophysiological findings in SZ, particularly in the auditory modality, is the P300 response (Braff, 1993; Bramon et al., 2005; Bramon et al., 2004; Duncan, 1988; Jeon and Polich, 2003; Roth and Cannon, 1972; Solowij and Michie, 2007; Turetsky et al., 2007; Turetsky et al., 1998). The P300 is a late positive, postattentional ERP component thought to be related to directed attention, contextual updating of working memory, and the attribution of salience to deviant or novel stimuli (Polich and Criado, 2006). This response is typically elicited utilizing standard "oddball" paradigms in which low probability target tones (~20%) are embedded within a repeating sequence of high probability standard tones (~80%) differing in some physical dimension (e.g. frequency or duration).

Rather than being generated by a single neural source, it this thought that the P300, particularly the P300b component, reflects activity from a distributed neural ensemble including such areas as the thalamus, hippocampus, inferior parietal lobe, superior temporal gyrus, and frontal cortex (Kiehl et al., 2001). Abnormal reductions in P300 amplitude and increased latencies haves been reliably shown in both schizophrenia patients and unaffected relatives, with moderate effect sizes reported (Bramon et al., 2005; Bramon et al., 2004; Jeon and Polich, 2003). While P300 deficits are one of the most robust findings in the neurobiology of SZ, it should also be noted that abnormalities of the P300 are not specific to psychosis, and have been reported in Alzheimer's disease, bipolar disorder (O'Donnell et al., 2004; Thaker, 2008), and especially alcoholism and substance abuse (Polich et al., 1994; Singh and Basu, 2009).

Several studies have reported on the effect of acute cannabinoids on the P300 response I humans. Using standardized active THC cigarettes, Ilan et al. (2005) reported a reduction in P300 amplitude during a visuospatial N-back working memory task (Ilan et al., 2005). In another study, oral THC (10 mg) was shown to reduce the amplitude of

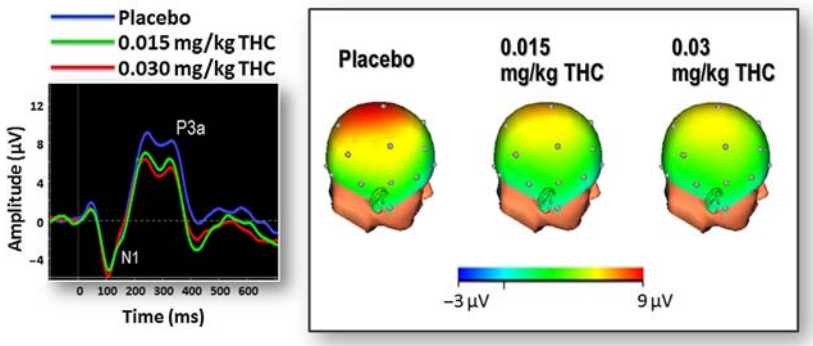

Figure 5 Effect of Δ^9–THC on P300a in healthy subjects. (Left). Grand-averaged novelty P300a waveforms at electrode Cz across THC dose conditions. (Right). Topographic voltage maps from the peak grand-averaged P300a across THC dose conditions.

the P300 measured during an auditory choice reaction task in healthy humans (Roser et al., 2008). More recently, D'Souza et al. (2012) examined the effect of several doses of intravenous (IV) THC on the novelty P300a and target P300b in healthy participants They showed that THC decreased of the amplitude of both the P300a (Figure 5) and P300b (Figure 6) in a dose-dependent manner (D'Souza et al., 2012). Further, these doses of THC also produced concomitant psychotomimetic effects. No effects on P300a or P300b latency were observed. These results suggest that acute THC can disrupt cortical processes responsible for context updating (P300b) and the automatic orientation of attention (P300a), while leaving processing speed intact. Furthermore, no effects of THC on the N100 (Figures 5 and 6) was observed suggesting that cannabinoids do not have significant effects on early sensory registration.

The results of studies assessing the effect of chronic cannabis use on the P300 response have been equivocal. Solowij et al. (1991) reported that a small sample of current cannabis users (12 h of abstinence) exhibited decreased P300 amplitudes during an auditory selective attention task (Solowij et al., 1991). While a follow up study with a larger sample size was unable to replicate the amplitude results, Solowij et al. (1995) demonstrated increased P300 latencies in heavy cannabis users utilizing the same task. Interestingly, it was reported that frequency of cannabis use was correlated with P300 latency (Solowij et al., 1995). More recently, decreased P300 amplitudes during a complex auditory selective attention task in cannabis users were reported, which was more pronounced in early onset users (Kempel et al., 2003).

By contrast, using a simple dual-stimulus oddball task (both auditory and visual), Patrick et al. (1999) were unable to detect P300 amplitude differences in age-matched, psychiatrically screened heavy cannabis users (tested after 24 h of abstinence). It was actually demonstrated increased P300 amplitudes in a small sample of cannabis users

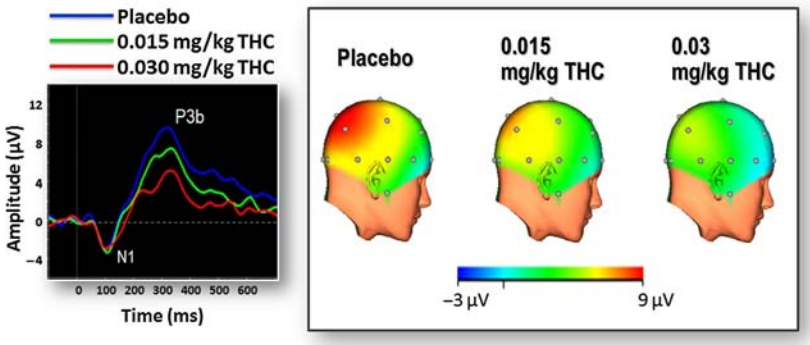

Figure 6 Effect of Δ^9–THC on P300b in healthy subjects. Left: Grand-averaged target P300b waveforms at electrode Pz across THC dose conditions. Right: Topographic voltage maps from the peak grand-averaged P300b across THC dose conditions.

during a dual-stimulus visual discrimination task (Skosnik et al., 2008b). Further, de Sola et al. (2008) reported that cannabis users exhibited normal P300 responses in a simple auditory P300 task, and that higher cannabis use was correlated with shorter latency (de Sola et al., 2008). The reasons for these discrepant results are unclear. The initial pattern that seems to have emerged is that chronic cannabis users are impaired during more cognitively challenging selective attention tasks (Kempel et al., 2003; Solowij et al., 1991; Solowij et al., 1995), but retain normal ERP responses when simple dual-stimulus discrimination tasks are utilized (de Sola et al., 2008; Skosnik et al., 2008b).

To summarize the data on the P300 ERP, the majority of studies to date examining the P300 response in the context of both chronic and acute cannabinoids are suggestive of impairments in novelty detection, selective attention and working memory. These findings indicate some level of neurobiological overlap between the ERP deficits observed in psychosis and in the context of chronic and acute cannabinoids.

2.4.2.3. Mismatch Negativity (MMN)

MMN is an automatic, preattentive, negative voltage ERP component that is generated primarily in the superior temporal and prefrontal cortex (Naatanen and Alho, 1995; Rinne et al., 2000). It occurs approximately 100200 ms after an auditory stimulus that deviates in frequency or duration from a sequence of standard auditory stimuli. It is thought to index basic auditory processing and sensory memory, and is relatively independent of attention. Early studies of MMN in schizophrenia patients found abnormal amplitudes to stimuli deviating in either duration or frequency. Since then, numerous studies have observed alterations in the MMN ERP, which have been recently reviewed by Näätänen and Kahkonen (2009). A metanalysis of over 39 studies of MMN on schizophrenia patients (up to year 2003) reported a large effect size of 0.99 (Umbricht and Krljes, 2005). Interestingly, MMN does not appear to be altered in other psychiatric disorders such as unipolar and bipolar depression (Umbricht et al., 2003). Hence, MMN may be a particularly specific and useful biomarker for auditory disturbances in schizophrenia.

To date, only two studies have examined auditory MMN in relation to cannabinoids. Juckel et al. (2007) determined the acute effects of oral THC or cannabis extract containing both THC and the nonpsychoactive constituent cannabidiol (CBD) on MMN using a frequency deviance paradigm. Surprisingly, oral THC did not alter MMN amplitude as compared to placebo (Juckel et al., 2007). Further, THC + CBD was actually shown to increase the amplitude of the MMN ERP. The authors postulated that cannabis extract, with the addition of CBD, enhanced MMN by virtue of CBD's reputed antipsychotic effects (Zuardi et al., 2006a; Zuardi et al., 2009; Zuardi et al., 2006b; Zuardi et al., 1995; Zuardi et al., 1991). The lack of a MMN effect with pure THC could be related to the dose of THC chosen (10 mg orally), or due to the inter and intraindividual variability inherent in oral routes of administration.

More recently, the effect of chronic cannabis exposure on MMN utilizing frequency and duration deviance was examined. Initial analysis showed that cannabis users exhibited decreased MMN amplitudes at electrode Cz in the frequency deviance condition (Roser et al., 2008). More striking was the fact that both long-term and heavier users of cannabis had significantly lower MMN amplitudes compared to short-term or light users (Roser et al., 2008). Moreover, duration of cannabis exposure negatively correlated with MMN amplitudes in the frequency deviance condition at frontal electrode sites (Fz and F4). In other words, those showing smaller amplitudes had greater overall chronicity of cannabis use. While these data are only preliminary, it appears that chronic, heavy use of cannabis may be associated with MMN ERP deficits in a pattern similar to schizophrenia patients.

2.4.2.4. N100

While less well studied than the EEG biomarkers discussed above, an additional psychophysiological index that may prove useful in the study of psychosis and cannabinoids is the N100 ERP. The N100 component (or N160/N170 in the visual modality) is a large exogenous ERP that exists regardless of task demands (although it can me modulated by attention) (Hillyard et al., 1973). It is thought to be related to basic perceptual processing, and in the auditory domain, is likely generated by auditory and frontal cortices. While initially reported to be aberrant in schizophrenia in the 1970s (Saletu et al., 1971), most studies assaying this response have demonstrated abnormal N100s in both schizophrenia patients and their clinically unaffected relatives (Rosburg et al., 2008; Turetsky et al., 2008). Given the parallel auditory and visual disturbances in both schizophrenia patients and individuals consuming cannabis, this ERP component could prove useful in examining the neural mechanisms linking cannabinoids and psychosis.

The acute administration of cannabinoids (IV THC) failed to affect the N100 component during an auditory oddball paradigm (D'Souza et al., 2012). In contrast, Skosnik et al. (2006) demonstrated robust differences in the visual N160 response in chronic cannabis users tested after 24 h of abstinence (Skosnik et al., 2006) using a repetitive photic stimuli paradigm. No differences in N160 latencies were shown. This effect was further demonstrated in the auditory modality for discrete 1000 Hz tones during an associative learning task (N100) (Skosnik et al., 2008a). However, a subsequent study utilizing the same auditory stimuli with a new sample of cannabis users failed to replicate this finding (Edwards et al., 2008). Furthermore, a recent study of the effect of chronic cannabis use on the gamma-band (40 Hz) auditory steady state response (ASSR) showed no differences in the N100 component. It therefore appears that effect of cannabinoids on the N100 ERP remains equiviocal, and may vary depending on modality and experimental paradigm.

2.5. PERSISTENT BEHAVIORAL AND COGNITIVE EFFECTS OF CANNABINOIDS

The evidence for the persistent effects of cannabinoids in humans, derives primarily from nonexperimental, epidemiological studies of cannabis. The latter have a number of limitations including sampling biases, power of the study (i.e overpowered/underpowered sample sizes), presence of unknown confounders, lifetime exposure to multiple drugs, period-, time-, cohort- effects and direction of causality also applies to this extensive literature.

2.5.1. Positive Symptoms

The question of whether chronic exposure to cannabinoids can "cause" persistent symptoms or a psychotic disorder is an important one.

One of the first large epidemiological studies that attempted to answer this question was a longitudinal, 15-year cohort study of 45,570 Swedish conscripts who had been conscripted between 1969 and 1970 (Andreasson et al., 1987). Since Sweden mandates military service, almost all of the male population of Sweden (97%) aged 1820 years were included. Andreasson et al (1987) observed a dose-response relationship between self-reported cannabis use at conscription (age 18 years) and psychiatric hospitalization for schizophrenia over the ensuing 15 years. Conscripts who reported having used cannabis at least once in their lifetime had a 2.4-fold (95% confidence interval 1.83.3) increased risk of developing schizophrenia over the course of 15 years. This relative risk rose to 6 fold (95% CI = 48.9) in those who had used cannabis more than 50 times in their lifetime. Furthermore, the risk remained significantly high despite adjusting for other factors such as psychiatric illness at the time of conscription, solvent abuse and parental separation.

In a 27-year follow-up study of the same cohort and a re-analysis of the data, Zammit et al (2002) replicated the findings of Andreasson et al, (1987) showing that cannabis use was associated with a linear risk of developing schizophrenia with a relative risk increasing from 2.2 (95% CI 1.72.8) in those who had used cannabis at least once to 6.7% (95% CI 4.510) in those who had used cannabis more than 50 times in their lifetime (Zammit et al., 2002). When potential confounders such as psychiatric diagnosis at conscription, IQ score, degree of social integration, disturbed behavior in childhood, cigarette smoking and place of upbringing were included in the regression analysis, the adjusted relative risk was 1.5 (95% CI = 1.12.0) in those who had used cannabis at least once to 3.1 (95% CI = 1.75.5) from in those who had used cannabis more than 50 times in their lifetime. The relative risk for schizophrenia was significantly higher in those who developed schizophrenia within 5 years of conscription which brings into question the direction of causality, i.e. whether cannabis use led to schizophrenia or whether subjects used cannabis in an attempt to

self-medicate incipient symptoms of schizophrenia. The study attempted to answer this question in a secondary analysis that excluded those who developed a diagnosis of schizophrenia within 5 years of conscription. In this secondary analysis the adjusted relative risk remained significant only for those who had used cannabis more than 50 times (adjusted relative risk = 2.5, 95% CI = 1.25.1). The study needs to be interpreted with caution since while 24.3% of the sample had used any drug, a very small percent (3.4%) had used only cannabis. While the analysis controlled for cigarette smoking, it failed to control for the use of stimulants and other drugs. Also, the fact that presumably weak confounders such as "place of upbringing" and "cigarette smoking" contributed substantially, along with other variables in reducing the adjusted relative risk by approximately 50% in the regression analysis highlights the difficulties inherent in interpreting epidemiological data and raises the issue of other unknown confounders. Similar criticism has been raised by other authors (Johnson, 1990; Johnson et al., 1988; Negrete, 1989), including the facts that (1) the use of other drugs was more common in the cannabis-using group, (2) the association between cannabis use and schizophrenia may be mediated by a third, as yet unknown factor, and (3) the follow-up study, a quarter century later, failed to address the issue of confounding due to use of other drugs, many of which are also known to precipitate psychosis.

A longitudinal Dutch study, the Netherlands Mental Health Survey and Incidence Study (NEMESIS), reported that cannabis use at baseline was associated with an increased risk of psychosis (van Os et al., 2002). The study assessed 7,076 subjects at baseline (1996), 5,618 subjects at a first time-point (1997) and 4,848 subjects at a second time-point (1999) via telephonic interviews, and found 10 subjects who developed psychosis, while 38 subjects endorsed individual items on the Brief Psychiatric Rating Scale (BPRS). The findings of the study are limited by the small numbers in the outcome of interest (psychosis) despite the large sample size, also reflected in the wide confidence intervals of the relative risk. The German prospective Early Developmental Stages of Psychopathology study (EDSP) which used in-person interviews in the assessment of 923 individuals from the general population (aged 1424 years) showed that cannabis use was associated with an increased risk of psychotic symptoms and persistent use increased this risk (Kuepper et al., 2011b). The EDSP study importantly points to the directionality of the association between cannabis use and psychosis. This is in contrast with other recent studies (Ferdinand et al., 2005; McGrath et al., 2010), which have shown the relationship to be bidirectional, alluding to the possibility of a phenomenon of "self-medication".

Fergusson et al, (2005) attempted to tease apart the causal link between cannabis use and psychosis in a dataset of a 25-year longitudinal study in New Zealand, the Christchurch Health and Development Study (CHDS) birth cohort comprising 1265 children (635 males, 630 females) (Fergusson et al., 2005). The study showed that daily use of cannabis was associated with 2.33.3-fold higher risk of psychosis that among nonusers. One of the limitations of the study is that the data was derived from 10 items of the Symptom

Checklist-90, the items on which overlap with personality traits such as schizotypy and paranoia and that the study did not attempt to delineate psychotic symptoms due to the acute effects of cannabis use from persistent effects (Mirken and Earleywine, 2005).

This finding of increased psychosis risk has been reported in several other prospective studies (Arseneault et al., 2002; Henquet et al., 2005a; van Os et al., 2002; Weiser et al., 2002). The issue of reverse causality i.e. psychosis leading to cannabis use rather than cannabis use leading to psychosis, can be addressed to some extent in prospective studies by excluding subjects with psychosis at the outset of the study. In a systematic review of longitudinal studies Moore et al. found that any cannabis use (pooled adjusted OR = 1.41, 95% CI 1.20 ± 1.65) was associated with a 40% increased risk of psychotic disorder, and the risk increased in a dose-dependent fashion with greater cannabis exposure (OR = 2.09, 1.54 ± 2.84) (Moore et al., 2007).

Recent studies have attempted to explore other factors that may moderate the increased risk of psychosis outcomes with cannabis use. It is being increasingly recognized that adolescence may be a particular period of increased vulnerability to the effects of cannabis and additional factors such as, schizotypy or other trait measures of liability to psychosis, and childhood abuse may mediate the causation of schizophrenia with prolonged and persistent cannabis use. In a 26-year follow-up study of another birth cohort in New Zealand ($n = 1037$) called the Dunedin Multidisciplinary Health and Development Study, Arseneault et al (2002) reported that individuals using cannabis at age 15 years were 4 times more likely to have a diagnosis of schizophreniform disorder at age 26 years (Arseneault et al., 2002). This risk was higher than the risk with cannabis use at age 18 years, after controlling for the presence of self-reported psychotic symptoms at age 11 years. The study design has significant strengths in that it provided data on psychotic symptoms at age 11 years (i.e. before the onset of cannabis use), on cannabis use at ages 15 years and 18 years and DSM-IV diagnosis at age 26 years. However, psychotic symptoms at age 11 years significantly increased the risk of a diagnosis of schizophreniform psychosis at age 26 years, and when used as a covariate in the analysis the risk of cannabis use was no longer significant, although it remained elevated (Odds Ratio = 3.1). The small sample size is another factor that limits the interpretation of these results.

In a sibling-pair analysis using samples of patients with a psychotic disorder ($n = 1120$), their siblings ($n = 1057$) and community controls ($n = 590$), the Genetic Risk and Outcome in Psychosis (GROUP) investigators found that siblings of patients with psychosis had greater sensitivity to positive and negative schizotypy, strait measures of psychosis liability and had higher psychotic experiences as measured on the CAPE (Community Assessment of Psychic Experiences) (GROUP, 2011). An exploratory analysis showed that familial risk moderated, rather than mediated the increased sensitivity to cannabis (GROUP, 2011).

More recently, the interactive effects of childhood maltreatment and cannabis abuse have been examined. While two cross-sectional and one prospective study show that

cannabis use and childhood maltreatment act additively to increase the risk of psychosis (Harley et al., 2010; Houston et al., 2008; Konings et al., 2012), this finding was not replicated in the German EDSP dataset (Kuepper et al., 2011a). Future studies that examine the interaction between genetic liability, trait measures of psychosis liability, cannabis use and other environmental factors may provide greater insights into the complex architecture and mechanisms that lead to the causation of psychosis.

Interestingly, although meta-analytical studies suggest that cannabis might account for between 8% and 14% of schizophrenia cases (Henquet et al., 2005b; Moore et al., 2007), the four fold increase in the rates of cannabis use over the last four decades (Aust et al., 2002; Zammit et al., 2002) has not resulted in a commensurate 40% to 70% increase in prevalence of schizophrenia. Some studies suggest that the rates of schizophrenia may be decreasing (Der et al., 1990), while others suggest the contrary (Ajdacic-Gross et al., 2007; Hickman et al., 2007).

2.5.2. Negative Symptoms

Apart from the link with psychosis, as detailed above, chronic heavy cannabis use has also been associated with an "amotivational syndrome" (Halikas et al., 1982; Hall and Solowij, 1998; Kolansky and Moore, 1971; Millman and Sbriglio, 1986; Tennant and Groesbeck, 1972). This syndrome is characterized by apathy, amotivation, social withdrawal, narrowing of one's personal repertoire of interests, lethargy, impairment in memory and concentration, impaired judgment and decision making, and poor sociooccupational functioning. All these symptoms share similarities with the negative symptoms of schizophrenia. The nosological status of the syndrome is however, debated and the confounding effects of concomitant polydrug abuse, poverty, low socioeconomic status, or preexisting psychiatric disorders cannot be ruled out.

2.5.3. Cognitive Deficits

Several studies suggest that chronic, heavy cannabis use may lead to impairments in memory and attention (Bolla et al., 2002; Lundqvist, 2005; Pope et al., 2001a; Pope et al., 1995; Pope and Yurgelun-Todd, 1996; Solowij and Battisti, 2008). Solowij and Mitchie (2007) have suggested that cognitive dysfunction associated with long-term or heavy cannabis use is a cognitive endophenotype of schizophrenia (Solowij and Michie, 2007). In a comprehensive review, Solowij and Battisti (2008) concluded that chronic heavy cannabis use was associated with impairments in memory (Solowij and Battisti, 2008) that persisted beyond the period of acute intoxication and was related to the frequency, duration, dose and age of onset of cannabis use. Fontes, et al (2011), evaluated the neuropsychological performance of 104 chronic, heavy cannabis users and found that, compared to controls, chronic cannabis users had significant impairment on the cognitive domains of sustained attention, impulse control and executive functioning (Fontes et al., 2011). Additionally, similar to the literature on the risk of psychosis, individuals who used cannabis in adolescence (before the age of 15 years)

had greater deficits. The authors however, did not assess whether subjects were in withdrawal or had residual effects from their last use of cannabis at the time of assessment.

While chronic, heavy cannabis users have deficits in cognitive processes, especially memory and attention in the context of ongoing cannabis use, the question of whether these impairments are persistent or a result of withdrawal and residual effects is unclear. While one study demonstrated an absence of persistent neuropsychological deficits in frequent long-term cannabis users after 28 days of abstinence (Pope et al., 2001b), other studies have shown variable durations to full recovery, ranging from a week (Jager et al., 2006), to 28 days (Pope et al., 2001a), to three months of abstinence (Fried et al., 2005), with some studies showing recovery only after an average of two years of abstinence (Hall and Solowij, 1998; Solowij, 1995). A recent review provides a summary of the literature to date (Crean et al., 2011).

Among studies in which neuropsychological assessments were performed 3 weeks or later after the last use of cannabis, five out of seven studies showed no impairment in attention (Lyons et al., 2004; Pope, 2002; Pope et al., 2003; Pope et al., 2001a; Pope et al., 2002; Pope et al., 2001b; Verdejo-Garcia et al., 2005), while two showed persisting impairment (Bolla et al., 2002; Solowij, 1995). One study revealed a trend toward impairment in decision making/risk taking (Verdejo-Garcia et al., 2006). There was, no impairment on response inhibition measured by the Stroop test (Bolla et al., 2002; Lyons et al., 2004; Pope et al., 2003; Pope et al., 2001a; Pope et al., 2002), and on working memory (Verdejo-Garcia et al., 2005) while all (Bolla et al., 2002; Pope et al., 2003; Pope et al., 2001a; Pope et al., 2002), but one (Lyons et al., 2004) found an impairment on the Wisconsin Card Sorting Test, a test of reasoning/problem solving. There was no impairment in verbal memory in two (Pope et al., 2002; Pope et al., 2001b) of the three studies that used the Buschke's Selective Reminding Test (BSRT), a test of memory of word lists. When the data from the third study (Pope et al., 2003) was stratified based on age at onset of cannabis use, significantly greater impairment was noticed in those who had first use cannabis before the age of 17 years again suggesting that like for positive symptoms, earlier age of onset of cannabis use may be associated with greater persistent cognitive deficits. It is important to note that none of these studies were designed to determine whether the cognitive impairments predated cannabis use.

2.6. CANNABINOIDS, PSYCHOSIS, AND CAUSALITY

Does exposure to cannabinoids "cause" psychosis where none would have otherwise existed? The commonly applied criteria to establish disease causality include temporality, strength and direction of the association, biological gradient (dose), consistency, specificity, coherence, experimental evidence, and biologic plausibility.

2.6.1. Temporality

Experimental evidence from laboratory studies clearly demonstrates a robust temporal relationship between exposure to cannabinoids and psychotic *symptoms*. The onset of

cannabis use may precede, follow or co-occur with the onset of schizophrenia. Allebeck and colleagues reported that in 69% of a schizophrenic patient sample from a Swedish case registry ($n = 112$), cannabis abuse preceded the onset of psychotic symptoms by at least one year (Allebeck et al., 1993b). Further, in only 11% did the onset of psychotic symptoms precede the onset of cannabis abuse. Similarly, Linszen et al. found that cannabis abuse preceded the onset of psychotic symptoms by at least 1 year in 23 of 24 cannabis-abusing recent onset schizophrenic patients (Linszen et al., 1994). Hambrecht and Hafner in their study of first-episode schizophrenic patients found that 14.2% of the sample had a lifetime history of drug abuse with cannabis being the most frequently abused drug (88%) (Hambrecht and Hafner, 1996; Hambrecht and Hafner, 2000). Furthermore, drug abuse preceded the first sign of schizophrenia by more than a year but typically by more than 5 years in 27.5% of patients. In 37.9% of individuals, drug abuse followed the first sign of schizophrenia, and in 34.6% of individuals, the first sign of schizophrenia and drug abuse started within the same month. Related to the above, some studies suggest that cannabis and other substance use is associated with an earlier age of and more abrupt onset of psychotic symptoms in schizophrenic patients (Addington and Addington, 1998; Allebeck et al., 1993a; Andreasson et al., 1987; Andreasson et al., 1989; Cleghorn et al., 1991; Green et al., 2004b; Hambrecht and Hafner, 1996; Linszen et al., 1994; McGuire et al., 1994; Van Mastrigt et al., 2004; Veen et al., 2004).

However, schizophrenia begins insidiously, and evolves through several identifiable stages with the emergence of psychotic symptoms as the final step in the evolution of the disorder. As a result, while it may be easy to pinpoint the emergence of positive psychotic symptoms in retrospective studies, pinpointing the onset of the less obvious prodromal symptoms is extremely challenging. Further, if as the neurodevelopmental hypothesis posits, that the pathophysiological processes underlying the illness precede the clinical manifestations by years or even decades and that these processes may even begin in utero, then, the argument about a temporal relationship is no longer relevant.

Thus, while there is evidence suggesting a temporal association between cannabis use and the onset of positive psychotic symptoms, the temporal relationship between cannabis use and the less obvious symptoms has not been studied.

Dose: Several studies reviewed here provide evidence of a doseresponse relationship between exposure to cannabinoids and the risk of both psychotic symptoms and disorder.

Direction: The case of reverse causality has been proposed whereby risk for schizophrenia predisposes to cannabis use, rendering the association between cannabis and psychotic illness merely an epiphenomenon of a shared vulnerability for both psychosis and cannabis (Collip et al., 2008; Macleod, 2007). Since several longitudinal studies excluded people with psychosis at baseline, or adjusted for psychotic symptoms in the analysis, the observed association between cannabis and psychosis is unlikely to reflect reverse causation (Moore et al., 2007).

Strength: Cannabis exposure increases the odds of developing schizophrenia modestly (by 40%) even after controlling for many potential confounding variables (Moore et al., 2007).

Specificity: While there is a strong association between cigarette smoking and schizophrenia, there is little evidence to support the notion that cigarette smoking "causes" schizophrenia. Further, the association between cannabis use is weaker for anxiety or affective disorders (Moore et al., 2007).

Biologic Plausibility: The effects of cannabinoids on key neurotransmitters and known to be implicated in psychosis, and also neurodevelopmental processes provide biological plausibility for the association (D'Souza, 2007; D'Souza et al., 2009; Sewell et al., 2009). The acute effects of cannabinoids on DA, GABA and glutamate neurotransmission may explain some of the acute positive, negative and cognitive symptoms of cannabinoids. But these acute effects may be difficult to explain how exposure to cannabinoids causes a persistent psychotic disorder such as schizophrenia. The findings that early exposure to cannabis is associated with a greater risk for psychosis outcome than later exposure may provide some clues toward the underlying mechanism.

2.7. THE EFFECTS OF CANNABINOIDS ON NEURODEVELOPMENT

The acute effects of cannabinoids on DA, GABA and glutamate neurotransmission may explain some of the acute positive, negative and cognitive symptoms of cannabinoids. But these acute effects may be difficult to explain how exposure to cannabinoids contributes to the risk for a persistent psychotic disorder such as schizophrenia. The findings that early exposure to cannabis is associated with a greater risk for psychosis outcome than later exposure may provide some clues toward the underlying mechanism. Emerging evidence suggest that cannabinoids can influence neurodevelopment. The effect of cannabinoids on neurodevelopment is particularly relevant since schizophrenia, one view of schizophrenia is that it is a neurodevelopmental disorder (Rapoport et al., 2005; Weinberger, 1996).

An important feature of the endocannabinoid signaling system is that its different components are present in the embryo even at a preneuronal stage i.e. even before the onset of neurogenesis (Psychoyos et al., 2012). Exposure to the THC analogue, O-2545, has been shown to impair early processes in the differentiation of the primordial brain (Psychoyos et al., 2008). Endocannabinoids also regulate important neurodevelopmental processes such as neurogenesis, neural specification, neural maturation, neuronal migration, axonal elongation, and glia formation (Berghuis et al., 2005; Berghuis et al., 2007; Galve-Roperh et al., 2009; Watson et al., 2008).

The distribution of CB-1R receptors over the time course from the embryonal stage to adulthood is telling in this regard. CB-1R receptors are present on neural proliferator cells and immature neural cells in the embryo (Aguado et al., 2006). In the postnatal period CB1-R are present on radial-type glial cells and B-type cells, (which are thought to constitute neural stem cells) (Berghuis et al., 2005) and subsequently, in the adult brain they are present on the subventricular/ ventricular zone progenitor cells and on both, glutamatergic neurons and GABAergic neurons (Oudin et al., 2011). This temporal distribution

is consistent with its role in neurogenesis, neural specification and neural maturation (Aguado et al., 2006; Berghuis et al., 2005; Berghuis et al., 2007; Fernandez-Ruiz et al., 2000; Galve-Roperh et al., 2007; Harkany et al., 2007; Jin et al., 2004; Mulder et al., 2008; Watson et al., 2008). Also, CB-1R receptors are initially abundant in the intermediate zone of the cortical plate region of the neocortical brain, are then found in white matter regions of the embryonic brain and gradually move to occupy layers IVI of the cortex in the adult brain, a pattern consistent with neuronal migration. The presence of CB-1R since early stages of brain development along with its transient presence in atypical locations like the white matter regions is further suggestive of its role in neuronal migration.

Another finding which supports this hypothesis is that the enzyme DAG Lipase which is involved in the synthesis of the endocannabinoid 2-archidonylglycerol (2-AG), appears to localize to axonal tracts in the embryo and transitions to localize onto dendritic fields in the adult brain (Harkany et al., 2007). This is also accompanied by a transition in endocannabinoid concentrations, 2-AG being most abundant in the early embryonal period while anandamide (AEA) peaks in the perinatal period (Galve-Roperh et al., 2009).

Further evidence for the role of endocannabinoids in neurodevelopmental processes comes from studies on knock-out mice. CB-1R receptor knock-out (KO) mice have reduced proliferation of neural progenitor cells in the hippocampus and subventricular zones (Jiang et al., 2005). A similar effect was found with the CB-1R antagonist, rimonabant (Gobbi et al., 2005). On the other hand, both mice deficient in Fatty Acid Amide Hydrolase (FAAH) the enzyme that breaks down endocannabinoids, and pharmacological inhibition of FAAH and DAGL led to increased proliferation of neural progenitor cells in the hippocampus. CB-1R KO and FAAH-1 deficient mice show altered radial migration and layering of pyramidal neurons (Mulder et al., 2008). Consistent with these results, inhibition of CB-1R led to failure of the corticothalamic axons to invade the dorsal striatum (Mulder et al., 2008). CB-1R are also found to play a role in interneuron migration and interneuron migration (Berghuis et al., 2005).

Chronic exposure to Δ^9-THC in early stages of neurodevelopment has been shown to result in altered pattern of cholecystokinin-positive (CCK) densities, a marker of GABAergic interneurons in the hippocampus (Berghuis et al., 2005). AEA is known to stimulate CCK-positive interneuron migration but inhibit brain derived neurotrophic factor (BDNF)-induced dendritic branching (Berghuis et al., 2005). Additionally, in animal studies, Δ^9-THC has been shown to alter BDNF expression (Butovsky et al., 2005; Derkinderen et al., 2003; Maj et al., 2007; Rubino et al., 2006; Valjent et al., 2001). Δ^9-THC has been shown to induce BDNF mRNA transcription via CB-1R receptors (Derkinderen et al., 2003; Rubino et al., 2006; Valjent et al., 2001). D'Souza et al. (2008a,b) showed that a socially relevant dose Δ^9-THC resulted in an increase in serum BDNF levels in healthy adult subjects (D'Souza et al., 2008a). Interestingly, light users of cannabis had lower basal BDNF levels. The lower basal BDNF levels in light users of cannabis suggest that chronic exposure to cannabinoids can lead to a suppression of BDNF release.

The effects of in utero exposure to cannabis on the developing brain is an area of great interest. Studies on a postmortem human fetal brain collection from midgestational mothers with cannabis use is currently underway (reviewed in (Jutras-Aswad et al., 2009)). In utero exposure to cannabis impacts the maturation of the dopamine neurotransmitter system (including tyrosine hydroxylase activity, decreased dopamine D1 and D2 receptor mRNA levels in amygdala), opioid system (decrease proenkephalin mRNA levels, increased mu receptor expression, decreased kappa receptor expression in mediodorsal nucleus of thalamus) and the serotonin system (decreased serotonin in raphe nucleus and ventral hippocampus) (Molina-Holgado et al., 1997). The effects of in utero cannabis exposure on the cannabinoid system are mixed, with some studies showing a change in CB-1R receptor density while other studies show no significant change (Garcia-Gil et al., 1999; Wang et al., 2004). There have been no systematic studies on the effects of in utero exposure on the GABA and glutamate systems.

The behavioral and cognitive effects of in utero exposure to cannabis have been examined in two longitudinal studies, namely the Maternal Health Practices and Child Development Project (MHPCD) (Goldschmidt et al., 2008) and the Ottawa Prenatal Prospective Study (OPPS) (Fried et al., 2003). The MHPCD is a prospective study (since 1982) of the effects of prenatal marijuana and alcohol exposure on the intelligence test performance of 648 children in a low-income, African-American and Caucasian population in Pittsburgh, Pennsylvania. Newborns and infants with prenatal marijuana exposure (PME) demonstrated increased tremors, exaggerated startle response, and poor habituation to novel stimuli (Fried, 1982; Fried and Makin, 1987; Fried and O'Connell, 1987). They showed increased hyperactivity, inattention, and impulsive symptoms by age 10 (Fried et al., 1998; Goldschmidt et al., 2000) and had higher rates of delinquency and externalizing behavioral problems as compared to age-appropriate nonexposed children (Goldschmidt et al., 2000). The study also found that PME predicted lower scores on the verbal reasoning and short-term memory area scores of the Stanford-Binet Intelligence Scale (SBIS) at age 3 and at age 6. PME predicted lower scores on the Bayley Scale of Infant Development, Mental Development Index at 8 months but this was no longer significant at age 18 months. A path analysis suggested that the effects on cognition were mediated by inattention and impulsivity (Goldschmidt et al., 2000). This also appears to be consistent with animal studies in which animals exposed prenatally to Δ^9-THC show a selective disturbance of the frontostriatopallidal proenkephalin/D2 dopamine receptor circuit, a circuit important in inhibitory control behavior (Frank et al., 2007).

In the OPPS, initiated in 1978, the effects of alcohol, cigarette smoking and marijuana use in the prenatal period of 698 women were studied in a birth cohort comprising of 190 children. The population was a low-risk, Caucasian, predominantly middle-class cohort in Canada. While prenatal cannabis use was associated with significantly lower performance on memory and verbal subscales of the McCarthy Scales of Children's Abilities at age 4, these were no longer significant at age 5 and age 6. The question

remains as to the validity of these scales in capturing significant differences in specific domains of cognition, rather than a global cognitive functioning.

Adolescence is another critical period of neurodevelopment as brain development continues well into young adulthood (around age 25) (Crews et al., 2007). Animal studies have shown that exposure to cannabinoids in adolescence has more deleterious effects than exposure in adulthood (Cha et al., 2006; O'Shea et al., 2004; Quinn et al., 2008; Schneider, 2008; Schneider et al., 2008). Acute administration of the cannabinoid agonist, WIN 55,212-2 resulted in greater anxiety-related behavior in rats when WIN was administered during puberty compared to when administered in adult rats. Chronic cannabinoid treatment during puberty induced persistent deficits in object recognition and social behavior such as, social play and self-grooming (Schneider et al., 2008). In another study, exposure of adolescent rats to Δ^9-THC during the critical pubertal period led to deficits in spatial memory in adulthood and corresponding changes in hippocampal morphology and NMDA receptor expression (Rubino et al., 2009). Studies in humans show that earlier onset of cannabis use is associated with poorer cognitive performance (Ehrenreich et al., 1999; Kempel et al., 2003), premature alteration in cortical gyrification pattern (Mata et al., 2010) and smaller gray matter volumes (Kumra et al., 2012).

In conclusion, the endocannabinoid system appears to influence neurodevelopment. Perturbation of the endocannabinoid system in the rapidly changing brain, as is the case in adolescence, by excessive or nonphysiological stimulation, as may be the case with exposure to exogenous cannabinoids, may have far reaching consequences. This would be especially so in the presence of already altered neurodevelopmental processes such as the case in individuals with a high risk for schizophrenia. While admittedly speculative, exogenous cannabinoids by disrupting the endocannabinoid system and interfering with neurodevelopmental processes may provide a mechanism by which exposure to cannabinoids during adolescence may increase the risk for the development of schizophrenia. Clearly further work is necessary to understand the consequences of perturbing the endocannabinoid system during critical periods of neurodevelopment.

3. CONCLUSIONS

Cannabinoids can induce transient schizophrenia-like positive, negative and cognitive symptoms in healthy individuals. Cannabinoids also produce some psychophysiological deficits also known to be present in schizophrenia. Also clear is that in individuals with an established psychotic disorder, cannabinoids can exacerbate symptoms, trigger relapse, and have negative consequences on the course of the illness. Schizophrenic patients and others who are psychosis prone may be more likely to experience transient positive, negative and cognitive symptoms following exposure to cannabinoids, and these effects may be greater in magnitude and duration relative to healthy individuals.

Whether cannabinoids "cause" a persistent psychotic disorder such as schizophrenia is not as clear. Increasing evidence suggests that early and heavy cannabis exposure may increase the risk of developing a psychotic disorder such as schizophrenia. The relationship between cannabis exposure and schizophrenia fulfills some, but not all, of the usual criteria for causality. However, most people who use cannabis do not develop schizophrenia, and many people diagnosed with schizophrenia have never used cannabis. Furthermore, the increase in cannabis use, the use of more potent forms of cannabis and the earlier age of first use should be accompanied or followed by a commensurate increase in the rates of schizophrenia or an earlier age of onset of the illness.

However, data on the rates of schizophrenia have been mixed with some studies suggesting a decrease, others suggesting an increase and others suggesting no change. Therefore, exposure to cannabis is neither a necessary nor a sufficient cause of schizophrenia — similar to cigarette smoking being neither necessary nor sufficient to cause lung cancer or the role of dietary sodium and hypertension. More likely, cannabis exposure is a component or contributing cause which interacts with other known (genetic, environmental) and unknown factors, culminating in schizophrenia. In the absence of known causes of schizophrenia, however, and the implications for public health policy should such a link be established (Hall and Pacula, 2003), the role of component causes such as cannabinoid exposure should remain a focus of further study. The increasing availability of high potency cannabis, the increasing use of "medicinal" cannabis, and the increased availability of highly potent, full agonist synthetic cannabinoids, might provide further evidence to either refute or prove the link between cannabinoids and psychosis. Finally, further studies are warranted to determine a biological mechanism by which cannabinoids "cause" psychosis.

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