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Cannabis and psychosis/schizophrenia: human studies

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Abstract

The association between cannabis use and psychosis has long been recognized. Recent advances in knowledge about cannabinoid receptor function have renewed interest in this association.

Converging lines of evidence suggest that cannabinoids can produce a full range of transient schizophrenia-like positive, negative, and cognitive symptoms in some healthy individuals. 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. The mechanisms by which cannabinoids produce transient psychotic symptoms, while unclear may involve dopamine, GABA, and glutamate neurotransmission. However, only a very small proportion of the general population exposed to cannabinoids develop a psychotic illness. It is likely that cannabis exposure is a “component cause” that interacts with other factors to “cause” schizophrenia or a psychotic disorder, but is neither necessary nor sufficient to do so alone. Nevertheless, in the absence of known causes of schizophrenia, the role of component causes remains important and warrants further study. Dose, duration of exposure, and the age of first exposure to cannabinoids may be important factors, and genetic factors that interact with cannabinoid exposure to moderate or amplify the risk of a psychotic disorder are beginning to be elucidated. The mechanisms by which exposure to cannabinoids increase the risk for developing a psychotic disorder are unknown.

However, novel hypotheses including the role of cannabinoids on neurodevelopmental processes relevant to psychotic disorders are being studied.

Keywords

Cannabis; Cannabinoids; THC; Psychosis; Schizophrenia; Cognition

Introduction

The observed relationship between cannabis consumption and psychosis has long been recognized [161,231]; recent epidemiological and pharmacological studies have renewed interest in this association. But until recently, little was known about the mechanism of action of cannabinoids. Advances in understanding and knowledge about cannabinoid receptor function have prompted a fresh look at a long-recognized association between cannabinoids

and psychosis. The purpose of this paper is to review the association between cannabis exposure and psychotic disorders, and offer some possible explanations underlying the association.

As a prelude to reviewing the relationship between cannabinoids and psychosis, a few important points need to be considered. First, the distinction between psychotic *symptoms* and a psychotic *disorder* such as schizophrenia needs to be considered. There are differences between these two outcomes with exposure to cannabinoids. Second, the symptoms of schizophrenia include not just *positive* symptoms (hallucinations, delusions, thought disorder, paranoia) but also *negative* symptoms (amotivation, social withdrawal, and emotional blunting) and *cognitive deficits* (impairments in memory, attention and executive function). Most of the literature has focused almost exclusively on positive symptoms. Third, in addition to its most active constituent Δ^9 -tetrahydrocannabinol (Δ^9 -THC), cannabis contains several other cannabinoids including cannabidiol (CBD), cannabigerol, etc. [62]. Several reports suggest that the average Δ^9 -THC content of cannabis may be increasing [170]. The psychoactive effects of cannabis vary according to its Δ^9 -THC content. Cannabidiol has been shown to have anxiolytic and antipsychotic effects [126,242] leading to the suggestion that CBD may offset some of the adverse effects of Δ^9 -THC. Just as there is variability in the Δ^9 -THC content of cannabis, there is variability in the CBD content of cannabis. Thus, if the consequences of cannabis exposure are related to Δ^9 -THC content and if CBD offsets some of the effects of Δ^9 -THC, then exposure to cannabis with a higher Δ^9 -THC content and/or low CBD content might be associated with greater negative consequences.

Evidence for an association between cannabis and psychosis comes from several sources, including anecdotal accounts, surveys of cannabis users in the general population, epidemiological studies, and pharmacological studies. The evidence is presented in order of strength, from the weakest evidence such as anecdotal reports to the strongest evidence such as double-blind, randomized placebo-controlled experiments. Further, the evidence is organized according to the temporal characteristics of the association between cannabis and psychosis.

Do cannabinoids cause short-lived positive psychotic symptoms, negative symptoms and cognitive deficits in the general population?

Anecdotal evidence, case reports, and surveys

In one of the first autobiographical accounts of cannabis effects, Moreau de Tours in 1845 described acute, transient, dose-related psychotic reactions that included “paranoid ideation, illusions, hallucinations, delusions, depersonalization, confusion, restlessness, and excitement. There can be delirium, disorientation and marked clouding of consciousness.”

As reviewed elsewhere [43], there are a number of anecdotal reports that cannabis can produce a range of acute psychotic symptoms that 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 [27,35,78,116,201,205,214,217]. These symptoms are sometimes accompanied by anxiety, panic reactions, and psychomotor agitation. Related to the above, while there has been some discussion in the literature proposing “cannabis psychosis” as a distinct diagnostic entity, there does not appear to be enough evidence to support this notion [102,117,145,149,189]. In fact, cannabis-induced psychosis could be an early sign of schizophrenia rather than a distinct clinical entity [15]. Generally these psychotic symptoms are transient (minutes to hours) but there have been a few reports of symptoms persisting for weeks [30,35]. Cannabis may also precipitate persistent psychotic symptoms even in individuals who do not have a history or family history of psychosis. However, severe

or persistent psychotic reactions are rare, and are more likely to occur in individuals with a preexisting psychiatric condition such as schizophrenia or personality disorders [35]. In some instances, psychotic symptoms have recurred in those individuals who resume using cannabis. Finally, psychotic symptoms appear to be dose-related.

Some of the limitations of anecdotal accounts, case reports, and case series can be addressed by surveys of larger samples of individuals who have used cannabis. In large community samples, between 20 and 50% of individuals report acute transient psychotic symptoms, including paranoia, persecutory ideas, and hallucinations under the influence of cannabis [77,114,115,185,218].

The effects of medicinal cannabinoids

Another source of data on the association between cannabis and psychosis comes from the known effects of synthetic cannabinoids, such as Δ^9 -THC, nabilone, and levonantradol, which have been used in the treatment of chemotherapy-induced nausea, spasticity from multiple sclerosis, and pain syndromes. The reported effects of these drugs include anxiety and panic, fear and paranoia, amnesia, “loss of control”, thought disturbances, feelings of unreality, apprehension, dissociation, depersonalization, dysphoria, difficulty concentrating, hallucinations, and other perceptual alterations (Marinol Product Monograph) [36,88,106, 122,136,219]. The incidence of these effects has been reported to increase both with increasing dose and with repeated dosing [36,206]. Finally, in some clinical trials, some subjects refused further testing because they experienced disturbing psychotropic effects.

Experimental evidence

Unfortunately, survey and anecdotal data have inherent methodological limitations, such as sampling bias, reliance on self-report, lack of structured scales to assess psychosis, and inability to determine dose–response relationship. Only a small number of studies were specifically designed to examine the psychotomimetic effects of cannabinoids.

The first reported study was conducted under the direction of the “LaGuardia Committee on Marihuana” [147]. With cannabis doses of about 30–50 mg (oral) and 8–30 mg (smoked), 12.5% of subjects experienced psychotic reactions. However, these subjects were prisoners and their mental status cannot be presumed to be healthy. Ames [10] studied the effects of unassayed oral doses of cannabis extract (about 50–70 mg Δ^9 -THC) in 12 physicians who were presumably healthy. Subjects reported fragmented thinking, dissociation between thoughts and action, disturbed temporal and spatial perception, visual illusions and hallucinations, derealization and depersonalization, mood alterations, anxiety and memory deficits. Some subjects reported delusions of the presence of hidden recorders, fear of being hypnotized, fears of electroconvulsive therapy, and fears of developing schizophrenia. One subject refused to answer questions for fear of being certified as insane. Isbell and colleagues [103] studied the effects of varying doses of Δ^9 -THC in 40 former opiate addicts. At a dose of Δ^9 -THC, 120 μ g/kg orally and 50 μ g/kg smoking, in addition to recognizing the effects as being similar to cannabis, the subjects reported alterations in visual, auditory, and time perception. However, at Δ^9 -THC doses of 300–480 μ g/kg orally and 200–250 μ g/kg by smoking, there were marked auditory and visual distortions, depersonalization, derealization, and hallucinations. Of note, “occasional” individuals experienced psychosis even at low doses of Δ^9 -THC. In a related study, Isbell and Jasinski [104] compared the effects of Δ^9 -THC (75–225 μ g/kg, smoked) and LSD (0.5–1.5) in ten “normal” controls. Both drugs produced perceptual distortions, mood changes and, at higher doses, hallucinations. Of note, two subjects dropped out from the study after experiencing psychotic “reactions” from Δ^9 -THC. Melges et al. [151], in a double-blind placebo-controlled study with high and low dose Δ^9 -THC, reported that cannabis users were noted to have core symptoms of psychosis, including thought disorder and paranoia. The

authors specifically described “tracking difficulties” that subjects reported, including racing thoughts, thought blocking, losing their train of thought, etc. Jones et al. [110] did not observe robust psychotomimetic effects in studies of “normal” controls with Δ^9 -THC (20 mg smoked or 40 mg orally). However, a “few” subjects reported ideas of reference and delusions that the researcher was using secret (unexplained) tests and hidden recording devices. At doses higher than 20 mg smoked or 40 mg orally, psychotomimetic effects, including delusions, loosening of associations, and marked illusions began to emerge. In a ^{18}F -2-fluoro-2-deoxyglucose Positron Emission Tomography (FDG-PET) study of intravenous Δ^9 -THC (2 mg) on regional brain metabolism, two of eight healthy subjects who occasionally used cannabis experienced paranoid-anxious reactions [229]. Leweke et al. [128] reported the effects of oral synthetic Δ^9 -THC (120 $\mu\text{g}/\text{kg}$) in 17 healthy individuals under controlled laboratory conditions. The primary outcome measure was binocular depth perception—a model of illusionary perception. Subjective reactions ranged from mild euphoria to more pronounced reactions, including feelings of loss of self-control and body distortion suggestive of psychotic-like symptoms. One subject experienced a transient psychotic episode described as “a paranoid psychotic state with persecutory delusions, delusions of thought insertion, attentional irritability, fear, and—to some extent—verbal aggressive behavior.” However, this study was not placebo-controlled. In a subsequent study with nabilone, a synthetic analog of Δ^9 -THC, Leweke et al. [127] observed that nabilone produced effects on binocular depth inversion that were similar to Δ^9 -THC.

The pharmacological studies discussed so far had several limitations, including the absence of placebo control, lack of a double blind, the inclusion of psychiatrically ill individuals, and the lack of standardized measures of psychosis. Recently, there have been a few laboratory studies examining the psychotogenic effects of cannabinoids that address some of these limitations.

D'Souza et al. [46] characterized the behavioral and cognitive effects of Δ^9 -THC (0, 2.5, and 5 mg) in the first double-blind, randomized, placebo-controlled study of healthy controls ($n = 22$) who were very carefully screened for any significant psychiatric disorder and family history of any DSM Axis I disorder. This study was also the first to assess for a full range of symptoms associated with schizophrenia, i.e., positive, negative, and cognitive symptoms and to measure these symptoms using validated measures. Δ^9 -THC produced transient positive symptoms (Fig. 1), perceptual alterations, negative symptoms, euphoria, anxiety, deficits in working memory and verbal recall, and the executive control of attention without altering general orientation.

Positive symptoms

Δ^9 -THC induced a range of positive symptoms of schizophrenia, including suspiciousness, paranoid and grandiose delusions, conceptual disorganization, fragmented thinking, and perceptual alterations. For example, healthy controls reported suspiciousness such as “I thought you all were trying to trick me by changing the rules of the tests to make me fail. I thought you were turning the clock back to confuse me,” or “I thought that this was real...I was convinced this wasn't an experiment,” or “I thought you all were giving me THC through the BP (blood pressure) machine and the sheets”. Healthy controls also reported conceptual disorganization such as “I couldn't keep track of my thoughts... they'd suddenly disappear,” or “It seemed as if all the questions were coming to me at once... everything was happening in staccato,” or “my thoughts were fragmented... the past present and future all seemed to happening at once.” Healthy subjects also reported unusual thoughts such as “I thought you could read my mind, that's why I didn't answer... I felt as if my mind was nude,” or “I felt I could see into the future... I thought I was God.” These effects reported by carefully screened healthy subjects appear to be remarkably similar to the kinds of psychotic symptoms reported by patients with schizophrenia.

Δ^9 -THC also produced distorted sensory perceptions, altered body perception, feelings of unreality, derealization, depersonalization and extreme slowing of time in healthy individuals (Fig. 1). Subjects were reported to be “spaced out,” looking “separated or detached,” and as if they said or did “something bizarre”, or “needing redirection”.

Negative symptoms

Δ^9 -THC also produced negative symptoms of schizophrenia which included blunted affect, reduced rapport, lack of spontaneity, psychomotor retardation, and emotional withdrawal. Of note, these schizophrenia-like negative symptoms may have been confounded by the known cataleptic and sedating effects of Δ^9 -THC and further, acute pharmacological studies may have limitations in their capacity to “model” negative symptoms. Nevertheless, a persistent “amotivational syndrome” has been described in chronic heavy cannabis users by some [81, 82,118,155,216] but not others [97,190]. This so-called “amotivational syndrome” is characterized by apathy, amotivation, social withdrawal, narrowing of interests, lethargy, impaired memory, impaired concentration, disturbed judgment, and impaired occupational achievement. The syndrome has resembled the negative symptoms of schizophrenia. However, other drug use, poverty, low socio-economic status, or preexisting psychiatric disorders existing data confound the interpretation of the existing literature.

Cognitive deficits

Δ^9 -THC produced dose-dependent impairments in immediate and delayed (+30 min) recall of a word list in healthy subjects (Fig. 2). Δ^9 -THC also increased the number of false-positive responses and intrusions during recall. More recently, Henquet et al. [94] showed that smoked Δ^9 -THC impaired verbal learning and recall, sustained attention, selective attention, and psychomotor speed in healthy subjects, schizophrenia patients, and relatives of patients with schizophrenia. The observations of Henquet [94] and D'Souza [46] are consistent with other reports showing acute dose-related effects of cannabinoids on learning, short-term memory, working memory, executive function, abstract ability, decision-making, and attention in humans [87,90,99,129,140,153,183]. Of note, impairments in memory, executive function, and attention are observed in schizophrenia [89]. The memory impairment produced by cannabinoids is perhaps their most reliable and robust effect [183], and impairment in verbal memory is also the most robust cognitive deficit observed in schizophrenia [89].

In summary, both natural and synthetic cannabinoids administered via different routes can produce a range of transient, dose-related, schizophrenia-like positive, negative and cognitive symptoms in individuals without any obvious risk of schizophrenia. Some but not all individuals experience robust psychotomimetic effects. What makes some individuals more vulnerable than others to the psychotomimetic effects of cannabinoids is not clear. In addition to the effects described above, cannabinoids produce a plethora of other acute transient effects, including euphoria, relaxation, increased appetite, anxiolysis or anxiety, tachycardia, the intensification of mundane sensory experiences [3,98,105].

Do cannabinoids transiently exacerbate symptoms in individuals with schizophrenia?

Epidemiological studies suggest that cannabis use has a negative impact on the expression and course of schizophrenia [48,133,143,166,167]. In contrast, studies based on self-report of subjective effects suggest that schizophrenia patients use substances such as cannabis to “self-medicate” negative symptoms, depression, and side-effects of antipsychotics, to relieve boredom, to provide stimulation, to “feel good”, to “get high”, or to “relax” and to socialize with peers [5,51,172,192,195]. However, these studies rely on retrospective self-report, and therefore are subject to denial and rationalization, both of which play a role in substance misuse

disorders. Cannabis alters perception and has amnesic effects, both of which influence the recall of events. Further, since cannabis is often used in combination with other substances, sometimes without knowledge of the user, attributing certain effects solely to cannabis is difficult. Finally, it is possible that the positive and negative effects of cannabis may be dose-related, and this could be only crudely assessed in existing studies. The contrasting conclusions of self-report and epidemiological studies raise the possibility that schizophrenia patients may derive some immediate “benefits” from cannabis at the expense of later, negative consequences.

There are very few experimental studies that have characterized the effects of cannabinoids in this sample. Lindeman and Malamud [132] administered unassayed doses of hashish to a group of schizophrenic patients, “neurotics” and normals. “Normal” individuals developed paranoid delusions, impulsivity, and marked perceptual changes, and schizophrenic patients experienced an exacerbation of symptoms [132].

D'Souza et al. [44] conducted a randomized, double-blind, placebo-controlled study of Δ^9 -THC (0, 2.5, and 5 mg) effects in schizophrenic patients similar to the one described earlier in healthy subjects. The patients were taking stable doses of antipsychotic medications and were clinically stable. Δ^9 -THC *transiently* exacerbated a range of positive and negative symptoms, perceptual alterations, cognitive deficits, and medication side-effects associated with schizophrenia without producing any obvious “beneficial” effects. The increases in psychosis were brief, modest, and occurred even though subjects were clinically stable, medication-responsive and were receiving therapeutic doses of antipsychotics. The positive symptoms induced in these patients were similar to their typical symptoms. Using a threshold score of clinically significant positive symptoms (PANSS positive symptom subscale score ≥ 3 points) defined a priori, schizophrenia patients appeared to be more sensitive to Δ^9 -THC effects. Eighty percent of the schizophrenia group but only 35% of controls had a suprathreshold response to 2.5 mg Δ^9 -THC, and 75% of schizophrenic patients but only 50% of controls had a suprathreshold response to 5 mg Δ^9 -THC (Fig. 3). Similarly, relative to controls, schizophrenia patients were specifically more vulnerable to the dose-related learning impairments produced by Δ^9 -THC [44]. Under the influence of 5 mg Δ^9 -THC, schizophrenia patients (solid lines) showed no learning whatsoever (Fig. 2). Δ^9 -THC also increased the number of intrusions and false-positives generated during recall. Further, 5 mg Δ^9 -THC reduced learning and recall in healthy controls to the level of schizophrenia patients in the placebo condition. While admittedly speculative, perhaps greater group differences between schizophrenic patients and controls might have been observed if the patients were not taking antipsychotic medications and/or were not clinically stable.

It seems clear that cannabinoids can produce transient schizophrenia-like symptoms in healthy individuals, and exacerbate symptoms in schizophrenic patients. The mechanisms by which cannabinoids produce transient psychotic symptoms will now be discussed.

What are the mechanisms by which cannabinoids cause transient psychotic symptoms?

The effects of Δ^9 -THC are mediated by agonist/partial agonist effects at CB₁ receptors (CB₁R) where it has modest affinity ($K_i = 35\text{--}80$ nmol) and low intrinsic activity [40,173]. CB₁Rs are mostly coupled to $G_{i/o}$ proteins, through which they inhibit adenylate cyclases and stimulate mitogen-activated protein kinases [100]. CB₁R also inhibits voltage-activated Ca²⁺ channels and stimulates inwardly rectifying K⁺ channels [148,173]. CB₁Rs are distributed with high density in the cerebellum and cerebral cortex, particularly frontal regions, basal ganglia, hippocampus, and anterior cingulate cortex, brain regions that have been implicated in the putative neural circuitry of psychosis. CB₁Rs are receptors encoded by the CNR1 gene, which

resides on chromosome 6q14–15. The two best-studied endocannabinoids are anandamide and 2-arachidonoylglycerol (2-AG). Anandamide is produced from phospholipid precursors by the enzyme *n*-acylphosphatidylethanolamine-selective phospholipase D (NAPE-PLD) and 2-AG by α - and β -diacylglycerol lipases (DAGL) [176]. Levels of 2-AG are 50–1,000 times higher than those of anandamide. Its proposed role is as an autocrine messenger in axonal guidance [86] and as a retrograde messenger in the adult brain [134]. CB₁Rs are predominantly presynaptic [61] and are mainly localized to axons and nerve terminals. CB₁Rs are particularly abundant in the hippocampus on the terminals of a cholecystokinin (CCK) GABAergic basket cell interneurons [111] as well as in the dentate gyrus [57] and, at a lower level, in glutamatergic pyramidal cells. The primary effect of cannabinoids is the modulation of neurotransmitter release via activation of presynaptic CB₁Rs (reviewed in [67]). There are several possible mechanisms by which cannabinoids induce positive, negative, and cognitive symptoms of schizophrenia.

Dopamine (DA)

According to the dopamine hypothesis, some of the symptoms of psychosis may be attributable to disturbed and hyperactive dopaminergic activity. Converging pre-clinical evidence suggests interactions between cannabinoid (CB₁R) and DA systems (reviewed in) [71,123]. CB₁R and D₂ receptors are coexpressed in several brain regions [95], and there is signal transduction convergence in these regions [152]. The effect of CB₁R activation on increasing mesolimbic dopaminergic activity may provide one explanation for the positive psychotic symptoms induced by Δ^9 -THC. Cannabinoids have been shown to activate firing of dopaminergic mesolimbic neurons [65,66,71,72], and induce DA release in the striatum [34,63,139,215] in animals through activation of CB₁R. Consistent with preclinical data, Bossong et al. [24], using the DA D₂/D₃ receptor tracer [¹¹C]raclopride and positron emission tomography in seven healthy subjects, showed that a clinically relevant dose of Δ^9 -THC induced dopamine release in the human striatum. The increase in dopamine levels in these regions showed regional specificity to the ventral striatum and precommissural dorsal putamen. Note that schizophrenic patients show increased amphetamine-induced dopamine release, and the degree of striatal DA release positively correlates with the severity of the psychotic symptoms [1,121]; this may also explain why schizophrenia patients are more vulnerable to the psychotogenic effects of cannabinoids.

However, DA D₂ receptor antagonism fails to block Δ^9 -THC-induced *c-fos* expression in both the striatum and nucleus accumbens of rats [157]. Similarly, in humans, the DA D₂ receptor antagonist haloperidol did not reduce any of the psychotomimetic, cognitive, and perceptual altering effects of Δ^9 -THC [45]. This is in contrast to the observation that haloperidol reverses the psychotomimetic effects of amphetamine [14]. In fact, haloperidol worsened some of the cognitive deficits produced by Δ^9 -THC. Collectively, these data suggest that it is unlikely that D₂ receptor mechanisms play a major role in mediating the positive (psychotomimetic) effects of Δ^9 -THC.

The effects of CB₁R activation in the prefrontal cortex (PFC) may provide a mechanism for the cognitive deficits and negative symptoms induced by cannabinoids. Systemically administered cannabinoids have been shown to modulate the activity of dopaminergic pathways in the PFC either directly or indirectly, by influencing the activity of dopaminergic neurons through either post- or presynaptic mechanisms [56,124,177]. By suppressing GABAergic and dopaminergic inhibitory neurotransmission, CB₁R activation might lead to non-specific activation of the PFC which in turn may disrupt normal signal processing and result in poor integration of transcortical inputs [178,237]. The stimulation of mesoprefrontal DA transmission by CB₁R activation [34,50,108,178] may contribute to working memory deficits associated with cannabis exposure. Given that either too high or low DAergic activity

in the PFC can lead to impairments in PFC-related cognitive functions [73,165,238], this may explain some of the cognitive effects of cannabinoids. The effects of cannabinoids on dopaminergic activity in the PFC may also exacerbate the effects of decreased mesocortical dopaminergic transmission and reduced D₁ receptor density reported in schizophrenia [2, 168,169] which would result in the worsening of working memory deficits and negative symptoms of schizophrenia.

Gamma-aminobutyric acid (GABA)

Interactions of CB₁R and GABAergic systems provide another potential explanation for the psychotomimetic effects of Δ^9 -THC given the converging preclinical evidence of important interactions between endocannabinoid and GABA systems [58]. Considering the high expression of CB₁R on GABAergic interneurons, the modulation of the activity of these interneurons is believed to mediate most of the effects of cannabinoids [67]. However, recent studies suggest that the loss of CB₁R from GABAergic neurons does not have any significant effect on any of the major effects of cannabinoids [158].

In the hippocampus and neocortex, CB₁Rs are present on axon terminals of cholecystokinin (CCK) containing GABA neurons that target the perisomatic regions of pyramidal cells [58, 111]. Activation of CB₁Rs reduces GABA release, resulting in disinhibition of pyramidal cell activity.

Furthermore, these CCK-containing, CB₁R-expressing GABA neurons are believed to play an important role in orchestrating pyramidal cell synchrony in the gamma (40 Hz) frequency range [96,220,230,234]. Gamma oscillations are synchronized over long distances in the brain and are hypothesized to “bind” together sensory perceptions and to play a role in perceptual, memory, and attentional processes (reviewed in [236]), all of which are also altered in psychosis. Activation of CB₁Rs located on GABAergic hippocampal neurons reduces GABA release [67,112,212] and this will disrupt the synchronization of pyramidal cell activity [80, 96,236]. The latter would interfere with memory consolidation, and associative functions and normal gating mechanisms, eventually leading to psychotic symptoms. Both in vivo and in vitro studies have reported that the CB₁R agonists disrupt neural synchrony (reduced power of 40 Hz oscillations) [79,80,188].

Since schizophrenic patients already display GABAergic deficits (reviewed in [130,131]), further reduction of GABA release by cannabinoids in the presence of a pre-existing GABA deficit may explain why schizophrenics show heightened sensitivity to the effects of cannabinoids.

Of note, GABAergic deficits have been observed in schizophrenia. Therefore, any reduction of GABA release by cannabinoids in the presence of a preexisting GABA deficit, as might be the case in schizophrenia, may explain why schizophrenia patients show heightened sensitivity to the effects of cannabinoids.

Glutamate

Interactions of CB₁R and glutamatergic systems may also provide an explanation for the psychotomimetic effects of Δ^9 -THC. CB₁Rs are also expressed in glutamatergic cortical principal neurons [7,52,113,141,142,146,159,213]. Several studies have reported that cannabinoids reduce glutamatergic synaptic transmission in several brain regions involved in the regulation of gating functions, such as the hippocampus [156], the prefrontal cortex [17], the nucleus accumbens [187], and the amygdala [18].

The initial iteration of the glutamate hypothesis of psychosis/schizophrenia was based on the similarities between the effects of the NMDA receptor antagonists phencyclidine (PCP) and

ketamine, and the symptoms of psychosis/schizophrenia [107,120]. According to the hypothesis, the schizophrenia-like effects of these compounds was related to their capacity to induce NMDA receptor hypofunction. Therefore, the effects of cannabinoids on reducing glutamate release may provide one mechanism by which they produce psychosis.

In summary, it seems clear that cannabinoids can produce transient schizophrenia-like symptoms in healthy individuals, and exacerbate symptoms in schizophrenic patients. Whether exposure to cannabis can “cause” a persistent psychotic disorder is less clear and is discussed below.

Do cannabinoids cause persistent psychotic symptoms or a psychotic disorder?

Epidemiological studies have contributed most significantly to the evidence suggesting that cannabis can “cause” a persistent psychotic disorder. The study that first brought significant attention to the topic was a large historical, longitudinal cohort study of all Swedes conscripted between 1969 and 1970 [11]. Since Sweden mandates military service, 97% of males aged 18–20 years were included. The relationship between self-reported cannabis use at the time of conscription and psychiatric hospitalization for schizophrenia in the ensuing 15 years was examined. A dose–response relationship was observed between cannabis use at conscription (age 18 years) and schizophrenia diagnosis in the following 15 years. Individuals who reported having used cannabis more than 50 times were six times more likely than non-users to have been diagnosed with schizophrenia in the ensuing 15 years. Adjusting for other relevant risk factors reduced but did not eliminate the higher risk (odds ratio = 2.3) of schizophrenia conferred by cannabis use.

A reanalysis and extension of the same Swedish conscript cohort reconfirmed that heavy cannabis users by the age of 18 years were 6.7 times more likely than non-users to be hospitalized for schizophrenia in the following 27 years [239]. This study addressed the confounding effects of concomitant use of other drugs of abuse, pre-morbid personality traits, and cannabis use as a form of self medication of schizophrenia. The adjusted odds ratio for cannabis use and schizophrenia remained significant (1.2), despite adjusting for a number of confounds including low IQ, urbanicity, cigarette smoking, poor social integration, occupational function, and stimulant use. Further, even after excluding subjects who developed schizophrenia within 5 years of conscription in an effort to control for the possibility that cannabis use was a consequence of prodromal manifestations of psychosis, the finding of an increased risk of schizophrenia conferred by cannabis use persisted. The authors concluded that cannabis use was associated in a causal way with an increased risk of developing schizophrenia.

These historical studies have been complemented by a number of recent prospective cohort studies. In a general-population birth-cohort study of 1,037 people born in Dunedin, New Zealand, and followed until age 26 years, cannabis use conferred a higher risk for the subsequent development of schizophrenia [16]. One of the strengths of this study was that it collected data on self-reported psychotic symptoms at age 11 years, to address whether psychosis preceded cannabis use. Self-reported cannabis use at both ages 15 and 18 years was also measured. Further, the entire sample was assessed at age 26 years using a standardized psychiatric interview that allowed the determination of both schizophrenia symptoms and categorical disorder. Compared to non-users, individuals using cannabis at ages 15 and 18 years had higher rates of psychotic symptoms and schizophreniform disorder at age 26 years, even after controlling for psychotic symptoms predating the onset of cannabis use. Cannabis users at age 15 years had a higher rate (OD = 3.1) of developing schizophreniform disorder at

age 26 years, even after controlling for psychotic symptoms predating the onset of cannabis use.

In the Netherlands Mental Health Survey and Incidence Study (NEMESIS), 4,045 psychosis-free individuals and 59 individuals with a psychotic disorder were assessed at baseline, 1, and 3 years [225] using a measure of psychosis. Individuals using cannabis at baseline were nearly three times more likely to manifest psychotic symptoms at follow-up even after adjustment for a range of factors. Further, a dose-response relationship was established with the highest risk (OD = 6.8) for the highest level of cannabis use. The relationship between cannabis use and psychotic symptoms was stronger for cases with more severe psychotic symptoms. Individuals who reported psychotic symptoms at baseline were also more likely to develop schizophrenia if they used cannabis, than were individuals who did not. The attributable risk of cannabis to psychosis was estimated at 13% for psychotic symptoms and 50% for cases with psychotic disorders that required psychiatric treatment.

Henquet et al. [92] studied the relation between cannabis use and psychotic symptoms in individuals at risk for psychosis who first used cannabis during adolescence. They tracked 2,437 subjects (14–24 years) with and without risk for psychosis from the general population for 4 years and found a dose-dependent increased risk of psychosis in subjects exposed to cannabis [92]. Interestingly, predisposition to psychosis was not found to be a predictor of future cannabis use at 4-year follow-up. Adding to these studies, Stefanis et al. [207] reported that both positive and negative symptoms can be induced by cannabis consumption and are independent of each other.

A recent systematic review of longitudinal studies of cannabis use and subsequent psychotic outcomes reported a 40% increased risk of psychotic outcome in individuals who had ever used cannabis (pooled adjusted OR = 1.41, 95% CI 1.20 ± 1.65) [160]. The risk rose in a dose-dependent fashion with greater cannabis exposure (OR = 2.09, 1.54 ± 2.84). Meta-analyses suggest that cannabis might account for between 8 and 14% of schizophrenia cases [93,160].

However, the longitudinal studies did not specifically examine cognitive symptoms as an outcome, even though cognitive deficits are a core feature of schizophrenia.

Do cannabinoids cause persistent cognitive deficits?

Acute exposure to cannabinoids clearly produces cognitive impairments that are transient. Heavy and prolonged cannabis exposure may be associated with deficits in memory, sustained attention, and executive functioning [75,135,182,203,204]. But whether these impairments persist and for how long is unclear. Some studies suggest full recovery after 28 days [181] or 3 months of abstinence [69], but others show some recovery only after an average of 2 years' abstinence [82,203]. Others have found persistent cognitive impairments and other indices of alterations in brain function even after 4 weeks of abstinence [22,23,60,175,196,202]. Early cannabis use may be associated with greater vulnerability to persistent cognitive deficits [59, 180]. Finally, very early exposure (prenatal) to cannabinoids has been associated with long-lasting cognitive, motor and social deficits [68,74].

Even though millions of people use cannabis, only a minority experience psychotic symptoms and even fewer develop a psychotic disorder. Clearly, other factors must interact with exposure to cannabis to increase the likelihood of a psychotic outcome.

What is the basis of individual vulnerability to psychotic outcomes with exposure to cannabinoids?

Individuals who are psychosis-prone may be more likely to have a psychotic outcome (both acute and long-term) following exposure to cannabis. Psychosis-proneness may be defined on the basis of a psychometric measure or by family history of psychotic disorder. Cannabis exposure has been shown to be associated with higher rates of psychotic outcomes in individuals with higher scores on measures of psychosis-proneness [19,92,211,228]. Similarly, individuals with a high risk for developing psychosis (either because of family history or prodromal symptoms) have higher rates of psychotic outcomes associated with cannabis use [15,41,119,150,154]. McGuire [150] reported that individuals who developed acute psychosis after cannabis exposure were more likely to have a positive family history of schizophrenia than patients who screened negative for cannabis use. Recently Arendt [15] showed that risk of psychiatric disorders in first-degree relatives of individuals treated for cannabis-induced psychosis were the same as in those of individuals treated for schizophrenia, suggesting that cannabis causes psychotic symptoms mainly in those who are predisposed to psychosis.

Corcoran et al. [41] prospectively followed 32 cases of prodromal psychosis for up to 2 years and found that these cases had significantly more perceptual disturbances and worse functioning during epochs of increased cannabis use. They concluded that the use of cannabis was a risk factor for the exacerbation of subthreshold psychotic symptoms (perceptual aberrations) in these high-risk cases. Similarly, Cadenhead et al. [119] reported that in a sample of individuals with a high risk for developing psychosis, those individuals with cannabis use were ten times more likely to convert to psychosis than individuals without cannabis use. This interaction of psychosis-proneness and cannabis exposure has also been observed in an experimental approach—in a controlled laboratory study, Henquet [94] showed that psychosis-proneness influenced the effects of Δ^9 -THC on cognition and psychosis.

Several models have been proposed to explain the interaction between cannabis exposure and psychosis-proneness. It may be that the psychosis-prone individuals are attracted to using cannabis (an association model), or that cannabis use increases psychosis-proneness (a causal model), or that there is another factor that causes both psychosis-proneness and cannabis use (an indicator-variable model) [91,193]. While cannabis users tend to exhibit higher psychosis-proneness scores in some [54,200,235] but not all studies [55,193], psychosis-prone individuals are not more likely to use cannabis [92]. Recently, Veling et al. [227] showed that individuals with schizophrenia had higher rates of cannabis use than either their siblings or controls, while their siblings had similar rates of cannabis use to controls, suggesting (1) that cannabis use predicted schizophrenia and (2) that risk for developing schizophrenia did not confer a higher risk for cannabis use.

Psychosis-proneness may in part have a genetic basis. A number of recent studies illustrate how specific genetic factors moderate the effect of cannabis exposure on the risk for psychosis [91]. Catechol-*O*-methyltransferase (COMT) is the enzyme that degrades DA, epinephrine, and norepinephrine. COMT is critical in the breakdown of DA in the prefrontal cortex. A functional polymorphism of the COMT gene results in two common allelic variants, the valine (Val), and the methionine (Met) allele, associated with high versus low enzyme activity, respectively. Increased COMT activity associated with the Val allele may result in a combination of reduced DA neurotransmission in the prefrontal cortex (cognitive deficits) and subsequent increased levels of mesolimbic DA signaling (psychosis). In a longitudinal birth cohort study ($n > 1,000$), adolescents homozygous for the COMT Val^{108/158}Met allele were most likely to exhibit psychotic symptoms or develop schizophrenia if they used cannabis [31]. Similarly, in a randomized, double-blind, placebo-controlled study, carriers of the Val

allele were more sensitive to Δ^9 -THC-induced psychotomimetic and amnesic effects than Met carriers, but this was conditional on psychometric evidence of psychosis-proneness [94]. Unlike Caspi et al. [31], Zammit et al. [240] failed to find evidence supporting differential effects of cannabis use on psychosis risk according to variation of the COMT gene.

The neuregulin 1 gene (Nrg1) has been implicated in schizophrenia. Nrg1 has a role in the expression and activation of neurotransmitter receptors, including the NMDA, GABA, and acetylcholine receptors [171,210], and is relevant to several schizophrenia-related neurodevelopmental processes (reviewed in [163]). A number of studies have identified associations between Nrg1 haplotypes and schizophrenia in various populations [53,101,164,198,208–210]. Heterozygous deletion of Nrg1 has been shown to increase sensitivity of mice to the behavioral effects of cannabinoids, especially under conditions of stress [25,26]. These mice also showed greater increases in prepulse inhibition (PPI), a marker for sensorimotor gating known to be impaired in schizophrenia, following Δ^9 -THC administration [25].

The cannabinoid receptor gene (CNR1) is thought to modulate the striatal response to rewarding stimuli [32] and polymorphisms of this gene are associated with alcoholism and intravenous drug use in humans [39,179,194,241]. A variety of CNR1 polymorphisms have been studied for associations with schizophrenia, with mixed results [33,125,144,197,221,222,240]. However, in a case-only design Zammit et al. [240] failed to find an effect of a CNR1 polymorphism on schizophrenia between those who did not use cannabis and those who claimed to have used cannabis at least 1 year prior to illness onset.

Several other genes relevant to schizophrenia and the mechanism of action of cannabinoids will also need to be studied. For example, as discussed earlier, there are extensive interactions between endocannabinoid and GABA systems. Thus, whether there are any interactions between cannabis exposure and variations in genes that regulate GABA on the risk of psychosis will be important to study.

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 (reviewed in [43]).

Dose

Several studies reviewed here provide evidence of a dose–response relationship between exposure to cannabinoids and the risk of both psychotic symptoms and disorder.

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 et al. [9] 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 1 year. Further, in only 11% did the onset of psychotic symptoms precede the onset of cannabis abuse. Similarly, Linszen et al. [133] 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. Hambrecht and Hafner, [83,84] 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%). Furthermore, drug abuse preceded the first sign of schizophrenia by more than 1 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 [4,8,11,12,^{37,76,84},133,149,224,226].

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 less obvious symptoms has not been studied.

Strength

Cannabis exposure increases the odds of developing schizophrenia modestly (40%) even after controlling for many potential confounding variables [160].

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 [38,137]. 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 [160].

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 [160].

Biologic plausibility

The effects of cannabinoids on key neurotransmitters and known to be implicated in psychosis, and also neurodevelopmental processes (discussed below) provide biological plausibility for the association.

What are the potential mechanisms by which cannabinoids cause a psychotic disorder?

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 it is 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 psychotic outcome than later exposure may provide some clues towards the underlying mechanism.

One view of schizophrenia is that it is a neurodevelopmental disorder [184,233]. As reviewed by Galve-Roperh et al. [70] in this issue, endocannabinoids play an important role in several processes important in neurodevelopment, including neurogenesis, neural specification, neural maturation, neuronal migration, axonal elongation, and glia formation. Brain development continues into young adulthood (25 years) [42], and therefore any factors that interfere with brain development during this time may have far-reaching consequences. Perturbation of the endocannabinoid system in the adolescent brain, by excessive or non-physiological 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. Therefore, 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.

As discussed in greater detail in this special issue, the expression profile of CB₁Rs evolves over time and across regions from a predominantly white matter distribution in embryonic brain to a definitive pattern in gray matter areas in the adult brain. Neurogenesis involves the proliferation of progenitor cells, migration, neuronal specification, final positioning, and synaptogenesis. Emerging evidence suggests that the endocannabinoid system influences these processes in fundamental ways [6,20,21,64,⁷⁰,85,109,162,232]. The cannabinoid system has been shown to regulate neural progenitor proliferation, differentiation, and migration, thus contributing to determining the final positions and densities of immature pyramidal cells. Endocannabinoids are developmental cues that help determine neuronal identity at both the cellular and neuronal network levels. Thus, endocannabinoid signaling influences the process by which developing neurons differentiate into both glutamatergic [162] and GABAergic phenotypes [20]. Furthermore, the cannabinoid system plays a key role in dendrite arborization, neurite outgrowth or retraction, axonal specification, axonal elongation, axonal fasciculation, axonal navigation, migration, and positioning of inhibitory GABAergic interneurons and excitatory glutamatergic neurons [20,21,232].

Interference with the endocannabinoid system during different stages of development can have far reaching effects. Adolescence and young adulthood are critical phases for cerebral development. During this period of neuronal plasticity, there is sprouting and pruning of synapses, myelination, changes in neurotransmitter concentrations and their receptor levels in brain areas necessary for behavioral and cognitive functions [186]. This is also the time that exposure to cannabis typically starts. In this issue, Schneider and Justras-Aswad et al. discuss the effects of early cannabis exposure in animals and humans, respectively.

The work of Justras-Aswad et al. and Schneider described in this special issue, should propel further investigations aimed at understanding to what extent perturbation of the endocannabinoid system by exposure to exogenous cannabinoids alters developmental processes relevant to schizophrenia. Furthermore, understanding the mechanisms by which exposure to endocannabinoids disrupt neurodevelopmental processes relevant to schizophrenia is also critical. For example, one potential mechanism by which cannabinoids may alter neurodevelopmental processes is by their known effects on neurotrophins.

Neurotrophins are a class of growth factor proteins that promote neurons to survive, differentiate, or grow. Neurotrophins include nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4). Neurotrophic factors have been implicated in the pathophysiology of several neuropsychiatric disorders including schizophrenia [28,174,199].

Δ^9 -THC has been shown to alter BDNF expression in animals [29,49,138,191,223]. Acute injection of Δ^9 -THC has been shown to induce BDNF mRNA transcription by stimulating CB₁R and activating the ERK signaling pathway [49,191,223]. D'Souza et al. [47] showed that a socially relevant dose Δ^9 -THC increased serum BDNF levels in healthy control subjects. Furthermore, 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. How this impacts the developing brain is not known. While admittedly speculative, this may provide a mechanism underlying the observation that cannabis precipitates schizophrenia or alters the course of the disorder.

On the other hand, Angelucci et al. [13] failed to find differences in serum BDNF levels between cannabis abusers and controls. Instead, they found that serum NGF levels were significantly reduced in cannabis abusers as compared to healthy controls. In contrast, Jockers-Scherubl clearly found elevated serum NGF levels in schizophrenic patients with cannabis abuse relative to non-abusers and controls. They concluded that the increase in serum NGF reflected an increase in NGF in response to neuronal "damage" induced by cannabis abuse. Clearly, further work is needed in this area.

Conclusions

Cannabinoids can induce transient schizophrenia-like positive, negative, and cognitive symptoms, and exacerbate symptoms in schizophrenic patients. 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. The effects of cannabinoids on increasing DA, reducing GABA, and reducing glutamatergic neurotransmission may contribute to their capacity to induce transient positive, negative, and cognitive symptoms, but the precise mechanism remains unclear.

Increasing evidence suggests that early and heavy cannabis exposure may increase the risk of developing a psychotic disorder. The relationship between cannabis exposure and schizophrenia fulfills some but not all of the usual criteria for causality. Despite some empirical support for a causal hypothesis between cannabis use and psychotic outcome, most people who use cannabis do not develop schizophrenia, and most people with schizophrenia have never used cannabis. This is similar to the role of genetics in schizophrenia—identical twins are not concordant for schizophrenia, and most people with schizophrenia do not have a family history of the disorder. Furthermore, there is a significant mismatch between the rates of cannabis abuse and those of schizophrenia. This might be similar to the role of dietary sodium and hypertension—the rates of salt consumption far exceed the rates of hypertension. The increase in cannabis use, the use of more potent forms of cannabis, and the earlier age of first use has not been accompanied or followed by a commensurate increase in the rates of schizophrenia or an earlier age of onset of the illness. This is difficult to explain—unless perhaps, the increase in the rates of schizophrenia is lagging behind the increase in cannabis use by the general population. It is important to note that schizophrenia is unlikely a homogenous illness. Therefore, it is unlikely for any one environmental factor such as, cannabis exposure or any one gene can account for the disorder. More likely, schizophrenia includes a collection of disorders with some general overlap in manifestations but with diverse pathophysiologies.

Taken collectively, 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. More likely, cannabis exposure is a component or contributing cause that interacts with other known (genetic, environmental) and unknown factors, culminating in schizophrenia. In the absence of known causes of schizophrenia, however, the role of component causes such

as cannabinoid exposure should remain a focus of further study. Further work is necessary to identify the factors that underlie individual vulnerability to cannabinoid-related psychosis and to elucidate the biological mechanisms underlying this risk.

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Fig. 1.

Δ^9 -THC induces transient psychotomimetic effects in healthy individuals. Effects of Δ^9 -THC on the seven-item positive symptom subscale of the Positive and Negative Syndrome Scale (PANSS) (*left panel*) and the clinician rated subscale of the clinician administered dissociative symptoms scale (CADSS) (*right panel*). The PANSS is used to measure the symptoms associated with schizophrenia. Scores for each item range from 0 (absent) to 7 (extremely). The range of scores on the PANSS positive subscale is 0–49. The CADSS is used to measure perceptual alterations. Scores for each item range from 0 (absent) to 4 (extremely). The range of scores on the CADSS clinician-rated subscale is 0–32. *Green circles* placebo (vehicle); *blue squares* 2.5 mg Δ^9 -THC; *red triangle* 5 mg Δ^9 -THC

Fig. 2.

Δ^9 -THC induces memory impairments. Effects of Δ^9 -THC on learning, immediate free recall, delayed free recall, delayed cued and recognition recall measured by a 12-word learning task (Hopkins verbal learning test). *Green circles* placebo (vehicle); *blue squares* 2.5 mg Δ^9 -THC; *red triangle* 5 mg Δ^9 -THC; *solid line* schizophrenia; *dotted line* controls