Behavioral, cognitive and psychophysiological effects of cannabinoids: relevance to psychosis and schizophrenia

Efeitos comportamentais, cognitivos e psicofisiológicos de canabinoids: relevância para a psicose e esquizofrenia

R. Andrew Sewell,[1,2,3] Patrick D. Skosnik,[1,2,3] Icelini Garcia-Sosa,[1,2,3] Mohini Ranganathan,[1,2,3] Deepak Cyril D'Souza[1,2,3]

[1] Psychiatry Service, VA Connecticut Healthcare System, West Haven, CT, USA
[2] Abraham Ribicoff Research Facilities, Connecticut Mental Health Center, New Haven, CT, USA
[3] Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA

Abstract

Recent advances in knowledge about cannabinoid receptor function have renewed interest in the association between *cannabis* and psychosis. Converging lines of evidence suggest that cannabinoids can produce a full range of transient schizophrenia-like positive, negative and cognitive symptoms. 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. 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.* Therefore, it is likely that *cannabis* exposure is a "component cause" that interacts with other factors to "cause" schizophrenia or other psychotic disorder, but is neither necessary nor sufficient to do so alone. In the absence of known causes of schizophrenia, however, and the implications for public health policy should such a link be established the role of component causes such as cannabinoid exposure should remain a focus of further study. Finally, 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.

Descriptors: Cannabis; Cannabinoids; Schizophrenia; Cognition; Adaptation, physiological/drug effects

Resumo

Avanços recentes no conhecimento sobre a função do receptor de canabinoide renovaram o interesse na associação entre cannabis *e psicose. Linhas convergentes de evidências sugerem que os canabinoides podem produzir uma ampla gama de sintomas transitórios positivos, negativos e cognitivos assemelhados aos de esquizofrenia. Os canabinoides também produzem alguns déficits psicofisiológicos sabidamente presentes na esquizofrenia. É igualmente claro que em indivíduos com um transtorno psicótico estabelecido, os canabinoides podem exacerbar sintomas, desencadear recaídas e ter consequências negativas no curso da doença. Evidências crescentes sugerem que a exposição precoce e pesada à* cannabis *pode aumentar o risco de se desenvolver um transtorno psicótico como a esquizofrenia. A relação entre exposição à* cannabis *e esquizofrenia preenche alguns, mas não todos os critérios usuais de causalidade. Porém, a maioria das pessoas que utilizam* cannabis *não desenvolve esquizofrenia e muitas pessoas diagnosticadas com esquizofrenia nunca utilizaram* cannabis*. Portanto, é provável que a exposição à* cannabis *seja uma "causa componente" que interage com outros fatores para "causar" esquizofrenia ou outro transtorno psicótico, mas não é nem necessária nem suficiente para fazê-lo sozinha. No entanto, na ausência de causas conhecidas da esquizofrenia e com as implicações de políticas de saúde pública, se tal vínculo for estabelecido, as causas componentes, tais como a exposição a canabinoide, devem continuar sendo um foco de estudos futuros. Finalmente, são necessárias mais pesquisas para identificar os fatores subjacentes à vulnerabilidade à psicose relacionada a canabinoide e para elucidar os mecanismos biológicos subjacentes a esse risco.*

Descritores: *Cannabis; Canabinoides; Esquizofrenia, Cognição; Adaptação fisiológica/efeitos de drogas*

Introduction

The relationship between cannabinoids and psychosis has been known for almost a thousand years. In 1235, Ibn Beitar related the use of *cannabis* to insanity,[1] and in 1845 Moreau de Tours wrote that *cannabis* could precipitate "acute psychotic reactions,

Correspondence
Deepak Cyril D'Souza
Psychiatry Service
116A, VA Connecticut Healthcare System, 950 Campbell Avenue,
West Haven, CT 06516
Phone: (203) 932-5711 Fax: (203) 937-4860
E-mail: deepak.dsouza@yale.edu

generally lasting but a few hours, but occasionally as long as week".[2] The rise in *cannabis* use worldwide and recent advances in our understanding of the brain cannabinoid system have renewed and reinvigorated interest in the association between *cannabis* use and psychosis. This paper provides a review of the association between *cannabis* exposure and psychotic disorders. The transient and persistent behavioral, cognitive and psychophysiological effects of cannabinoids are reviewed. While the mechanisms underlying the association between cannabinoids and psychosis are not reviewed, a discussion about causality is presented.

But first, several terms used in this review need to be defined. The distinction between psychotic symptoms and a psychotic disorder is important. Psychotic symptoms include disorganized thinking and speech, delusions, hallucinations and other alterations in perception. A psychotic disorder, such as schizophrenia, is a condition characterized by persistent psychotic symptoms and accompanied by functional deficits in most spheres of life. The symptoms of schizophrenia include not just positive psychotic symptoms, as described above, but also negative symptoms (amotivation, social withdrawal, and emotional blunting, among others) and cognitive deficits (impairments in memory, attention and executive function). Furthermore, *cannabis* is a collection of nearly 70 cannabinoids,[3] including Δ^9-tetrahydrahydrocannabinol (Δ^9-THC) and cannabidiol (CBD). Therefore, *cannabis* is more than just Δ^9-THC.

Transient behavioral and cognitive effects of cannabinoids

1. Nonexperimental evidence

Several lines of evidence suggest that *cannabis* and other cannabinoids can produce a range of transient psychotic symptoms in an otherwise clear sensorium. Anecdotal reports provide rich descriptions of psychotic symptoms that can occur during *cannabis* intoxication.[2,4-13] The symptoms 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. While rich in detail, individual accounts are fraught with some confounds and are hard to generalize. Some of the limitations of anecdotal accounts can be addressed in population-based surveys which suggest that between 20 and 50% of individuals report paranoia, persecutory ideas, and hallucinations while under the influence of *cannabis*.[14,15]

The observed effects of cannabinoids used for medicinal purposes provide another source of data on the association between *cannabis* and psychosis. Δ^9-THC, nabilone (9-trans-ketocannabinoid), and levonantradol have been used treatment of a number of medical conditions, including chemotherapy-induced nausea, spasticity from multiple sclerosis and pain syndromes.

Psychotic symptoms reported with the use of these cannabinoids include "loss of control", thought disturbances, feelings of unreality, apprehension, fear and paranoia, anxiety and panic, dissociation, depersonalization, dysphoria, difficulty concentrating, hallucinations, other perceptual alterations, amnesia and accompanying anxiety.[16-30] In fact, Levonantradol which was developed as an analgesic agent, was abandoned because of a high incidence of intolerable behavioral side-effects. In systematic reviews of randomized controlled trials comparing the antiemetic effects of synthetic cannabinoids with placebo or other antiemetics, 6% of patients receiving these cannabinoids presented with hallucinations and 5% with "paranoia", while no patient treated with control drugs presented with such side effects.[31,32] These effects appear to increase both with increasing dose and with repeated dosing.

2. Experimental evidence

In one of the earliest experimental studies conducted under the auspices of the LaGuardia Committee on Marihuana in 1944, 12.5% of subjects reportedly experienced psychotic reactions at doses of about 30-50mg oral and 8-30mg smoked *cannabis*.[33] However, these subjects were prisoners and cannot be presumed to have been free of psychiatric disorders. Ames studied the effects of unassayed oral doses of *cannabis* extract (about 50 to 70mg Δ^9-THC) in 12 presumably healthy physicians.[34] 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 had delusions of the presence of hidden recorders, fears of being hypnotized, subjected to ECT, or—presciently—developing schizophrenia. One subject became hypomanic, with persecutory delusions, refused to answer questions altogether for fear of being certified as insane, and required IM chlorpromazine. Other similar quasi-experimental studies of *cannabis* have reported a range of dose-related psychotic symptoms with *cannabis*.[35-37]

In addition to studies with *cannabis*, there have been a few studies with Δ^9-THC and other cannabinoids. Melges, in a double-blind, placebo-controlled study with high- and low-dose Δ^9-THC, reported *cannabis* users to have had core symptoms of psychosis, including thought disorder and paranoia.[38] The authors specifically described the "tracking difficulties" that subjects reported, including racing thoughts, thought blocking, and loss of train of thought. Hollister and Gillespie showed that Δ^9-THC was not associated with as prominent psychotomimetic effects as LSD.[39] Reese Jones observed not-particularly-robust psychotomimetic effects in studies of "normal" controls given Δ^9-THC at doses of 20mg smoked or 40mg oral, but noted that a "few" subjects experienced ideas of reference and delusions that he was using secret (unexplained) tests and hidden recording devices on them.[40] At higher doses, psychotomimetic effects began to emerge, including delusions, loosening of associations, and marked illusions.

Few controlled studies have specifically examined the psychotomimetic effects of cannabinoids using well-validated measures. D'Souza et al., characterized the dose-related behavioral and cognitive effects of intravenous Δ^9-THC (0mg, 2.5mg, and 5mg), in a double blind, randomized, placebo-controlled study

of healthy controls (n = 22) who were screened for the presence of any significant psychiatric disorder or family history of Axis I disorders.[41,42] The full range of symptoms associated with schizophrenia—positive, negative, and cognitive symptoms—were measured using well-validated measures. Δ^9-THC produced transient positive symptoms (Figure 1), perceptual alterations, negative symptoms, euphoria, anxiety, and deficits in working memory, verbal recall, and attention, without altering general orientation.

3. 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. Δ^9-THC also produced depersonalization, derealization, distorted sensory perceptions, altered body perception, feelings of unreality, and extreme slowing of time in healthy individuals. These effects, reported by carefully screened healthy subjects, appear remarkably similar to the kinds of psychotic symptoms reported by patients with schizophrenia. More recently, Morrison et al. showed that Δ^9-THC (2.5mg i.v.) produced similar effects in healthy subjects. Leweke et al., observed that nabilone, a synthetic analog of Δ^9-THC, altered binocular depth inversion, a potential surrogate marker for psychosis.[43]

4. Negative symptoms

D'Souza et al. also showed that Δ^9-THC produced effects similar to the negative symptoms of schizophrenia, including blunted affect, reduced rapport, and lack of spontaneity, psychomotor retardation, and emotional withdrawal. These "negative symptoms" may have overlapped or been confounded by the known cataleptic and sedating effects of cannabinoids and furthermore, acute pharmacological studies may be limited in their capacity to "model" negative symptoms. As discussed later, chronic exposure to cannabinoids has been linked to persistent negative-like symptoms.

5. Cognitive deficits

Cannabinoids have been reported to produce transient dose-related cognitive impairments including deficits in learning, short-term memory, working memory, executive function, abstract ability, decision making, and attention.[44-50] Similar effects have been reported in rodents and non-human primates reviewed in.[51,52] Not only is this pattern of cognitive deficits also observed

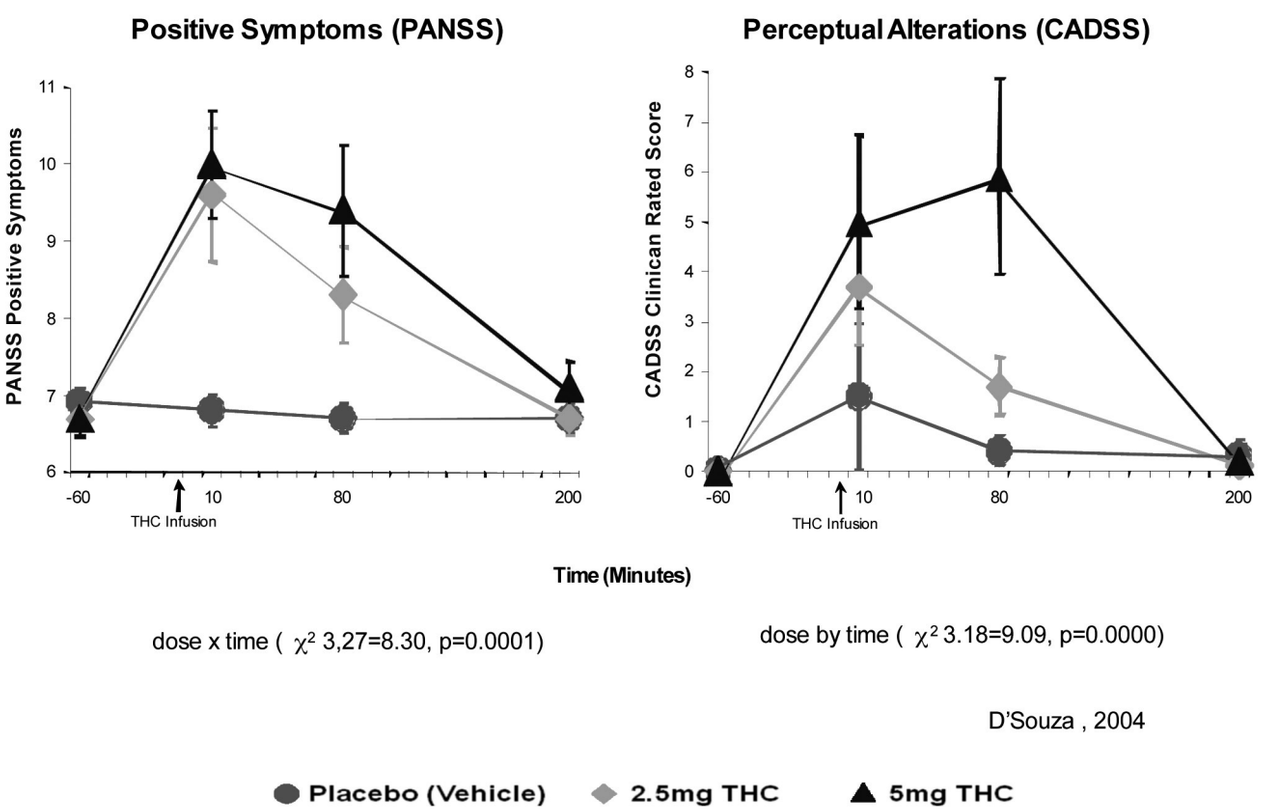

Figure 1 - Δ^9-THC induces transient psychotomimetic effects in healthy individuals. Effects of Δ-9-THC on the seven-item positive symptom subscale of the Positive and Negative Syndrome Scale (PANSS) (left panel) and the clinician rated subscale of the Clinician Administered Dissociative Symptoms Scale 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.

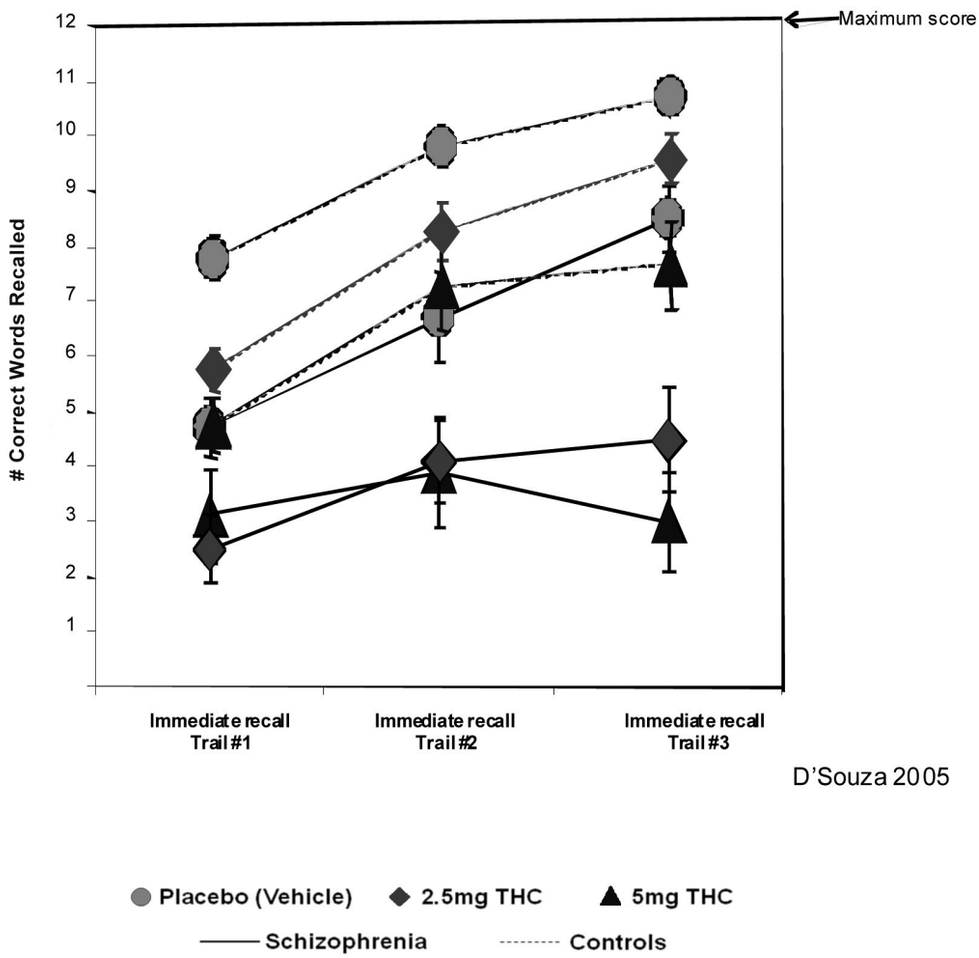

Figure 2 - Δ^9-THC impairs immediate verbal memory (Hopkins Verbal Learning Test). Effects of Δ-9-THC on the learning and immediate free recall measured by a 12-word learning task (Hopkins Verbal Learning Test).

in schizophrenia,[53] but the most robust cognitive deficit induced by Δ^9-THC —verbal memory[44]—is also the most robust cognitive deficit observed in schizophrenia.[53] As illustrated in Figure 2, D'Souza et al., showed that intravenous Δ^9-THC produced robust dose-dependent impairments in immediate and delayed (30-minute) verbal memory in healthy subjects. Δ^9-THC also increased the number of false positives and intrusions during verbal recall. Similar findings have been recently reported by Henquet et al., and Morrison et al.

6. Schizophrenia patients

In general, *cannabis* exposure is associated with a negative impact on the course and expression of schizophrenia. *Cannabis* smoking can exacerbate the symptoms of schizophrenia,[54,55] and continued use predicts the presence of more psychotic symptoms[56] and worsens the prognosis of people who already have schizophrenia.[57-60] Other studies suggest that *cannabis* using schizophrenic patients had lower negative symptoms scores[61] and adolescents with first-episode psychosis had lower negative symptoms scores and a better prognosis that those who did not use *cannabis*.[62]

There have been very few experimental studies of cannabinoid effects in schizophrenic patients. In 1934, Lindeman and Malamud administered unassayed doses of hashish to a group of schizophrenic patients, who experienced an exacerbation of their symptoms.[63] Almost a century later, D'Souza characterized the effects of Δ^9-THC in schizophrenic patients using the same methodology described earlier in healthy subjects.[64] All the patients were taking stable doses of antipsychotic medications (dopamine D2 receptor antagonists) 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. Schizophrenic patients were more sensitive to the Δ^9-THC effects than controls (Figure 3). Similarly, relative to controls, schizophrenia patients were more vulnerable to Δ^9-THC -related learning impairments, demonstrating an increase in the number of intrusions and false positives generated during recall; at 5mg, schizophrenics (solid lines) were unable to learn at all (Figure 3).[64] The increases in symptoms experienced were brief, modest, similar to the patients' typical symptoms, and occurred

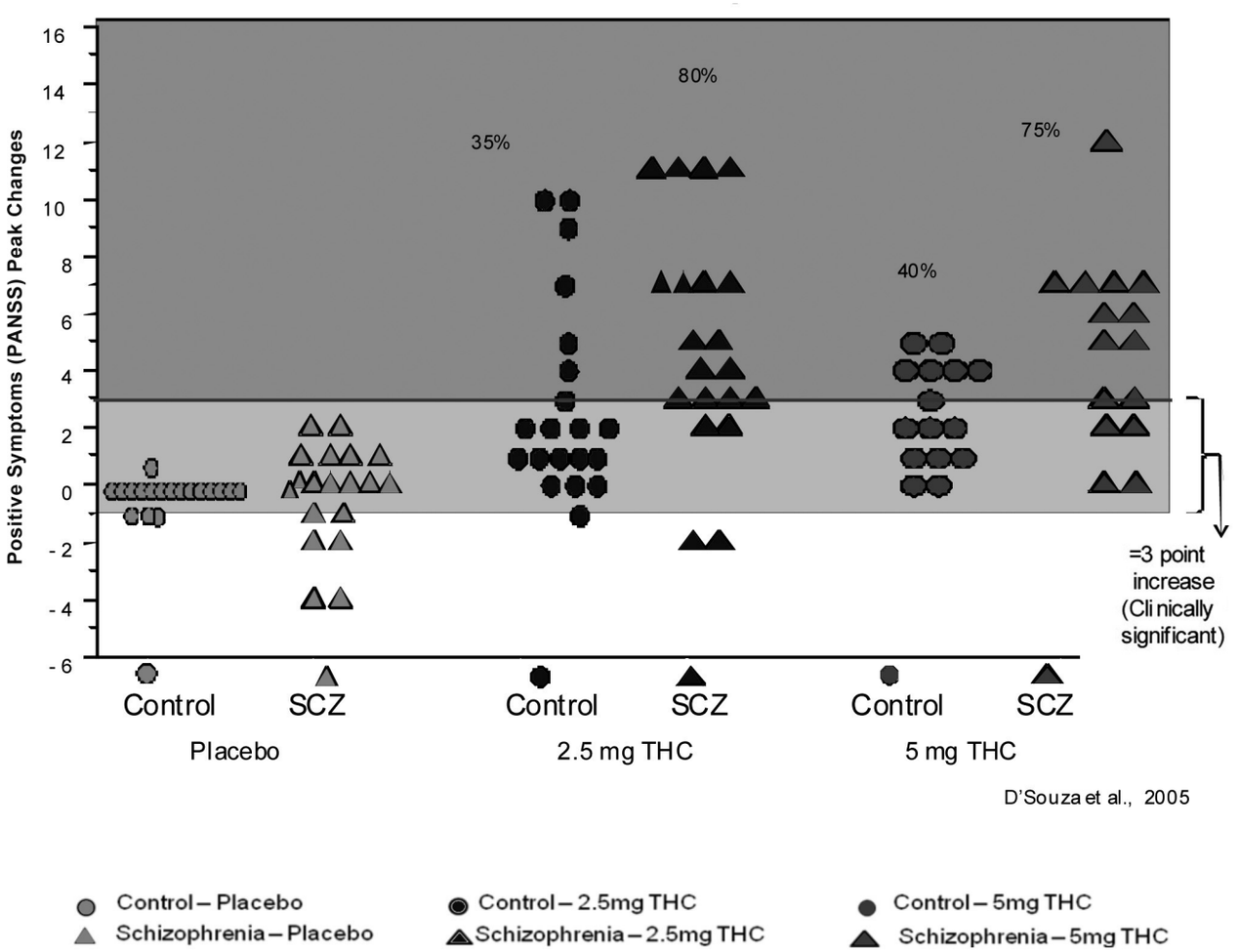

Figure 3 – Enhanced sensitivity to the psychotomimetic effects of Δ^9-THC in schizophrenia. Peak increase in positive symptoms measured by the positive symptoms subscale of the Positive and Negative Symptoms Scale (PANNS). Group means 1 SD. Clinically significant increase= 3 point or greater increase in PANSSS positive symptom subscale score.

even though subjects were clinically stable, medication-responsive, and receiving therapeutic doses of antipsychotics. It is possible that Δ^9-THC effects of an even greater magnitude and greater group differences relative to controls might have been elicited in schizophrenic patients who were not taking antipsychotic medications or not clinically stable.

Henquet et al., also studied the effects of smoked Δ^9-THC in patients with a psychotic disorder, relatives of patients with a psychotic disorder and healthy controls. Patients were more sensitive to the effects of Δ^9-THC on attention and cognitive flexibility, but not to its memory impairing effects.

In summary, *cannabis*, natural and synthetic cannabinoids administered via different routes can produce a range of positive symptoms, negative symptoms, and cognitive deficits in healthy individuals that resemble the symptoms of schizophrenia. These effects are dose-related, do not disrupt orientation, and last for minutes to hours. A small number of vulnerable individuals experience robust psychotomimetic effects, but what produces that vulnerability is unclear. In schizophrenic patients, exposure to cannabinoids transiently exacerbates symptoms. Finally, in addition to its psychotomimetic effects, cannabinoids produce a plethora of other acute transient effects including euphoria, relaxation, increased appetite, anxiolysis or anxiety and tachycardia.[39,65,66]

Persistent behavioral and cognitive effects of cannabinoids

1. Positive symptoms

While it seems clear that cannabinoids can produce transient schizophrenia-like symptoms in healthy individuals, and exacerbate symptoms in schizophrenic patients, the question of whether exposure to cannabinoids can "cause" persistent symptoms or a psychotic disorder has been the subject of intensive study.

Interest in the association between *cannabis* and schizophrenia was sparked by a large longitudinal cohort study of all Swedes conscripted between 1969 and 1970, which included 97% (50,053) of all males aged 18 to 20 years, since Sweden mandates military service.[57] A dose-response relationship was observed between self-reported *cannabis* use at conscription (age 18 years) and psychiatric hospitalization for schizophrenia over the ensuing 15 years, with those who reported having used *cannabis* more than

50 times were three times more likely than non-users to carry a diagnosis of schizophrenia 15 years later. Adjustment for other relevant risk factors reduced but did not eliminate the higher risk (OR = 2.3) of schizophrenia associated with *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 over the following 27 years.[67] 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 predating schizophrenia shrank but remained significant (1.2), despite adjusting for a number of confounds that included low IQ, urban dwelling, cigarette smoking, poor social integration, function, and stimulant use. The increased risk of schizophrenia conferred by *cannabis* use persisted even when subjects who developed schizophrenia within five years of conscription were excluded from the analysis, to control for the possibility that *cannabis* use had been merely a manifestation of the schizophrenia prodrome. The original study has been criticized on a number of points:[68-70] 1) the use of other drugs was more common in the *cannabis*-using group, 2) some other factor may have predisposed subjects to both schizophrenia and *cannabis* use, and 3) in the follow-up study a quarter century later, investigators did not ask any questions about intervening use of other drugs, many of which are also known to precipitate psychosis.

Several prospective studies have been conducted that complement the historical studies.[71-74] Moore et al. systematically reviewed longitudinal studies of *cannabis* exposure and a range of subsequent psychosis outcomes including disorders (e.g., schizophrenia, schizophreniform, schizoaffective) and symptoms (delusions, hallucinations, or thought disorder). They found 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), a risk that rose in a dose-dependent fashion with greater *cannabis* exposure (OR = 2.09, 1.54±2.84).[75,76]

Meta-analyses suggest that *cannabis* might account for between 8% and 14% of schizophrenia cases,[75,77] although the quintupling of rates of *cannabis* use over the last four decades[67,78] has not been matched by a commensurate 40% to 70% increase in prevalence of schizophrenia. While some studies suggest that the rates of schizophrenia may be decreasing[79] others find an increase.[76,80]

2. Negative symptoms

An "amotivational syndrome" has been described in chronic, heavy *cannabis* users.[59,81-84] The syndrome resembles the negative symptoms of schizophrenia and is characterized by apathy, amotivation, social withdrawal, narrowing of interests, lethargy, impaired memory, impaired concentration, disturbed judgment, and impaired occupational achievement. However, polydrug use, poverty, low socio-economic status, or preexisting psychiatric disorders confound interpretation of these studies and other investigators have argued that the syndrome does not exist.[85,86]

3. Cognitive deficits

While it is clear that cannabinoids can cause acute transient impairments in memory, attention, and executive function, whether exposure to cannabinoids are associated with persistent cognitive deficits is not as clear, more controversial and difficult to study. Several studies suggest that chronic, heavy *cannabis* use may lead to memory impairments and attentional dysfunction.[87-92] Solowij and Mitchie have suggested that cognitive dysfunction associated with long-term or heavy *cannabis* use is similar to the cognitive endophenotypes that have been proposed as vulnerability markers of schizophrenia.[93]

In a meta-analysis of 15 studies, Gonzalez concluded that a majority of studies found evidence for persistent but subtle cognitive deficits associated with nonacute (remote) *cannabis* use.[94] In a recent comprehensive review, Solowij and Battisti concluded that chronic heavy *cannabis* use is associated with impaired memory function[91] that persists beyond the period of acute intoxication and is related to the frequency, duration, dose and age of onset of *cannabis* use. Whether these *persistent* cognitive deficits fully resolve with prolonged abstinence has not been conclusively determined. Pope et al. demonstrated an absence of persistent neuropsychological deficits in frequent long-term *cannabis* users after 28 days of abstinence. However, other studies suggest full recovery after a week,[95] 28 days,[96] or three months of abstinence,[97] and some show some recovery only after an average of two years' abstinence.[59,98] It is important to note that none of these studies were designed to determine whether the cognitive impairments predated *cannabis* use.

Interestingly, a recent review of 23 studies on *cannabis*, schizophrenia, and cognition by Løberg found that 14 studies reported *better* cognition in the *cannabis*-using groups.[99] Their interpretation of this unexpected finding was that *cannabis* causes a transient cognitive breakdown enabling the development of psychosis, imitating the typical cognitive vulnerability seen in schizophrenia; i.e., in the presence of *cannabis*, less neurodevelopmental abnormality (and thus cognitive deficits) is necessary for the development of a psychotic disorder.

Structural brain abnormalities associated with cannabinoids

Animal studies suggest that chronic exposure to cannabinoids is associated with neurotoxicity in the hippocampus.[100-104] Few studies have examined the impact of *cannabis* use on brain function in humans and the results of these studies have been mixed. An early small (n = 10) study using pneumoencephalography reported cerebral atrophy in *cannabis* users.[105] But subsequent studies using computerized tomography failed to find did not detect any structural abnormalities.[106-108] Recent studies using magnetic resonance imaging (MRI) studies have also reported mixed results. Some studies failed to find any changes,[109,110] whereas other studies reported global or focal changes to gray and white matter density changes, either global changes[111] or in focal

regions, most notably in the hippocampal and parahippocampal areas.[112,113] In the well-designed study that accounted for the confounds of polydrug abuse and co-occurring psychiatric disorders, Yucel et al., reported that chronic heavy *cannabis* users showed reductions in hippocampal and amygdala volumes. Furthermore, left hippocampal volume was inversely associated with subthreshold positive psychotic symptoms. A small number of studies have investigated the effect of *cannabis* use on structural brain abnormalities in patients with psychotic disorders (Table 1). Two studies found no differences between *cannabis* users and non-users,[114.115] two found that *cannabis* smokers had lower volumes in the anterior and posterior cingulate cortices,[116,117] and one found that *cannabis*-using patients had greater ventral striatal grey matter density.[118] The sole longitudinal study found that while there were no differences at baseline, schizophrenic subjects with *cannabis* use lost greater amounts of grey matter over five years, with subsequent enlargement of lateral and third ventricles, than both schizophrenic patients without *cannabis* use and healthy controls. Finally, two diffusion tensor imaging (DTI) studies examining white matter integrity found an earlier age of onset of *cannabis* use amongst patients with schizophrenia was associated with increased anisotropy, suggestive of an enhanced connectivity. The lack of consistent findings in these studies may be from differences in the samples of subjects studied, who varied in *cannabis* use (current vs. lifetime history), other drug use (ranging from *cannabis* only to polydrug users), and treatment history.

Psychophysiological abnormalities associated with cannabinoids

The effects of acute and chronic cannabinoid exposure on a number of psychophysiological biomarkers for schizophrenia have also been studied. While early studies foucsed on electroencephalography (EEG),[122] more recent research has focused on event-related potentials (ERPs). The latter refers to averaged EEG responses time-locked to particular stimuli or events. These have been shown to be particularly robust biomarkers for schizophrenia, and yield large effect sizes in studies of psychosis.[123,124]

1. Auditory Sensory Gating (P50)

This positive-voltage, mid-latency (~50ms), pre-attentive ERP component is related to the capacity of the central nervous system to register salient stimuli, and can be elicited by *discrete auditory stimuli* (e.g. brief white noise clicks). When two equal clicks (S1 and S2) are separated by 500ms, the amplitude of the P50 is less for S2 than S1. Alterations in sensory gating may represent an inability to filter out redundant and irrelevant sensory information, resulting perceptual overload that could theoretically contribute to positive psychotic symptoms.[125,126] P50 suppression deficits have been observed in schizophrenia[123,125,127-129] with robust effect sizes.[128,130,131] P50 suppression deficits have also been observed in clinically unaffected relatives, and individuals with schizotypal personality disorder.[130,132]

P50 suppression is mediated by the hippocampus, temporoparietal region, and prefrontal cortex,[133,134] all areas dense in cannabinoid receptors.[135] While no studies have measured the effect of acute cannabinoid administration on sensory gating in humans, preclinical studies suggest that cannabinoid agonists disrupt sensory gating in animal analogs of the P50.[136-138] Chronic *cannabis* exposure has been associated with disruptions in P50 suppression,[139,140] and this effect correlates with the magnitude of *cannabis* exposure.[141] Another study performed after 28 days of abstinence demonstrated P50 gating deficits that correlated with the number of years of *cannabis* consumption.[142]

2. P300

The P300 is a late positive, post-attentional ERP component thought to be related to directed attention, contextual updating of working memory, and the attribution of salience to deviant or novel stimuli.[143] It reflects activity from a distributed network encompassing the thalamus, hippocampus, inferior parietal lobe,

Table 1 - *Cannabis* effects on brain structure in schizophrenia

Reference	Method	Participants	Results
114	MRI	27 S+C, 20 S–CB (naïve)	No difference in total brain, GM, WM or caudate nucleus volumes
116	MRI	20 S+C, 31 S–C, 56 HC	Anterior cingulate GM volume: S+C < S-C, HC
118	MRI	12 S+SM; 5 S+C; 2 S+EtOH; 5 S+C+ EtOH; 11 S-C; 15 HC	Ventral striatal GM density: S+SM > S
119	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
117	MRI	Untreated first episode psychosis:15 S+C; 24 S–C	Right posterior cingulate GM density: S+C < S-C
115	MRI	20 S+SM (primarily C); 21 S-SM	No change in volume of amygdala, hippocampus, superior temporal gyrus and cingulate cortex.
120	DTI	24 S+C (onset < 17y); 11 S-C	Fractional anisotropy in frontal WM, uncinate fasciculus and anterior internal capsule: S+C > S-C
121	DTI	10 S+C (onset < 15y); 8 S+C (≥ 17y); 8 S-C	Fractional anisotropy density in splenium: S-C < S+C (<15y); WM density in splenium, right occipital lobe and left temporal lobe: S-C < S+C (<15y)

S+C = Patients with psychotic illness and cannabis use; S-C = Patients with psychotic illness without cannabis use; GM = Grey 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

superior temporal gyrus, and frontal cortex.[144] P300 deficits, particularly in the auditory modality, are one of the most consistent biomarkers of SZ.[93,123,131,145-150] Reductions in P300 amplitude and increased latencies have been observed in both SZ patients and unaffected relatives,[131,145,146] however these deficits have also been reported in several other conditions.[125,151-154]

Both oral and smoked Δ^9-THC, have been reported to reduce P300 amplitude.[155,156] Interestingly, a polymorphism of the CB_1 receptor gene has been associated with decreased P300 amplitude[157] suggesting that CB_1 receptor function may play a role in the regulation of P300 amplitude.

In contrast, studies assessing the effect of chronic *cannabis* use on the P300 have produced mixed results. Solowij et al., reported decreased P300 amplitudes in a small sample of recently abstinent *cannabis* users.[158] However, in a subsequent larger study, they failed to replicate the P300 amplitude deficits, but observed slower P300 latencies, and furthermore, the latency deficits correlated with frequency of *cannabis* use.[159] Kempel et al., reported reduced P300 amplitudes,[160] Skosnik reported increased P300 amplitudes,[161] and Patrick et al. and de Sola et al. were unable to detect P300 amplitude differences in *cannabis* users.[162,163] While the reasons for these discrepant results are unclear, they may be related to differences in samples and the cognitive load of the task such that P300 is impaired in studies using cognitively challenging tasks,[158-160] but unimpaired with simple tasks.[161,163]

3. Mismatch Negativity (MMN)

MMN is an automatic, pre-attentive, negative-voltage ERP component that occurs approximately 100 to 200 milliseconds after an auditory stimulus that deviates in frequency or duration from a sequence of standard auditory stimuli. It is thought to reflect basic auditory processing and sensory memory, and is generated primarily in the superior temporal and prefrontal cortex.[164,165] Numerous studies have demonstrated abnormal MMN amplitudes to stimuli deviating in either duration or frequency in SZ patients.[166,167] As MMN does not appear to be altered in other psychiatric disorders such as unipolar and bipolar depression,[168] it may be a particularly specific and useful biomarker for auditory disturbances in SZ.

The acute administration of oral Δ^9-THC did not alter MMN amplitude compared to placebo.[169] However, the combination of Δ^9-THC and CBD actually increased MMN amplitudes. The authors postulated that the MMN was enhanced by CBD's putative antipsychotic effects. It is likely that the lack of an effect of Δ^9-THC may be related to the dose and route of administration.

The same group reported that chronic *cannabis* users exhibited decreased MMN amplitudes at the central electrode in the frequency deviance condition.[170] 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, and that duration of *cannabis* exposure was negatively correlated with MMN amplitudes. 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 SZ patients.

4. N100

This large exogenous ERP is independent of task demand, although it can be modulated by attention.[171] It is thought to be related to basic perceptual processing, and in the auditory domain, is likely generated by auditory and frontal cortices.[172] Schizophrenia patients and their unaffected relatives exhibit abnormal N100s, which have been reported in both schizophrenia patients and their clinically unaffected relatives.[173,174]

The acute effects of cannabinoids on the N100 ERP are yet to be examined. However, recently abstinent chronic *cannabis* users show robust differences in the visual N160 response but no difference in latency to repetitive photic stimuli.[175] This effect was further demonstrated in the auditory modality for discrete 1000 Hz tones during an associative learning task.[176] However, a subsequent study failed to replicate this finding.[177]

Vulnerability to the propsychotic effects of cannabinoids

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.

Psychosis proneness may be defined psychometrically or by the presence of some other obvious risk, such as family history of psychosis. *Cannabis* exposure has been shown to be associated with higher rates of psychotic outcomes in individuals with higher scores on measures of psychosis proneness.[74,178-180] 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.[181-185]

McGuire reported that individuals who developed acute psychosis after *cannabis* exposure were 10 times more likely to have a positive family history of schizophrenia than patients who screened negatively for *cannabis* use.[181] Recently Arendt showed that predisposition rates of psychiatric disorders from first-degree relatives of individuals treated for *cannabis*-induced psychosis were the same as those of individuals treated for schizophrenia suggesting that *cannabis* causes psychotic symptoms mainly in those who are predisposed for psychosis.[184]

In a prospective study of *cannabis* using prodromal patients, Corcoran noted significantly more perceptual disturbances and worse functioning during epochs of increased *cannabis* use[185] and concluded that *cannabis* use was a risk factor for the exacerbation of subthreshold psychotic symptoms. Similarly, Cadenhead et al., reported that individuals with a high risk for developing psychosis who used *cannabis* use were 10 times more likely convert to psychosis than individuals who did not use *cannabis*.[183] This interaction of psychosis proneness and *cannabis* exposure has also been observed in an experimental approach - in a controlled laboratory study, Henquet showed that psychosis proneness influenced the effects of Δ^9-THC on cognition and psychosis.[186]

Similarly, Verdoux reported that only psychosis-prone individuals reported marked perceptual changes and feelings of increased suspicion and hostility after consuming *cannabis*.[180]

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), that *cannabis* use increases psychosis proneness (a causal model), or that there is some other common factor that causes both psychosis proneness and *cannabis* use (an indicator-variable model).[187,188] While *cannabis* users tend to exhibit higher psychosis proneness scores in some[189-191] but not all studies,[187,192] psychosis prone individuals are not more likely to use *cannabis*.[74] Cannabis users as a group tend to exhibit higher schizotypy scores.[187,190,191] Recently, Veling et al., 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 that 1) *cannabis* use predicted schizophrenia and 2) that risk for developing schizophrenia does not confer a higher risk for *cannabis* use.[193]

Psychosis proneness may at least 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.[188] Catechol-O-methyltransferase (COMT) is critical in the breakdown of dopamine in the prefrontal cortex. In a longitudinal birth cohort study (n > 1000), adolescents homozygous for the COMT Val[108]Met allele were more likely than those without the allele to exhibit psychotic symptoms or develop schizophrenia if they used *cannabis*.[194] Similarly, in a randomized, double blind, placebo-controlled study carriers of the Val allele were more sensitive to Δ^9-THC induced psychotomimetic and amnestic effects than Met carriers, but this was conditional on psychometric evidence of psychosis proneness.[186] Unlike Caspi et al., Zammit failed to find evidence supporting differential effects of *cannabis* use on psychosis risk according to variation of the COMT gene.[195]

Neuregulin 1 (*NRG1*), a candidate gene for schizophrenia, is relevant to several schizophrenia-related neurodevelopmental processes reviewed in [196]. Heterozygous deletion of NRG1 results in increased sensitivity of mice to the neurobehavioral effects of Δ^9-THC on an array of different behaviors including those that model symptoms of schizophrenia, especially under stressful conditions.[197] 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.[197]

The cannabinoid receptor gene (CNR1) is thought to modulate the striatal response to rewarding stimuli[198] and polymorphisms of this gene are associated with alcoholism and intravenous drug use in humans.[199-202] A variety of CNR1 polymorphisms have been studied for associations with schizophrenia, with mixed results.[196,203-208] The (AAT)n microsatellite is associated with drug use,[199] decreased frontal P300,[157] and childhood attention-deficit hyperactivity disorder (ADHD) in alcoholics.[202] An association between the (AAT) n microsatellite and schizophrenia in Japanese,[203] Spanish,[204] and Costa Rican populations,[205] but not in a Chinese population.[206] Association studies of single nucleotide polymorphisms (SNPs) within the CNR1 gene have also been mixed, with positive[207] and negative results.[196,208] A 1359G/A polymorphism of the CNR1 gene (also known as the "G allele") has been associated with better response to antipsychotics in a population of French schizophrenic patients.[209] It is possible that genetic variants of the CNR1 gene may underlie individual vulnerability to schizophrenia and explain the high comorbidity between schizophrenia and substance abuse.

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 [5].

***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. 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.[210] 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.[211] 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%).[212,213] 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.[57,211,212,214-221]

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 dose-response 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*.[222,223] 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.[75]

Strength: *Cannabis* exposure increases the odds of developing schizophrenia modestly (by 40%) even after controlling for many potential confounding variables.[75]

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.[75]

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.[5,224,225]

Conclusion

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. Cannabinoids can also induce a range of psychophysiological abnormalities that are also known to be present in schizophrenia.

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,[226] the role of component causes such as cannabinoid exposure should remain a focus of further study.

Acknowledgments

The authors wish to acknowledge support from the Department of Veterans Affairs (RAS, IGS, MR, DCD), National Institute of Mental Health (DCD), National Institute of Drug Abuse (PDS, DCD), Stanley Medical Research Institute (MR), and NARSAD (MR, PDS).

Disclosures

Writing group member	Employment	Research grant[1]	Other research grant or medical continuous education[2]	Speaker's honoraria	Ownership interest	Consultant/ Advisory board	Other[3]
R. Andrew Sewell	VA Connecticut Healthcare System Abraham Ribicoff Research Facilities Yale University	Department of Veterans Affairs	-	-	-	-	-
Patrick D. Skosnik	VA Connecticut Healthcare System Abraham Ribicoff Research Facilities Yale University	National Institute of Drug Abuse	-	-	-	-	-
Icelini Garcia-Sosa	VA Connecticut Healthcare System Abraham Ribicoff Research Facilities Yale University	Department of Veterans Affairs	-	-	-	-	-
Mohini Ranganathan	VA Connecticut Healthcare System Abraham Ribicoff Research Facilities Yale University	Department of Veterans Affairs Stanley Medical Research Institute NARSAD	-	-	-	-	-
Deepak Cyril D'Souza	VA Connecticut Healthcare System Abraham Ribicoff Research Facilities Yale University	Department of Veterans Affairs NIMH National Institute of Drug Abuse NARSAD	-	-	-	-	-

** Modest*
*** Significant*
**** Significant: Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.*
Note: NIMH = National Institute of Mental Health; NARSAD = National Alliance for Research on Schizophrenia and Depression.
For more information, see Instructions for authors.

References

1. Warnock J. Insanity from hasheesh. *J Mental Science*. 1903;49:96-110.
2. Moreau J. *Hashish and Mental Illness*. New York: Raven; 1973.
3. Elsohly MA, Slade D. Chemical constituents of marijuana: the complex mixture of natural cannabinoids. *Life Sci*. 2005;78(5):539-48.
4. Marshall C. The active principle of Indian help; a preliminary communication. *Lancet*. 1897;1:235-8.
5. D'Souza DC. Cannabinoids and psychosis. *Int Rev Neurobiol*. 2007;78:289-326.
6. Chopra GS, Smith JW. Psychotic reactions following cannabis use in East Indians. *Arch Gen Psychiatry*. 1974;30(1):24-7.
7. Smith DE. Acute and chronic toxicity of marijuana. *J Psychedelic Drugs*. 1968;2:37-47.
8. Spencer DJ. Cannabis-induced psychosis. *Int J Addict*. 1971;6(2):323-6.
9. Grossman W. Adverse reactions associated with Cannabis products in India. *Ann Intern Med*. 1969;70(3):529-33.
10. Talbott JA, Teague JW. Marihuana psychosis. Acute toxic psychosis associated with the use of Cannabis derivatives. *JAMA*. 1969;210(2):299-302.
11. Thacore VR. Bhang psychosis. *Br J Psychiatry*. 1973;123(573):225-9.
12. Keeler MH, Moore E. Paranoid reactions while using marijuana. *Dis Nerv System*. 1974;35(11):535-6.
13. Brook M. Psychosis after cannabis abuse. *BMJ*. 1984;288:1381.
14. Green B, Kavanagh D, Young R. Being stoned: a review of self-reported cannabis effects. *Drug Alcohol Rev*. 2003;22(4):453-60.
15. Reilly D, Didcott P, Swift W, Hall W. Long-term cannabis use: characteristics of users in an Australian rural area. *Addiction*. 1998;93(6):837-46.
16. Citron ML, Herman TS, Vreeland F, Krasnow SH, Fossieck BE Jr, Harwood S, Franklin R, Cohen MH. Antiemetic efficacy of levonantradol compared to delta-9-tetrahydrocannabinol for chemotherapy-induced nausea and vomiting. *Cancer Treat Rep*. 1985;69(1):109-12.
17. Cronin CM, Sallan SE, Gelber R, Lucas VS, Laszlo J. Antiemetic effect of intramuscular levonantradol in patients receiving anticancer chemotherapy. Journal of clinical pharmacology. *J Clin Pharmacol*. 1981;21(8-9 Suppl):43S-50S.
18. Diasio RB, Ettinger DS, Satterwhite BE. Oral levonantradol in the treatment of chemotherapy-induced emesis: preliminary observations. *J Clin Pharmacol*. 1981;21(8-9 Suppl):81S-5S.
19. Heim ME, Queisser W, Altenburg HP. Randomized crossover study of the antiemetic activity of levonantradol and metoclopramide in cancer patients receiving chemotherapy. *Cancer Chemother Pharmacol*. 1984;13(2):123-5.
20. Heim ME, Romer W, Queisser W. Clinical experience with levonantradol hydrochloride in the prevention of cancer chemotherapy-induced nausea and vomiting. *J Clin Pharmacol*. 1981;21(8-9 Suppl):86S-9S.
21. Jain AK, Ryan JR, McMahon FG, Smith G. Evaluation of intramuscular levonantradol and placebo in acute postoperative pain. *J Clin Pharmacol*. 1981;21(8-9 Suppl):320S-6S.
22. Kenny JB, Wilkinson PM. Levonantradol effectiveness in cancer patients resistant to conventional anti-emetics. *Clin Oncology*. 1982;8(4):335-9.
23. Laszlo J, Lucas VS Jr, Hanson DC, Cronin CM, Sallan SE. Levonantradol for chemotherapy-induced emesis: phase I-II oral administration. *J Clin Pharmacol*. 1981;21(8-9 Suppl):51S-6S.
24. Sheidler VR, Ettinger DS, Diasio RB, Enterline JP, Brown MD. Double-blind multiple-dose crossover study of the antiemetic effect of intramuscular levonantradol compared to prochlorperazine. *J Clin Pharmacol*. 1984;24(4):155-9.
25. Stuart-Harris RC, Mooney CA, Smith IE. Levonantradol: a synthetic cannabinoid in the treatment of severe chemotherapy-induced nausea and

vomiting resistant to conventional anti-emetic therapy. *Clin Oncology*. 1983;9(2):143-6.

26. Roxane US. *Marinol product monograph*. Montvale, NJ: Medical Economics Company;1998.

27. Volkow N, Fowler J, Wolf A, Gillespi H. *Metabolic studies of drugs of abuse*. Bethesda, MD: National Institute of Drug Abuse; 1991. Report No.:105.

28. Leweke FM, Schneider U, Thies M, Munte TF, Emrich HM. Effects of synthetic delta9-tetrahydrocannabinol on binocular depth inversion of natural and artificial objects in man. *Psychopharmacology* (Berl). 1999;142(3):230-5.

29. Wesnes K, Annas P, Edgar C, Deeprose C, Karlsten R, Philipp A, Kalliomäki J, Segerdahl M. Nabilone produces marked impairments to cognitive function and changes in subjective state in healthy volunteers. *J Psychopharmacol*. In press 2009.

30. Stambaugh JE Jr, McAdams J, Vreeland F. Dose ranging evaluation of the antiemetic efficacy and toxicity of intramuscular levonantradol in cancer subjects with chemotherapy-induced emesis. *J Clin Pharmacol*. 1984;24(11-12):480-5.

31. Machado Rocha FC, Stefano SC, De Cassia Haiek R, Rosa Oliveira LM, da Silveira DX. Therapeutic use of Cannabis sativa on chemotherapy-induced nausea and vomiting among cancer patients: systematic review and meta-analysis. *Eur J Cancer Care* (Engl). 2008;17(5):431-43.

32. Tramer MR, Carroll D, Campbell FA, Reynolds DJ, Moore RA, McQuay HJ. Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. *BMJ*. 2001;323(7303):16-21.

33. Mayor's Committee on Marijuana. *The LaGuardia Committee Report: The Marihuana Problem in the City of New York.* New York: The New York Academy of Medicine; 1944.

34. Ames F. A clinical and metabolic study of acute intoxication with Cannabis sativa and its role in the model psychoses. *J Mental Science*. 1958;104(437):972-99.

35. Isbell H, Gorodetzsky CW, Jasinski D, Claussen U, von Spulak F, Korte F. Effects of (--)delta-9-trans-tetrahydrocannabinol in man. *Psychopharmacologia*. 1967;11(2):184-8.

36. Isbell H, Jasinski DR. A comparison of LSD-25 with (-)-delta-9-trans-tetrahydrocannabinol (THC) and attempted cross tolerance between LSD and THC. *Psychopharmacologia*. 1969;14(2):115-23.

37. Renault PF, Schuster CR, Freedman DX, Sikic B, de Mello DN. Repeat administration of marihuana smoke to humans. *Arch Gen Psychiatry.* 1974;31(1):95-102.

38. Melges FT, Tinklenberg JR, Hollister LE, Gillespie HK. Marihuana and temporal disintegration. *Science*. 1970;168(935):1118-20.

39. Hollister LE. Health aspects of cannabis. *Pharmacol Rev*. 1986;38(1):1-20.

40. Jones RT, Stone GC. Psychological studies of marijuana and alcohol in man. *Psychopharmacologia*. 1970;18(1):108-17.

41. D'Souza DC, Perry E, MacDougall L, Ammerman Y, Cooper T, Wu YT, Braley G, Gueorguieva R, Krystal JH. The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. *Neuropsychopharmacology*. 2004;29(8):1558-72.

42. Morrison PD, Zois V, McKeown DA, Lee TD, Holt DW, Powell JF, Kapur S, Murray RM. The acute effects of synthetic intravenous Delta9-tetrahydrocannabinol on psychosis, mood and cognitive functioning. *Psychol Med*. 2009;39(10):1607-16.

43. Leweke FM, Schneider U, Radwan M, Schmidt E, Emrich HM. Different effects of nabilone and cannabidiol on binocular depth inversion in Man. *Pharmacol Biochem Behav*. 2000;66(1):175-81.

44. Ranganathan M, D'Souza DC. The acute effects of cannabinoids on memory in humans: a review. *Psychopharmacology* (Berl). 2006;188(4):425-44.

45. Miller LL, McFarland D, Cornett TL, Brightwell D. Marijuana and memory impairment: effect on free recall and recognition memory. *Pharmacol Biochem Behav*. 1977;7(2):99-103.

46. Marks DF, MacAvoy MG. Divided attention performance in cannabis users and non-users following alcohol and cannabis separately and in combination. *Psychopharmacology* (Berl). 1989;99(3):397-401.

47. Leweke M, Kampmann C, Radwan M, Dietrich DE, Johannes S, Emrich HM, Münte TF. The effects of tetrahydrocannabinol on the recognition of emotionally charged words: an analysis using event-related brain potentials. *Neuropsychobiology*. 1998;37(2):104-11.

48. Hooker WD, Jones RT. Increased susceptibility to memory intrusions and the Stroop interference effect during acute marijuana intoxication. *Psychopharmacology* (Berl). 1987;91(1):20-4.

49. Hart CL, van Gorp W, Haney M, Foltin RW, Fischman MW. Effects of acute smoked marijuana on complex cognitive performance. *Neuropsychopharmacology*. 2001;25(5):757-65.

50. Heishman SJ, Huestis MA, Henningfield JE, Cone EJ. Acute and residual effects of marijuana: profiles of plasma THC levels, physiological, subjective, and performance measures. *Pharmacol Biochem Behav*. 1990;37(3):561-5.

51. Lichtman AH, Varvel SA, Martin BR. Endocannabinoids in cognition and dependence. *Prostaglandins Leukot Essent Fatty Acids*. 2002;66(2-3): 269-85.

52. Wilson RI, Nicoll RA. Endocannabinoid signaling in the brain. *Science*. 2002;296(5568):678-82.

53. Heinrichs RW, Zakzanis KK. Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. *Neuropsychology*. 1998;12(3):426-45.

54. Turner WM, Tsuang MT. Impact of substance abuse on the course and outcome of schizophrenia. *Schizophr Bull*. 1990;16(1):87-95.

55. Negrete JC, Knapp WP, Douglas DE, Smith WB. Cannabis affects the severity of schizophrenic symptoms: results of a clinical survey. *Psychol Med*. 1986;16(3):515-20.

56. Linszen D, van Amelsvoort T. Cannabis and psychosis: an update on course and biological plausible mechanisms. *Curr Opin Psychiatry*. 2007;20(2):116-20.

57. Andreasson S, Allebeck P, Engstrom A, Rydberg U. Cannabis and schizophrenia. A longitudinal study of Swedish conscripts. *Lancet*. 1987;2(8574): 1483-6.

58. Thornicroft G. Cannabis and psychosis. Is there epidemiological evidence for an association? *Br J Psychiatry*. 1990;157:25-33.

59. Hall W, Solowij N. Adverse effects of cannabis. *Lancet*. 1998;352(9140): 1611-6.

60. Degenhardt L, Hall W, Lynskey M. Testing hypotheses about the relationship between cannabis use and psychosis. *Drug Alcohol Depende*. 2003; 71(1):37-48.

61. Peralta V, Cuesta MJ. Influence of cannabis abuse on schizophrenic psychopathology. *Acta Psychiatrica Scand*. 1992;85(2):127-30.

62. Baeza I, Graell M, Moreno D, Castro-Fornieles J, Parellada M, Gonzalez-Pinto A, Payá B, Soutullo C, de la Serna E, Arango C. Cannabis use in children and adolescents with first episode psychosis: influence on psychopathology and short-term outcome (CAFEPS study). *Schizophr Res*. 2009;113(2-3):129-37.

63. Lindemann E, Malamud W. Experimental analysis of the psychopathological effects of intoxicating drug. *Am J Psychiatry*. 1934;90:853-81.

64. D'Souza DC, Abi-Saab WM, Madonick S, Forselius-Bielen K, Doersch A, Braley G, Gueorguieva R, Cooper TB, Krystal JH. Delta-9-tetrahydrocannabinol effects in schizophrenia: implications for cognition, psychosis, and addiction. *Biol Psychiatry.* 2005;57(6):594-608.

65. Adams IB, Martin BR. Cannabis: pharmacology and toxicology in animals and humans. *Addiction.* 1996;91(11):1585-614.

66. Iversen L. Cannabis and the brain. *Brain*. 2003;126(Pt 6):1252-70.

67. Zammit S, Allebeck P, Andreasson S, Lundberg I, Lewis G. Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study. *BMJ*. 2002;325(7374):1199.

68. Johnson BA, Smith BL, Taylor P. Cannabis and schizophrenia. *Lancet*. 1988;1(8585):592-3.

69. Johnson BA. Psychopharmacological effects of cannabis. *Br J Hospital Med*. 1990;43(2):114-6, 118-20, 122.

70. Negrete JC. Cannabis and schizophrenia. *Br J Addiction*. 1989;84(4):349-51.

71. Arseneault L, Cannon M, Poulton R, Murray R, Caspi A, Moffitt TE. Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. *BMJ*. 2002;325(7374):1212-3.

72. Weiser M, Knobler HY, Noy S, Kaplan Z. Clinical characteristics of adolescents later hospitalized for schizophrenia. *Am J Med Genet.* 2002;114(8):949-55.

73. van Os J, Bak M, Hanssen M, Bijl RV, de Graaf R, Verdoux H. Cannabis use and psychosis: a longitudinal population-based study. *Am J Epidemiol*. 2002;156(4):319-27.

74. Henquet C, Krabbendam L, Spauwen J, Kaplan C, Lieb R, Wittchen HU, van Os J.. Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. *BMJ*. 2005;330(7481):11.

75. Moore TH, Zammit S, Lingford-Hughes A, Barnes TR, Jones PB, Burke M, Lewis G. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet*. 2007;370(9584):319-28.

76. Hickman M, Vickerman P, Macleod J, Kirkbride J, Jones PB. Cannabis and schizophrenia: model projections of the impact of the rise in cannabis use

on historical and future trends in schizophrenia in England and Wales. *Addiction*. 2007;102(4):597-606.
77. Henquet C, Murray R, Linszen D, van Os J. The environment and schizophrenia: the role of cannabis use. *Schizophr Bull.* 2005;31(3):608-12.
78. Aust R, Sharp C, Goulden C. *Prevalence of drug use: key findings from the 2001/2002 British Crime Survey, findings 182.* London: Home Office Research, Development and Statistics Directorate; 2002.
79. Der G, Gupta S, Murray RM. Is schizophrenia disappearing? *Lancet*. 1990;335(8688):513-6.
80. Ajdacic-Gross V, Lauber C, Warnke I, Haker H, Murray RM, Rossler W. Changing incidence of psychotic disorders among the young in Zurich. *Schizophr Res*. 2007;95(1-3):9-18.
81. Millman RB, Sbriglio R. Patterns of use and psychopathology in chronic marijuana users. *Psychiatr Clin North Am*. 1986;9(3):533-45.
82. Halikas J, Weller R, Morse C. Effects of regular marijuana use on sexual performance. *J Osychoactive Drugs.* 1982;14(1-2):59-70.
83. Kolansky H, Moore WT. Effects of marihuana on adolescents and young adults. *J Psychiatr Nurs Mental Health Serv*. 1971;9(6):9-16.
84. Tennant FS Jr, Groesbeck CJ. Psychiatric effects of hashish. *Arch Gen Psychiatry.* 1972;27(1):133-6.
85. Hollister LE. Cannabis-1988. *Acta Psychiatrica Scand*. 1988;345:108-18.
86. Rubin V, Comitas L. *Ganja in Jamaica: a medical anthropological study of chronic Marihuana use.* The Hague: Mouton Publishers; 1975.
87. Pope HG Jr, Gruber AJ, Hudson JI, Huestis MA, Yurgelun-Todd D. Neuropsychological performance in long-term cannabis users. *Arch Gen Psychiatry*. 2001;58(10):909-15.
88. Pope HG Jr, Gruber AJ, Yurgelun-Todd D. The residual neuropsychological effects of cannabis: the current status of research. *Drug Alcohol Depend*. 1995;38(1):25-34.
89. Pope HG Jr, Yurgelun-Todd D. The residual cognitive effects of heavy marijuana use in college students. *JAMA*. 1996;275(7):521-7.
90. Lundqvist T. Cognitive consequences of cannabis use: comparison with abuse of stimulants and heroin with regard to attention, memory and executive functions. *Pharmacol Biochem Behav.* 2005;81(2):319-30.
91. Solowij N, Battisti R. The chronic effects of cannabis on memory in humans: a review. *Curr Drug Abuse Rev*. 2008;1(1):81-98.
92. Bolla KI, Brown K, Eldreth D, Tate K, Cadet JL. Dose-related neurocognitive effects of marijuana use. *Neurology*. 2002;59(9):1337-43.
93. Solowij N, Michie PT. Cannabis and cognitive dysfunction: parallels with endophenotypes of schizophrenia? *J Psychiatry Neurosci.* 2007;32(1):30-52.
94. Gonzalez R, Carey C, Grant I. Nonacute (residual) neuropsychological effects of cannabis use: a qualitative analysis and systematic review. *J Clin Pharmacol*. 2002;42(11 Suppl):48S-57S.
95. Jager G, Kahn RS, Van Den Brink W, Van Ree JM, Ramsey NF. Long-term effects of frequent cannabis use on working memory and attention: an fMRI study. *Psychopharmacology* (Berl). 2006;185(3):358-68.
96. Pope HG Jr, Gruber AJ, Hudson JI, Huestis MA, Yurgelun-Todd D. Neuropsychological performance in long-term cannabis users. *Arch Gen Psychiatry.* 2001;58(10):909-15.
97. Fried PA, Watkinson B, Gray R. Neurocognitive consequences of marihuana--a comparison with pre-drug performance. *Neurotoxicol Teratol*. 2005;27(2):231-9.
98. Solowij N. Do cognitive impairments recover following cessation of cannabis use? *Life Sci*. 1995;56(23-24):2119-26.
99. Loberg EM, Hugdahl K. Cannabis use and cognition in schizophrenia. *Front Hum Neurosci*. 2009;3:53.
100. Chan GC, Hinds TR, Impey S, Storm DR. Hippocampal neurotoxicity of Delta9-tetrahydrocannabinol. *J Neurosci.* 1998;18(14):5322-32.
101. Landfield PW, Cadwallader LB, Vinsant S. Quantitative changes in hippocampal structure following long-term exposure to delta 9-tetrahydrocannabinol: possible mediation by glucocorticoid systems. *Brain Res.* 1988;443(1-2):47-62.
102. Landfield PW. Delta-9-tetrahydrocannabinol-dependent alterations in brain structure. *NIDA Res Monogr.* 1987;78:143-57.
103. Lawston J, Borella A, Robinson JK, Whitaker-Azmitia PM. Changes in hippocampal morphology following chronic treatment with the synthetic cannabinoid WIN 55,212-2. *Brain Res.* 2000;877(2):407-10.
104. Scallet AC. Neurotoxicology of cannabis and THC: a review of chronic exposure studies in animals. *Pharmacol Biochem Behav.* 1991;40(3):671-6.
105. Campbell AM, Thomson JL, Evans M, Williams MJ. Cerebral atrophy in young cannabis smokers. *Lancet*. 1972;1(7743):202-3.
106. Co BT, Goodwin DW, Gado M, Mikhael M, Hill SY. Absence of cerebral atrophy in chronic cannabis users. Evaluation by computerized transaxial tomography. *JAMA*. 1977;237(12):1229-30.
107. Hannerz J, Hindmarsh T. Neurological and neuroradiological examination of chronic cannabis smokers. *Ann Neurol.* 1983;13(2):207-10.
108. Kuehnle J, Mendelson JH, Davis KR, New PF. Computed tomographic examination of heavy marijuana smokers. *JAMA*. 1977;237(12):1231-2.
109. Tzilos GK, Cintron CB, Wood JB, Simpson NS, Young AD, Pope HG Jr, Yurgelun-Todd DA. Lack of hippocampal volume change in long-term heavy cannabis users. *Am J Addict*. 2005;14(1):64-72.
110. Block RI, O'Leary DS, Ehrhardt JC, Augustinack JC, Ghoneim MM, Arndt S, Hall JA. Effects of frequent marijuana use on brain tissue volume and composition. *Neuroreport*. 2000;11(3):491-6.
111. Wilson W, Mathew R, Turkington T, Hawk T, Coleman RE, Provenzale J. Brain morphological changes and early marijuana use: a magnetic resonance and positron emission tomography study. *J Addict Dis*. 2000;19(1):1-22.
112. Matochik JA, Eldreth DA, Cadet JL, Bolla KI. Altered brain tissue composition in heavy marijuana users. *Drug Alcohol Depend.* 2005;77(1):23-30.
113. Medina KL, Schweinsburg AD, Cohen-Zion M, Nagel BJ, Tapert SF. Effects of alcohol and combined marijuana and alcohol use during adolescence on hippocampal volume and asymmetry. *Neurotoxicol Teratol.* 2007;29(1):141-52.
114. Cahn W, Hulshoff Pol HE, Caspers E, van Haren NE, Schnack HG, Kahn RS. Cannabis and brain morphology in recent-onset schizophrenia. *Schizophr Res*. 2004;67(2-3):305-7.
115. Wobrock T, Sittinger H, Behrendt B, D'Amelio R, Falkai P. Comorbid substance abuse and brain morphology in recent-onset psychosis. *Eur Arch Psychiatry Clin Neurosci*. 2009;259(1):28-36.
116. Szeszko PR, Robinson DG, Sevy S, Kumra S, Rupp CI, Betensky JD, Lencz T, Ashtari M, Kane JM, Malhotra AK, Gunduz-Bruce H, Napolitano B, Bilder RM. Anterior cingulate grey-matter deficits and cannabis use in first-episode schizophrenia. *Br J Psychiatry*. 2007;190:230-6.
117. Bangalore SS, Prasad KM, Montrose DM, Goradia DD, Diwadkar VA, Keshavan MS. Cannabis use and brain structural alterations in first episode schizophrenia--a region of interest, voxel based morphometric study. *Schizophr Res*. 2008;99(1-3):1-6.
118. Potvin S, Mancini-Marie A, Fahim C, Mensour B, Levesque J, Karama S, Beauregard M, Rompré PP, Stip E. Increased striatal gray matter densities in patients with schizophrenia and substance use disorder: a voxel-based morphometry study. *Psychiatry Res*. 2007;154(3):275-9.
119. Rais M, Cahn W, van Haren N, Schnack H, Caspers E, Hulshoff Pol H, Kahn R Excessive brain volume loss over time in cannabis-using first-episode schizophrenia patients. *Am J Psychiatry.* 2008;165(4):490-6.
120. Peters BD, de Haan L, Vlieger EJ, Majoie CB, den Heeten GJ, Linszen DH. Recent-onset schizophrenia and adolescent cannabis use: MRI evidence for structural hyperconnectivity? *Psychopharmacol Bull*. 2009;42(2):75-88.
121. Dekker N, Schmitz N, Peters BD, van Amelsvoort TA, Linszen DH, de Haan L. Cannabis use and callosal white matter structure and integrity in recent-onset schizophrenia. *Psychiatry Res*. 2010;181(1):51-6.
122. Struve FA, Straumanis JJ. Electroencephalographic and evoked-potential methods in human Marijuana research: Historical review and future-trends. *Drug Develop Res*. 1990;20(3):369-88.
123. Turetsky BI, Calkins ME, Light GA, Olincy A, Radant AD, Swerdlow NR. Neurophysiological endophenotypes of schizophrenia: the viability of selected candidate measures. *Schizophr Bull.* 2007;33(1):69-94.
124. Heinrichs RW. Meta-analysis and the science of schizophrenia: variant evidence or evidence of variants? *Neurosci Biobehav Rev*. 2004;28(4):379-94.
125. Thaker GK. Neurophysiological endophenotypes across bipolar and schizophrenia psychosis. *Schizophr Bull.* 2008;34(4):760-73.
126. Boutros NN, Belger A, Campbell D, D'Souza C, Krystal J. Comparison of four components of sensory gating in schizophrenia and normal subjects: a preliminary report. *Psychiatry Res.* 1999;88(2):119-30.
127. Braff DL, Light GA. Preattentional and attentional cognitive deficits as targets for treating schizophrenia. *Psychopharmacology* (Berl). 2004;174(1):75-85.
128. Patterson JV, Hetrick WP, Boutros NN, Jin Y, Sandman C, Stern H, Potkin S, Bunney WE Jr. P50 sensory gating ratios in schizophrenics and controls: a review and data analysis. *Psychiatry Res.* 2008;158(2):226-47.
129. Potter D, Summerfelt A, Gold J, Buchanan RW. Review of clinical correlates of P50 sensory gating abnormalities in patients with schizophrenia. *Schizophr Bull.* 2006;32(4):692-700.

130. de Wilde OM, Bour LJ, Dingemans PM, Koelman JH, Linszen DH. A meta-analysis of P50 studies in patients with schizophrenia and relatives: differences in methodology between research groups. *Schizophr Res.* 2007;97(1-3):137-51.

131. Bramon E, Rabe-Hesketh S, Sham P, Murray RM, Frangou S. Meta-analysis of the P300 and P50 waveforms in schizophrenia. *Schizophr Res.* 2004;70(2-3):315-29.

132. Cadenhead KS, Light GA, Geyer MA, Braff DL. Sensory gating deficits assessed by the P50 event-related potential in subjects with schizotypal personality disorder. *Am J Psychiatry.* 2000;157(1):55-9.

133. Grunwald T, Boutros NN, Pezer N, von Oertzen J, Fernandez G, Schaller C, Elger CE. Neuronal substrates of sensory gating within the human brain. *Biol Psychiatry*. 2003;53(6):511-9.

134. Luntz-Leybman V, Bickford PC, Freedman R. Cholinergic gating of response to auditory stimuli in rat hippocampus. *Brain Res.* 1992;587(1):130-6.

135. Eggan SM, Lewis DA. Immunocytochemical distribution of the cannabinoid CB1 receptor in the primate neocortex: a regional and laminar analysis. *Cereb Cortex*. 2007;17(1):175-91.

136. Zachariou M, Dissanayake DW, Coombes S, Owen MR, Mason R. Sensory gating and its modulation by cannabinoids: electrophysiological, computational and mathematical analysis. *Cogn Neurodyn*. 2008;2(2): 159-70.

137. Dissanayake DW, Zachariou M, Marsden CA, Mason R. Auditory gating in rat hippocampus and medial prefrontal cortex: effect of the cannabinoid agonist WIN55,212-2. *Neuropharmacology*. 2008;55(8):1397-404.

138. Hajos M, Hoffmann WE, Kocsis B. Activation of cannabinoid-1 receptors disrupts sensory gating and neuronal oscillation: relevance to schizophrenia. *Biol Psychiatry.* 2008;63(11):1075-83.

139. Patrick G, Straumanis JJ, Struve FA, Fitz-Gerald MJ, Leavitt J, Manno JE. Reduced P50 auditory gating response in psychiatrically normal chronic marihuana users: a pilot study. *Biol Psychiatry.* 1999;45(10):1307-12.

140. Patrick G, Struve FA. Reduction of auditory P50 gating response in marihuana users: further supporting data. *Clin Electroencephalogr.* 2000;31(2):88-93.

141. Edwards CR, Skosnik PD, Steinmetz AB, O'Donnell BF, Hetrick WP. Sensory gating impairments in heavy cannabis users are associated with altered neural oscillations. *Behav Neurosci.* 2009;123(4):894-904.

142. Rentzsch J, Penzhorn A, Kernbichler K, Plockl D, Gomez-Carrillo de Castro A, Gallinat J, Jockers-Scherübl MC. Differential impact of heavy cannabis use on sensory gating in schizophrenic patients and otherwise healthy controls. *Exp Neurol.* 2007;205(1):241-9.

143. Polich J, Criado JR. Neuropsychology and neuropharmacology of P3a and P3b. *Int J Psychophysiol*. 2006;60(2):172-85.

144. Kiehl KA, Laurens KR, Duty TL, Forster BB, Liddle PF. Neural sources involved in auditory target detection and novelty processing: an event-related fMRI study. *Psychophysiology*. 2001;38(1):133-42.

145. Jeon YW, Polich J. Meta-analysis of P300 and schizophrenia: patients, paradigms, and practical implications. *Psychophysiology*. 2003;40(5):684-701.

146. Bramon E, McDonald C, Croft RJ, Landau S, Filbey F, Gruzelier JH, Sham PC, Frangou S, Murray RM. Is the P300 wave an endophenotype for schizophrenia? A meta-analysis and a family study. *Neuroimage*. 2005;27(4):960-8.

147. Roth WT, Cannon EH. Some features of the auditory evoked response in schizophrenics. *Arch Gen Psychiatry.* 1972;27(4):466-71.

148. Turetsky BI, Colbath EA, Gur RE. P300 subcomponent abnormalities in schizophrenia: I. Physiological evidence for gender and subtype specific differences in regional pathology. *Biol Psychiatry.* 1998;43(2):84-96.

149. Braff DL. Information processing and attention dysfunctions in schizophrenia. *Schizophr Bull.* 1993;19(2):233-59.

150. Duncan CC. Event-related brain potentials: a window on information processing in schizophrenia. *Schizophr Bull.* 1988;14(2):199-203.

151. Polich J, Corey-Bloom J. Alzheimer's disease and P300: review and evaluation of task and modality. *Curr Alzheimer Res.* 2005;2(5):515-25.

152. O'Donnell BF, Vohs JL, Hetrick WP, Carroll CA, Shekhar A. Auditory event-related potential abnormalities in bipolar disorder and schizophrenia. *Int J Psychophysiol.* 2004;53(1):45-55.

153. Polich J, Pollock VE, Bloom FE. Meta-analysis of P300 amplitude from males at risk for alcoholism. *Psychol Bull.* 1994;115(1):55-73.

154. Singh SM, Basu D. The P300 event-related potential and its possible role as an endophenotype for studying substance use disorders: a review. *Addict Biol.* 2009;14(3):298-309.

155. Ilan AB, Gevins A, Coleman M, ElSohly MA, de Wit H. Neurophysiological and subjective profile of marijuana with varying concentrations of cannabinoids. *Behav Pharmacol.* 2005;16(5-6):487-96.

156. Roser P, Juckel G, Rentzsch J, Nadulski T, Gallinat J, Stadelmann AM. Effects of acute oral Delta9-tetrahydrocannabinol and standardized cannabis extract on the auditory P300 event-related potential in healthy volunteers. *Eur Neuropsychopharmacol.* 2008;18(8):569-77.

157. Johnson JP, Muhleman D, MacMurray J, Gade R, Verde R, Ask M, Kelley J, Comings DE. Association between the cannabinoid receptor gene (CNR1) and the P300 event-related potential. *Mol Psychiatry.* 1997;2(2):169-71.

158. Solowij N, Michie PT, Fox AM. Effects of long-term cannabis use on selective attention: an event-related potential study. *Pharmacol Biochem Behav.* 1991;40(3):683-8.

159. Solowij N, Michie PT, Fox AM. Differential impairments of selective attention due to frequency and duration of cannabis use. *Biol Psychiatry.* 1995;37(10):731-9.

160. Kempel P, Lampe K, Parnefjord R, Hennig J, Kunert HJ. Auditory-evoked potentials and selective attention: different ways of information processing in cannabis users and controls. *Neuropsychobiology*. 2003;48(2):95-101.

161. Skosnik PD, Park S, Dobbs L, Gardner WL. Affect processing and positive syndrome schizotypy in cannabis users. *Psychiatry Res.* 2008;157(1-3):279-82.

162. Patrick G, Straumanis JJ, Struve FA, Nixon F, Fitz-Gerald MJ, Manno JE, Soucair M. Auditory and visual P300 event related potentials are not altered in medically and psychiatrically normal chronic marihuana users. *Life Sci*. 1995;56(23-24):2135-40.

163. de Sola S, Tarancon T, Pena-Casanova J, Espadaler JM, Langohr K, Poudevida S, Farré M, Verdejo-García A, de la Torre R. Auditory event-related potentials (P3) and cognitive performance in recreational ecstasy polydrug users: evidence from a 12-month longitudinal study. *Psychopharmacology* (Berl). 2008;200(3):425-37.

164. Naatanen R, Alho K. Generators of electrical and magnetic mismatch responses in humans. *Brain Topogr.* 1995;7(4):315-20.

165. Rinne T, Alho K, Ilmoniemi RJ, Virtanen J, Naatanen R. Separate time behaviors of the temporal and frontal mismatch negativity sources. *Neuroimage*. 2000;12(1):14-9.

166. Naatanen R, Kahkonen S. Central auditory dysfunction in schizophrenia as revealed by the mismatch negativity (MMN) and its magnetic equivalent MMNm: a review. *Int J Neuropsychopharmacol.* 2009;12(1):125-35.

167. Umbricht D, Krljes S. Mismatch negativity in schizophrenia: a meta-analysis. *Schizophr Res.* 2005;76(1):1-23.

168. Umbricht D, Koller R, Schmid L, Skrabo A, Grubel C, Huber T, Stassen H. How specific are deficits in mismatch negativity generation to schizophrenia? *Biol Psychiatry*. 2003;53(12):1120-31.

169. Juckel G, Roser P, Nadulski T, Stadelmann AM, Gallinat J. Acute effects of Delta9-tetrahydrocannabinol and standardized cannabis extract on the auditory evoked mismatch negativity. *Schizophr Res.* 2007;97(1-3):109-17.

170. Roser P, Della B, Norra C, Uhl I, Brune M, Juckel G. Auditory mismatch negativity deficits in long-term heavy cannabis users. *Eur Arch Psychiatry Clin Neurosci.* In press 2010.

171. Hillyard SA, Hink RF, Schwent VL, Picton TW. Electrical signs of selective attention in the human brain. *Science*. 1973;182(108):177-80.

172. Naatanen R, Picton T. The N1 wave of the human electric and magnetic response to sound: a review and an analysis of the component structure. *Psychophysiology*. 1987;24(4):375-425.

173. Rosburg T, Boutros NN, Ford JM. Reduced auditory evoked potential component N100 in schizophrenia--a critical review. *Psychiatry Res.* 2008;161(3):259-74.

174. Turetsky BI, Greenwood TA, Olincy A, Radant AD, Braff DL, Cadenhead KS, Dobie DJ, Freedman R, Green MF, Gur RE, Gur RC, Light GA, Mintz J, Nuechterlein KH, Schork NJ, Seidman LJ, Siever LJ, Silverman JM, Stone WS, Swerdlow NR, Tsuang DW, Tsuang MT, Calkins ME. Abnormal auditory N100 amplitude: a heritable endophenotype in first-degree relatives of schizophrenia probands. *Biol Psychiatry.* 2008;64(12):1051-9.

175. Skosnik PD, Krishnan GP, Vohs JL, O'Donnell BF. The effect of cannabis use and gender on the visual steady state evoked potential. *Clin Neurophysiol.* 2006;117(1):144-56.

176. Skosnik PD, Edwards CR, O'Donnell BF, Steffen A, Steinmetz JE, Hetrick WP. Cannabis use disrupts eyeblink conditioning: evidence for cannabinoid

modulation of cerebellar-dependent learning. *Neuropsychopharmacology*. 2008;33(6):1432-40.

177. Edwards CR, Skosnik PD, Steinmetz AB, Vollmer JM, O'Donnell BF, Hetrick WP. Assessment of forebrain-dependent trace eyeblink conditioning in chronic cannabis users. *Neurosci Lett.* 2008;439(3):264-8.

178. Barkus E, Lewis S. Schizotypy and psychosis-like experiences from recreational cannabis in a non-clinical sample. *Psychol Med*. 2008;38(9):1267-76.

179. Stirling J, Barkus EJ, Nabosi L, Irshad S, Roemer G, Schreudergoidheijt B, Lewis S. Cannabis-induced psychotic-like experiences are predicted by high schizotypy. Confirmation of preliminary results in a large cohort. *Psychopathology*. 2008;41(6):371-8.

180. Verdoux H, Gindre C, Sorbara F, Tournier M, Swendsen JD. Effects of cannabis and psychosis vulnerability in daily life: an experience sampling test study. *Psychol Med*. 2003;33(1):23-32.

181. McGuire PK, Jones P, Harvey I, Williams M, McGuffin P, Murray RM. Morbid risk of schizophrenia for relatives of patients with cannabis-associated psychosis. *Schizophr Res.* 1995;15(3):277-81.

182. Miller P, Lawrie SM, Hodges A, Clafferty R, Cosway R, Johnstone EC. Genetic liability, illicit drug use, life stress and psychotic symptoms: preliminary findings from the Edinburgh study of people at high risk for schizophrenia. *Soc Psychiatry Psychiatr Epidemiol*. 2001;36(7): 338-42.

183. Kristensen K, Cadenhead KS. Cannabis abuse and risk for psychosis in a prodromal sample. *Psychiatry Res*. 2007;151(1-2):151-4.

184. Arendt M, Mortensen PB, Rosenberg R, Pedersen CB, Waltoft BL. Familial predisposition for psychiatric disorder: comparison of subjects treated for cannabis-induced psychosis and schizophrenia. *Arch Gen Psychiatry.* 2008;65(11):1269-74.

185. Corcoran CM, Kimhy D, Stanford A, Khan S, Walsh J, Thompson J, Schobel S, Harkavy-Friedman J, Goetz R, Colibazzi T, Cressman V, Malaspina D. Temporal association of cannabis use with symptoms in individuals at clinical high risk for psychosis. *Schizophr Res.* 2008106(2-3):286-93.

186. Henquet C, Rosa A, Krabbendam L, Papiol S, Fananas L, Drukker M, Ramaekers JG, van Os J. An experimental study of catechol-o-methyltransferase Val158Met moderation of delta-9-tetrahydrocannabinol-induced effects on psychosis and cognition. *Neuropsychopharmacology*. 2006;31(12):2748-57.

187. Schiffman J, Nakamura B, Earleywine M, LaBrie J. Symptoms of schizotypy precede cannabis use. *Psychiatry Res*. 2005;134(1):37-42.

188. Henquet C, Di Forti M, Morrison P, Kuepper R, Murray RM. Gene-environment interplay between cannabis and psychosis. *Schizophr Bull*. 2008;34(6):1111-21.

189. Williams JH, Wellman NA, Rawlins JN. Cannabis use correlates with schizotypy in healthy people. *Addiction*. 1996;91(6):869-77.

190. Skosnik PD, Spatz-Glenn L, Park S. Cannabis use is associated with schizotypy and attentional disinhibition. *Schizophr Res.* 2001;48(1):83-92.

191. Dumas P, Saoud M, Bouafia S, Gutknecht C, Ecochard R, Dalery J, Rochet T, d'Amato T. Cannabis use correlates with schizotypal personality traits in healthy students. *Psychiatry Res.* 2002;109(1):27-35.

192. Earleywine M. Schizotypy, marijuana, and differential item functioning. *Hum Psychopharmacol.* 2006;21(7):455-61.

193. Veling W, Mackenbach JP, van Os J, Hoek HW. Cannabis use and genetic predisposition for schizophrenia: a case-control study. *Psychol Med. 2008*;38(9):1251-6.

194. Caspi A, Moffitt TE, Cannon M, McClay J, Murray R, Harrington H, Taylor A, Arseneault L, Williams B, Braithwaite A, Poulton R, Craig IW. Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene X environment interaction. *Biol Psychiatry.* 2005;57(10):1117-27.

195. Zammit S, Spurlock G, Williams H, Norton N, Williams N, O'Donovan MC, Owen MJ. Genotype effects of CHRNA7, CNR1 and COMT in schizophrenia: interactions with tobacco and cannabis use. *Br J Psychiatry.* 2007;191:402-7.

196. Munafo MR, Attwood AS, Flint J. Neuregulin 1 genotype and schizophrenia. *Schizophr Bull.* 2008;34(1):9-12.

197. Boucher AA, Arnold JC, Duffy L, Schofield PR, Micheau J, Karl T. Heterozygous neuregulin 1 mice are more sensitive to the behavioural effects of Delta9-tetrahydrocannabinol. *Psychopharmacology* (Berl). 2007;192(3):325-36.

198. Chakrabarti B, Kent L, Suckling J, Bullmore E, Baron-Cohen S. Variations in the human cannabinoid receptor (CNR1) gene modulate striatal responses to happy faces. *Eur J Neurosci*. 2006;23(7):1944-8.

199. Comings DE, Muhleman D, Gade R, Johnson P, Verde R, Saucier G, MacMurray J. Cannabinoid receptor gene (CNR1): association with i.v. drug use. *Mol Psychiatry.* 1997;2(2):161-8.

200. Schmidt LG, Samochowiec J, Finckh U, Fiszer-Piosik E, Horodnicki J, Wendel B, Rommelspacher H, Hoehe MR Association of a CB1 cannabinoid receptor gene (CNR1) polymorphism with severe alcohol dependence. *Drug Alcohol Depend.* 2002;65(3):221-4.

201. Zhang PW, Ishiguro H, Ohtsuki T, Hess J, Carillo F, Walther D, Onaivi ES, Arinami T, Uhl GR. Human cannabinoid receptor 1: 5' exons, candidate regulatory regions, polymorphisms, haplotypes and association with polysubstance abuse. *Mol Psychiatry.* 2004;9(10):916-31.

202. Ponce G, Hoenicka J, Rubio G, Ampuero I, Jimenez-Arriero MA, Rodriguez-Jimenez R, Palomo T, Ramos JA. Association between cannabinoid receptor gene (CNR1) and childhood attention deficit/hyperactivity disorder in Spanish male alcoholic patients. *Mol Psychiatry.* 2003;8(5):466-7.

203. Ujike H, Takaki M, Nakata K, Tanaka Y, Takeda T, Kodama M, Fujiwara Y, Sakai A, Kuroda S. CNR1, central cannabinoid receptor gene, associated with susceptibility to hebephrenic schizophrenia. *Mol Psychiatry.* 2002;7(5):515-8.

204. Martinez-Gras I, Hoenicka J, Ponce G, Rodriguez-Jimenez R, Jimenez-Arriero MA, Perez-Hernandez E, Ampuero I, Ramos-Atance JA, Palomo T, Rubio G. (AAT)n repeat in the cannabinoid receptor gene, CNR1: association with schizophrenia in a Spanish population. *Eur Arch Psychiatry Clin Neurosci*. 2006;256(7):437-41.

205. Chavarria-Siles I, Contreras-Rojas J, Hare E, Walss-Bass C, Quezada P, Dassori A, Contreras S, Medina R, Ramírez M, Salazar R, Raventos H, Escamilla MA. Cannabinoid receptor 1 gene (CNR1) and susceptibility to a quantitative phenotype for hebephrenic schizophrenia. *Am J Med Genet B Neuropsychiatr Genet.* 2008;147(3):279-84.

206. Tsai SJ, Wang YC, Hong CJ. Association study of a cannabinoid receptor gene (CNR1) polymorphism and schizophrenia. *Psychiatr Genet.* 2000;10(3):149-51.

207. Leroy S, Griffon N, Bourdel MC, Olie JP, Poirier MF, Krebs MO. Schizophrenia and the cannabinoid receptor type 1 (CB1): association study using a single-base polymorphism in coding exon 1. *Am J Med Genet*. 2001;105(8):749-52.

208. Seifert J, Ossege S, Emrich HM, Schneider U, Stuhrmann M. No association of CNR1 gene variations with susceptibility to schizophrenia. *Neurosci Lett*. 2007;426(1):29-33.

209. Hamdani N, Tabeze JP, Ramoz N, Ades J, Hamon M, Sarfati Y, Boni C, Gorwood P. The CNR1 gene as a pharmacogenetic factor for antipsychotics rather than a susceptibility gene for schizophrenia. *Eur Neuropsychopharmacol.* 2008;18(1):34-40.

210. Allebeck P, Adamsson C, Engstrom A, Rydberg U. Cannabis and schizophrenia: a longitudinal study of cases treated in Stockholm County. *Acta Psychiatrica Scand*. 1993;88(1):21-4. Erratum in: *Acta Psychiatr Scand.* 1993;88(4):304.

211. Linszen DH, Dingemans PM, Lenior ME. Cannabis abuse and the course of recent-onset schizophrenic disorders. *Arch Gen Psychiatry.* 1994;51(4):273-9.

212. Hambrecht M, Hafner H. Substance abuse and the onset of schizophrenia. *Biol Psychiatry*. 1996;40(11):1155-63.

213. Hambrecht M, Hafner H. Cannabis, vulnerability, and the onset of schizophrenia: an epidemiological perspective. *Aust N Z J Psychiatry.* 2000;34(3):468-75.

214. Green AI, Tohen MF, Hamer RM, Strakowski SM, Lieberman JA, Glick I, Clark WS. First episode schizophrenia-related psychosis and substance use disorders: acute response to olanzapine and haloperidol. *Schizophr Res.* 2004;66(2-3):125-35.

215. Addington J, Addington D. Effect of substance misuse in early psychosis. *Br J Psychiatry Suppl.* 1998;172(33):134-6.

216. Van Mastrigt S, Addington J, Addington D. Substance misuse at presentation to an early psychosis program. *Soc Psychiatry Psychiatr Epidemiol.* 2004;39(1):69-72.

217. Cleghorn JM, Kaplan RD, Szechtman B, Szechtman H, Brown GM, Franco S. Substance abuse and schizophrenia: effect on symptoms but not on neurocognitive function. *J Clin Psychiatry.* 1991;52(1):26-30.

218. Andreasson S, Allebeck P, Rydberg U. Schizophrenia in users and nonusers of cannabis. A longitudinal study in Stockholm County. *Acta Psychiatr Scand.* 1989;79(5):505-10.
219. Allebeck P, Adamsson C, Engstrom A, Rydberg U. Cannabis and schizophrenia: a longitudinal study of cases treated in Stockholm County. *Acta Psychiatr Scand.* 1993;88(1):21-4.
220. McGuire PK, Jones P, Harvey I, Bebbington P, Toone B, Lewis S, Murray RM. Cannabis and acute psychosis. *Schizophr Res*. 1994;13(2):161-7.
221. Veen ND, Selten JP, van der Tweel I, Feller WG, Hoek HW, Kahn RS. Cannabis use and age at onset of schizophrenia. *Am J Psychiatry.* 2004;161(3):501-6.
222. Macleod J. Cannabis use and symptom experience amongst people with mental illness: a commentary on Degenhardt et al. *Psychol Med*. 2007;37(7):913-6.
223. Collip D, Myin-Germeys I, Van Os J. Does the concept of "sensitization" provide a plausible mechanism for the putative link between the environment and schizophrenia? *Schizophr Bull.* 2008;34(2):220-5.
224. Sewell RA, Ranganathan M, D'Souza DC. Cannabinoids and psychosis. *Int Rev Psychiatry*. 2009;21(2):152-62.
225. D'Souza DC, Sewell RA, Ranganathan M. Cannabis and psychosis/schizophrenia: human studies. *Eur Arch Psychiatry Clin Neurosci.* 2009;259(7):413-31.
226. Hall W, Pacula R. *Cannabis use and dependence: public health and public policy.* London: Cambridge University Press; 2003.