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

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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

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.”

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generally lasting but a few hours, but occasionally as long as week". 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, including ∆9-tetrahydrahydrocannabinol (Δ9-THC) and cannabidiol (CBD). Therefore, cannabis is more than just Δ9-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. 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.

The observed effects of cannabinoids used for medicinal purposes provide another source of data on the association between cannabis and psychosis. Δ9-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. 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. 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. 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 Δ9-THC) in 12 presumably healthy physicians. 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.

In addition to studies with cannabis, there have been a few studies with Δ9-THC and other cannabinoids. Melges, in a double-blind, placebo-controlled study with high- and low-dose Δ9-THC, reported cannabis users to have had core symptoms of psychosis, including thought disorder and paranoia. 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 Δ9-THC was not associated with as prominent psychotomimetic effects as LSD. Reese Jones observed not-particularly-robust psychotomimetic effects in studies of “normal” controls given Δ9-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. 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 Δ9-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. The full range of symptoms associated with schizophrenia—positive, negative, and cognitive symptoms—were measured using well-validated measures. ∆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
∆9-THC induced a range of positive symptoms of schizophrenia including suspiciousness, paranoid and grandiose delusions, conceptual disorganization, fragmented thinking, and perceptual alterations. ∆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 ∆9-THC (2.5mg i.v.) produced similar effects in healthy subjects. Leweke et al., observed that nabilone, a synthetic analog of ∆9-THC, altered binocular depth inversion, a potential surrogate marker for psychosis.

4. Negative symptoms
D’Souza et al. also showed that ∆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. Similar effects have been reported in rodents and non-human primates reviewed in. Not only is this pattern of cognitive deficits also observed

![Positive Symptoms (PANSS)](image1)

![Perceptual Alterations (CADSS)](image2)

Figure 1 - ∆9-THC induces transient psychotomimetic effects in healthy individuals. Effects of ∆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.
Cannabinoids, psychosis and schizophrenia

in schizophrenia, but the most robust cognitive deficit induced by Δ⁹-THC—verbal memory—is also the most robust cognitive deficit observed in schizophrenia. As illustrated in Figure 2, D’Souza et al., showed that intravenous Δ⁹-THC produced robust dose-dependent impairments in immediate and delayed (30-minute) verbal memory in healthy subjects. Δ⁹-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, and continued use predicts the presence of more psychotic symptoms and worsens the prognosis of people who already have schizophrenia. Other studies suggest that cannabis using schizophrenic patients had lower negative symptoms scores and adolescents with first-episode psychosis had lower negative symptoms scores and a better prognosis that those who did not use cannabis.

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. Almost a century later, D’Souza characterized the effects of Δ⁹-THC in schizophrenic patients using the same methodology described earlier in healthy subjects. All the patients were taking stable doses of antipsychotic medications (dopamine D2 receptor antagonists) and were clinically stable. Δ⁹-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 Δ⁹-THC effects than controls (Figure 3). Similarly, relative to controls, schizophrenia patients were more vulnerable to Δ⁹-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). The increases in symptoms experienced were brief, modest, similar to the patients’ typical symptoms, and occurred.
even though subjects were clinically stable, medication-responsive, and receiving therapeutic doses of antipsychotics. It is possible that ∆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 ∆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 ∆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 use 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. 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: 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. 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 increasing frequency and amount of use. 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). Meta-analyses suggest that cannabis might account for between 8% and 14% of schizophrenia cases, although the quintupling of rates of cannabis use over the last four decades 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 others find an increase.

### 2. Negative symptoms

An “amotivational syndrome” has been described in chronic, heavy cannabis users. 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.

### 3. Cognitive deficits

While it is clear that cannabinoids can cause acute transient impairments in memory, attention, and executive function, whether exposure to cannabinoids is 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.

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.

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. In a recent comprehensive review, Solowij and Battisti concluded that chronic heavy cannabis use is associated with impaired memory function 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, 28 days, or three months of abstinence, and some show some recovery only after an average of two years’ abstinence.

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 Leberg found that 14 studies reported better cognition in the cannabis-using groups. 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. 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. But subsequent studies using computerized tomography failed to find detect any structural abnormalities. Recent studies using magnetic resonance imaging (MRI) studies have also reported mixed results. Some studies failed to find any changes whereas other studies reported global or focal changes to gray and white matter density changes, either global changes or in focal...
regions, most notably in the hippocampal and parahippocampal areas. 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, two found that cannabis smokers had lower volumes in the anterior and posterior cingulate cortices, and one found that cannabis-using patients had greater ventral striatal grey matter density. 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 focused on electroencephalography (EEG), 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.

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. P50 suppression deficits have been observed in schizophrenia, with robust effect sizes. P50 suppression deficits have also been observed in clinically unaffected relatives, and individuals with schizotypal personality disorder. P50 suppression is mediated by the hippocampus, temporoparietal region, and prefrontal cortex, all areas dense in cannabinoid receptors. 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. Chronic cannabis exposure has been associated with disruptions in P50 suppression, and this effect correlates with the magnitude of cannabis exposure. Another study performed after 28 days of abstinence demonstrated P50 gating deficits that correlated with the number of years of cannabis consumption.

2. P300

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

Table 1 - Cannabis effects on brain structure in schizophrenia

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

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); EIOH = Alcohol; LV = Lateral ventricle; TV = Third ventricle; DTI = Diffusion Tensor Imaging
superior temporal gyrus, and frontal cortex. P300 deficits, particularly in the auditory modality, are one of the most consistent biomarkers of SZ. Reductions in P300 amplitude and increased latencies have been observed in both SZ patients and unaffected relatives, however these deficits have also been reported in several other conditions.

Both oral and smoked Δ9-THC, have been reported to reduce P300 amplitude. Interestingly, a polymorphism of the CB1 receptor gene has been associated with decreased P300 amplitude, suggesting that CB1 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. 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. Kempel et al., reported reduced P300 amplitudes. Skosnik reported increased P300 amplitudes, and Patrick et al. and de Sola et al. were unable to detect P300 amplitude differences in cannabis users. 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, but unimpaired with simple tasks.

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. Numerous studies have demonstrated abnormal MMN amplitudes to stimuli deviating in either duration or frequency in SZ patients. As MMN does not appear to be altered in other psychiatric disorders such as unipolar and bipolar depression, it may be a particularly specific and useful biomarker for auditory disturbances in SZ.

The acute administration of oral Δ9-THC did not alter MMN amplitude compared to placebo. However, the combination of Δ9-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 Δ9-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. 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. It is thought to be related to basic perceptual processing, and in the auditory domain, is likely generated by auditory and frontal cortices. Schizophrenia patients and their unaffected relatives exhibit abnormal N100s, which have been reported in both schizophrenia patients and their clinically unaffected relatives.

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. This effect was further demonstrated in the auditory modality for discrete 1000 Hz tones during an associative learning task. However, a subsequent study failed to replicate this finding.

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. 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.

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. Recently Arendt showed that predipsisition 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.

In a prospective study of cannabis using prodromal patients, Corcoran noted significantly more perceptual disturbances and worse functioning during epochs of increased cannabis use 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 were 10 times more likely convert to psychosis than individuals who did not use cannabis. 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 Δ9-THC on cognition and psychosis.
Similarly, Verdoux reported that only psychosis-prone individuals reported marked perceptual changes and feelings of increased suspicion and hostility after consuming *cannabis*.

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.198,200 Recently, Veling et al., showed that individuals significantly impaired in schizophrenia, following psychosis proneness scores in some,189-191 but not all studies,187,192 cannabis use.193

Cannabis users as a group tend to exhibit higher schizotypy scores.198,200 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.194,195 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 Val108Met 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 Δ9-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 Δ9-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 Δ9-THC administration.197

The cannabinoid receptor gene (CNR1) is thought to modulate the striatal response to rewarding stimuli198 and polymorphisms of this gene are associated with alcoholism and intravenous drug use in humans.199-201 A variety of CNR1 polymorphisms have been studied for associations with schizophrenia, with mixed results.196,202-204 The (AAT)n microsatellite is associated with drug use,199 decreased frontal P300,197 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 positive207 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 3.

**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.198 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 Haftner 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. 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.

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

**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.

**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.

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

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