Curr Addict Rep (2014) 1:115–128
DOI 10.1007/s40429-014-0018-7

STIMULANTS, CANNABIS, AND CLUB DRUGS (AJ BUDNEY, R VANDREY AND D LEE, SECTION EDITORS)

Impact of Cannabis Use on the Development of Psychotic Disorders

Samuel T. Wilkinson · Rajiv Radhakrishnan · Deepak Cyril D'Souza

Published online: 17 April 2014

Abstract The link between cannabis use and psychosis comprises three distinct relationships: acute psychosis associated with cannabis intoxication; acute psychosis that lasts beyond the period of acute intoxication; and persistent psychosis not time-locked to exposure. Experimental studies reveal that cannabis, delta-9-tetrahydrocannabinol (THC) and synthetic cannabinoids reliably produce transient positive, negative, and cognitive symptoms in healthy volunteers. Case studies indicate that cannabinoids can induce acute psychosis that lasts beyond the period of acute intoxication but resolves within a month. Exposure to cannabis in adolescence is associated with a risk for later psychotic disorder in adulthood; this association is consistent, temporally related, shows a dose response, and is biologically plausible. However, cannabis is neither necessary nor sufficient to cause a persistent psychotic disorder. More likely, it is a component cause that interacts with other factors to result in psychosis. The link between cannabis and psychosis is moderated by age at onset of cannabis use, childhood abuse, and genetic vulnerability. While more research is needed to better characterize the relationship between cannabinoid use and the onset and persistence of psychosis, clinicians should be mindful of the potential risk of psychosis, especially in vulnerable populations, including adolescents and those with a psychosis diathesis.

S. T. Wilkinson · R. Radhakrishnan · D. C. D'Souza
Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA

D. C. D'Souza
Abraham Ribicoff Research Facilities, Connecticut Mental Health Center, New Haven, CT, USA

D. C. D'Souza (✉)
Schizophrenia and Neuropharmacology Research Group, Psychiatry Service, 116A, VA Connecticut Healthcare System, 950 Campbell Avenue, West Haven, CT 06516, USA
e-mail: deepak.dsouza@yale.edu

Keywords Cannabis · Psychotic disorders · Psychosis · Schizophrenia

Introduction

The etiology of psychotic disorders, exemplified by schizophrenia, remains elusive. While it is unlikely that there is one "cause" for schizophrenia, a number of genetic and environmental factors that may contribute to the risk of psychosis have been identified. One environmental factor that has received some attention as possibly contributing to the risk for psychotic disorders is exposure to cannabis. It should be noted that an overwhelming majority of individuals who are exposed to cannabis do not develop a psychosis outcome and most individuals with a psychotic disorder may never have been exposed to cannabis. Thus, cannabis is neither necessary nor sufficient to "cause" schizophrenia. More likely, as reviewed below, cannabis may contribute to the risk for a psychosis outcome in vulnerable individuals.

Here, we review the evidence investigating the association between cannabis and psychotic disorders—the exogenous cannabinoid hypothesis—with special attention to literature from the past 3 years. We describe three distinct relationships: (1) acute psychosis associated with cannabis intoxication; (2) acute psychosis that lasts beyond the period of acute intoxication; and (3) persistent psychosis not time-locked to exposure. We review the strength, consistency, specificity, biological plausibility, and temporality of the relationship between cannabis and psychosis and discuss recent findings implicating specific genes that might make some individuals more susceptible to psychosis-inducing effects of cannabis. Besides the exogenous hypothesis, we also discuss evidence supporting an *endo*genous cannabinoid hypothesis, suggesting that alterations in the endocannabinoid system may contribute to the pathophysiology of schizophrenia.

Schizophrenia, the prototypical psychotic disorder, is characterized by positive symptoms (e.g., hallucinations, delusions, thought disorganization), negative symptoms (e.g., amotivation, blunted affect, and social withdrawal), and cognitive deficits (e.g., deficits in memory, executive function, and attention). While most of the literature has focused on the link between cannabis exposure and positive symptoms of psychosis, here we also review the evidence linking cannabis exposure with both negative symptoms and cognitive deficits.

Overview of Cannabis, Cannabinoids, and the Endocannabinoid System

There are at least two identified cannabinoid receptors (CB1 and CB2), both of which are metabotropic G protein-coupled receptors. CB1 and CB2 are localized primarily in the brain and periphery, respectively [1, 2]. CB1 are G protein-coupled receptors that are distributed in the central nervous system, where they are primarily located presynaptically. Their activation inhibits the release of other neurotransmitters such as gamma-aminobutyric acid (GABA) and glutamate [3, 4]. Both receptors are believed to regulate the timing and release of GABA [5]. Relevant to psychosis, in the cerebral cortex and hippocampus, where they are abundant, CB1 modulates the release of GABA within networks of cholecystokinin-containing GABAergic interneurons [6–9, 10••, 11–13].

The principal psychoactive constituent of cannabis is delta-9-tetrahydrocannabinol (THC). However, cannabis contains over 70 cannabinoids besides THC, including cannabidiol (CBD), cannabigerol, cannabichromene, cannabidivarin, tetrahydrocannabivarin, and terpenoids. Many of these compounds have pharmacologic effects that are distinct from those of THC [14, 15]. Furthermore, while these minor cannabinoids and terpenoids may not have effects individually, they may have effects in combination with others—referred to as "entourage effects."[16]. THC produces its psychoactive effects via actions at CB1, where it functions as a partial agonist with modest affinity [inhibition constant (K_i) = 35–80 nmol] and low intrinsic activity [17]. CBD, a major constituent of cannabis that does not produce euphoria, may have anxiolytic and antipsychotic effects in both preclinical and humans studies (reviewed in Schubart et al. [18]). The CBD content of cannabis varies and lower levels of CBD in cannabis have been associated with higher rates of psychosis [19–23]. For example, a variant of South African cannabis that is nearly devoid of CBD is associated with higher rates of psychosis [21, 23, 24]. Of note, CBD has been shown to inhibit the psychotomimetic effects of THC [25••, 26]. Last, it warrants mention that a number of synthetic cannabinoids that are full CB1 agonists with generally higher affinity for CB1 are currently being used by a substantial number of individuals [27].

Acute Psychosis Associated with Intoxication

A link between cannabis intoxication and altered behavior, including psychosis has long been recognized [27]. In the nineteenth century, Moreau (de Tours) characterized transient hallucinations, paranoia, dissociative symptoms, thought disorganization, and impairments in attention and memory reminiscent of psychotic symptoms seen in schizophrenia in the context of acute cannabis intoxication (reviewed in Warnock [28]). These phenomena have also been documented in numerous case reports (reviewed by Warnock [28]) and are estimated to occur in about 20–50 % of individuals who use cannabis [29••, 30].

Consistent with the acute psychotogenic effects of cannabis, similar psychotic symptoms have been reported with the use of medicinal cannabinoids such as dronabinol, nabilone, and levonantradol (reviewed in Warnock [28] and Reilly et al. [31]). More recently, there is increasing recognition of psychosis related to the recreational use of newer synthetic cannabinoids [32], which are sold as Spice or K2, and which are more potent CB1 agonists than THC [27].

The best evidence for the acute psychotomimetic effects of cannabis comes from experimental studies using cannabis and THC. Cannabis, THC, and synthetic cannabinoids have been shown to produce a full range of positive symptoms (such as suspiciousness, paranoid and grandiose delusions, conceptual disorganization, fragmented thinking, and perceptual alterations), negative symptoms (such as blunted affect, emotional withdrawal, psychomotor retardation, lack of spontaneity, and reduced rapport), and cognitive impairments (such as deficits in verbal learning, short-term memory, working memory, executive function, abstract ability, decision making, attention, and time perception abnormalities) in healthy volunteers that bear resemblance to the symptoms of schizophrenia [25••, 33–36]. Further, THC exacerbates psychotic symptoms in patients with chronic schizophrenia, despite being on stable doses of antipsychotics [37].

Cannabinoids have also been shown to induce abnormalities in electrophysiological indices of brain function that are also known to be present in schizophrenia and other neuropsychiatric disorders. THC reduces amplitude of the novelty P300a and target P300b, measures of the automatic orientation of attention (P300a) and context updating (P300b) in healthy participants [38••, 39] in a dose-dependent manner [40] without affecting processing speed. Furthermore, THC does not affect the N100, suggesting that cannabinoids do not have significant effects on early sensory registration [40]. Self monitoring is compromised in schizophrenia and contributes to deficits in insight [41]. Error-related negativity, an event-related potential component, is theorized to be related to error monitoring and has shown to be reduced in healthy volunteers exposed to THC [42]. There is mounting evidence that disruptions in neural oscillations play a key role in the pathophysiology of psychosis (reviewed in Spronk et al. [43]). Neural oscillations in the theta

(θ; 4–7 Hz) and gamma (γ; 31–80 Hz) range are involved in sensory registration, the integration and binding of perceptual features, working memory, and conscious awareness [44–48], processes that are altered in psychosis. Studies in animals and hippocampal slices have provided evidence that cannabinoid agonists can disrupt synchronized neural oscillations at θ and γ frequencies [49–56]. In humans, smoked cannabis was shown to disrupt θ band power; further, the degree of disruption correlates with working memory performance [57].

Functional neuroimaging studies with THC and CBD have revealed that they have opposing actions in neural networks involving the medial temporal and prefrontal cortices, regions that are rich in CB1 receptors. The networks recruited in these studies also recapitulate the pattern of activity seen in schizophrenia, thus making a case for the endocannabinoid hypothesis of schizophrenia [58, 59, 60•]. Individuals who experience acute psychotic symptoms induced by THC have a different pattern (medial temporal cortex and cerebellum) of brain activation compared to placebo, suggesting that these brain regions mediate THC-induced psychotic symptoms [61]. THC attenuated activation in the left parahippocampal gyrus/fusiform gyrus, left middle temporal gyrus/superior temporal sulcus and right cerebellum/fusiform gyrus, and accentuated activation in the right middle temporal gyrus in individuals who experienced transient psychotic symptoms [60•].

Given the role of dopaminergic hyperactivity in the pathophysiology of positive symptoms, and prefrontal dopaminergic hypoactivity in the pathophysiology of negative symptoms and cognitive deficits [62, 63], a number of neuroreceptor imaging studies in humans have attempted to demonstrate THC-induced dopamine release. One small study showed reduced regional binding of the radiotracer [11C]raclopride to be suggestive of a very small increase in dopamine release following inhaled THC [64]. However, two other studies using comparable doses but different radiotracers failed to show any changes [65, 66]. Similarly the effects of dopamine D_2 antagonist antipsychotics on THC-induced effects have been mixed. The psychotomimetic effects of THC were not blocked by the dopamine receptor antagonist haloperidol [67] in healthy volunteers and THC was also shown to exacerbate psychotic symptoms in patients with chronic schizophrenia despite being on stable doses of antipsychotics [37]. However, other studies suggest that haloperidol [68] and olanzapine [69] may attenuate THC-induced psychotomimetic effects in healthy volunteers. In a study using [18 F]-fallypride, inhaled THC was associated with significant ligand displacement (dopamine release) in striatal subregions among schizophrenic patients and their relatives but not in controls [62].

In summary, cannabinoids can produce an array of transient positive symptoms, negative symptoms, cognitive deficits, and electrophysiological indices of information processing abnormalities that are relevant to psychosis. These effects appear to be dose related and do not last beyond the period of intoxication. For example, in the laboratory studies, the above-mentioned effects resolved between 2 and 4 h [25••].

Acute Psychosis Outlasting the Period of Intoxication

In some individuals, cannabis use is associated with immediate psychosis that lasts longer than the period of acute intoxication and warrants clinical intervention. Cannabis-induced acute persistent psychosis has been documented in multiple case-series [23, 70••, 71–77]. The psychosis is characterized by hallucinations, paranoia, delusions, depersonalization, emotional lability, amnesia, confusion and disorientation, which followed the ingestion of large doses of cannabis. These psychotic episodes tend to resolve relatively faster than schizophrenic psychotic episodes, and do not usually recur without re-use of cannabis [23, 74, 77–84, 86] (reviewed in Hall and Solowij [85]).

The long-term course and outcome of cannabis-induced acute psychosis is also under study. Several large longitudinal studies suggest that up to 50 % of individuals without a pre-existing condition who were initially hospitalized for cannabis-induced psychosis were re-diagnosed with a schizophrenia spectrum disorder during long-term (~8 years) follow-up [70••, 87]. That proportion increased to 75 % when the diagnosis was expanded to *any* psychotic outcome [70••]. However, in one of these studies [87] there were significant limitations to the diagnostic approach, including retrospective assessment, the validity of the diagnosis of schizophrenia, and confounds related to change from using *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised* (DSM-IIIR) to *International Classification of Diseases, 10th Edition* (ICD-10) criteria during the study [88]. Limitations notwithstanding, hospitalization for cannabis-induced persistent psychosis may portend a recurrent psychotic disorder that in our current knowledge base and diagnostic schema is categorized as schizophrenia. It is conceivable that these cases may represent a distinct recurrent psychotic disorder [89].

Cannabis and Persistent Psychotic Disorders

While accumulating evidence suggests a link between cannabis exposure and the development of schizophrenia, whether cannabinoids can "cause" *persistent* psychosis remains controversial (reviewed in Warnock [28]). Common criteria to establish disease causality include strength of association, consistency, biological gradient (dose), specificity, and biological plausibility (reviewed in D'Souza [90•]). Much of these data come from large epidemiological studies (see Table 1). We review the evidence in terms of these criteria, highlighting the most recent findings. It should be noted that most studies have focused on positive symptom outcomes; there is a dearth of studies examining negative symptoms and/or cognitive deficits.

One of the first studies that attempted to link cannabis exposure to schizophrenia was a longitudinal, 15-year cohort study of 45,570 Swedes [91••]. A dose–response relationship was observed between self-reported cannabis use at age 18 years and psychiatric hospitalization for schizophrenia over the ensuing 15 years [91••]. Zammit et al. replicated the findings in a subsequent analysis of these data [92••], and furthermore showed that adjustment for potential confounders such as psychiatric diagnosis, intelligence quotient (IQ) score, degree of social integration, disturbed behavior in childhood, cigarette smoking, and place of upbringing did not explain the association. The most recent follow-up of this cohort (see Table 1) found an increased risk for the development of schizophrenia in those who used cannabis compared with non-users [93••]. Notably, the risk for schizophrenia declined in the cannabis using group as follow-up time increased, suggesting a predisposing vulnerability such that those who are genetically vulnerable will develop schizophrenia within a certain window of time after exposure, while those who are not genetically vulnerable remain unaffected by exposure. A number of other large long-term and cross-sectional epidemiological studies, including the Dunedin cohort [94•], the Netherlands Mental Health Survey and Incidence Study (NEMESIS) [95], German Early Developmental Stages of Psychopathology (EDSP) Study [96], and the Christchurch Health and Development Study [97] have reported similar findings (reviewed in Warnock [28]).

Strength of Association and Consistency

Generally, the strength of the association between cannabis exposure and schizophrenia is modest but consistent. Meta-analyses have estimated odds ratios (ORs) of 1.41–2.34 [98, 99••, 100]. While the association between cannabis use and the later development of persistent psychotic disorders is consistent, it should be noted that methodological limitations may bias this association, including residual confounding, follow-up bias, direction of causality, and difficulty discriminating between psychotic symptoms from acute intoxication and psychotic disorder at the time of assessment [101••].

Temporal Relationship

Temporality is considered one of the more important criteria needed to establish causality. Establishing the temporal relationship between an environmental factor and schizophrenia may be particularly challenging in part because the onset of schizophrenia is difficult to establish. The emergence of positive symptoms may be the final step in the evolution of schizophrenia. Negative and cognitive symptoms are more difficult to recognize than positive psychotic symptoms, and often precede positive symptoms. This makes pinpointing the onset of illness, and therefore establishing the temporal relationship between cannabis exposure and schizophrenia, challenging.

Several recent retrospective studies have reported that in the majority of cases studied, cannabis use preceded the development of psychosis by a period of years in first-episode psychosis patients with a history of cannabis exposure [102–104]. Though these studies are limited by their retrospective approach, the finding that cannabis use precedes psychosis onset has also been supported by the findings of a number of earlier longitudinal, prospective studies [105–108].

A number of studies also suggest that cannabis exposure is associated with an earlier and more abrupt onset of psychosis. A meta-analysis of 83 studies investigating the association between cannabis and psychosis found that cannabis users who develop psychotic disorders do so on average 2.7 years before those who do not use cannabis [109••]. Additional studies report a similar trend [110, 111].

Interestingly, data for the converse temporal relationship also exist. As such, it is again emphasized that most epidemiological studies have not taken into account negative and cognitive symptoms, which are thought to occur earlier than positive ones. A prospective study of a large population of Dutch teenagers with assessments of psychosis and marijuana use at ages 13, 16, and 19 years showed a significant association between cannabis use and psychosis vulnerability across all time points [106]. Notably, there was a bidirectional association; that is, psychosis vulnerability at ages 13 and 16 years predicted cannabis use at ages 16 and 19 years, respectively.

Biological Gradient

Most large epidemiological studies have found a consistent biological gradient characterizing the cannabis–psychosis association [91••, 93••, 95, 97]. In general, those who report heavier cannabis use have a higher risk of a psychosis outcome. A recent analysis of the National Epidemiologic Survey on Alcohol and Related Conditions data set supported the existence of a biological gradient (see Table 1) [112]. Notwithstanding these findings, it should be noted that there are considerable limitations to assessing a dose–response effect of the cannabis–psychosis relationship. The concentration of THC in cannabis, which contributes to the dose of exposure, varies significantly; to our knowledge, no large epidemiological studies have attempted to measure or control for the variation in THC. Further, the concentration of CBD, which is believed to offset the pro-psychotic effects of THC [18], can also vary.

Specificity

The specificity of the association between cannabis and psychosis is stronger than the associations between cannabis and other mental illnesses, and the associations between other substances and psychosis. For instance, cannabis

Table 1 Recent epidemiological studies

Reference and study design	Methods/follow-up	Sample size	Follow-Up	Result
Meier et al., 2012 [144••] Longitudinal, prospective (Dunedin cohort)	Cannabis use assessed at ages 18, 21, 26, 32, and 38 years Neuropsychological testing at ages 13 and 38 years	1,037 subjects from general population	38 years	Decline in neuropsychological functioning in processing speed, memory, executive functioning, verbal comprehension 8-Point IQ decline in subjects with cannabis dependence, onset in adolescence
Manrique-Garcia et al., 2012 [93••] Longitudinal, prospective (Swedish military cohort)	Anonymous survey at time of conscription (ages 18–19 years for 93 %) Interview and psychological assessment after 35 years	50,087 military conscripts (mandated), 93 % were ages 18–19 years at initiation of service	35 years	The adjusted OR for the development of schizophrenia: 3.7 (95 % CI 2.3–5.8) in subjects who used cannabis >50 times vs. non-users 1.8 (95 % CI 1.3–2.5) in subjects ever using cannabis vs. non-users
Davis et al., 2013 [112] Cross-sectional analysis (NESARC data set)	Face-to-face, computer-assisted interview focusing on DSM-IV diagnoses	34,653 adults from general population	NA	The adjusted OR for schizotypal features: 2.02 (95 % CI 1.69–2.42) in subjects with lifetime cannabis use 2.83 (95 % CI 2.33–3.43) in subjects with lifetime cannabis abuse 7.32 (95 % CI 5.51–9.72) in subjects with lifetime cannabis dependence The adjusted OR for psychosis: 1.27 (95 % CI 1.03–1.57) in subjects with lifetime cannabis use 1.79 (95 % CI 1.35–2.38) in subjects with lifetime cannabis abuse 3.69 (95 % CI 2.49–5.47) in subjects with lifetime cannabis dependence
Kuepper et al., 2011 [96] Longitudinal, prospective (German early development stages of psychopathology study)	Cannabis use and psychosis assessed at baseline, 3.5, and 8.4 years using CIDI	1,923 adolescents/young adults (ages 14–24 years at baseline) from general population	10 years	OR for psychotic symptoms at 8.4 years' follow-up: 1.5 (95 % CI 1.1–2.1) in subjects with lifetime cannabis use at 3.5 years 1.9 (95 % CI 1.1–3.1) in subjects with new cannabis use at 3.5 years OR for cannabis use at 8.4 years based on psychotic experiences at 3.5 years: 0.8 (95 % CI 0.6–1.2) OR for persistent psychosis based on cannabis at baseline and 3.5 years: OR 2.2 (95 % CI 1.2–4.2)

CI confidence interval, *CIDI* composite international diagnostic interview, *DSM-IV* Diagnostic and Statistical Manual of Mental Disorders, 4th edition, *IQ* intelligence quotient, *NA* not applicable, *NESARC* National Epidemiologic Survey on Alcohol and Related Conditions, *OR* odds ratio

exposure has a stronger association with psychosis outcomes than depression or anxiety outcomes [99••]. In relation to other substance use, conversion to schizophrenia was found to be highest with cannabis (46 %) followed by amphetamines (30 %) and alcohol (5 %) in a large study [87], suggesting higher specificity of psychosis outcomes than for other substances. While there is a strong association between cigarette smoking and schizophrenia, there is little evidence to support the notion that cigarette smoking "causes" schizophrenia.

Biological Plausibility

The immediate effects of cannabinoids on dopamine, GABA, and glutamate neurotransmission may explain some of the acute cannabinoid-induced symptoms discussed above. However, the mechanism by which cannabinoid exposure results in schizophrenia has not yet been established. As discussed elsewhere [113], one hypothesis suggests that cannabinoid exposure alters brain development, which most believe continues until the age of 25 years [29••]. Factors that disrupt brain

maturation or development may have long-term consequences. The endocannabinoid system is central to a number of neurodevelopmental processes including axon elongation, neurogenesis, neural maturation, neural specification, glia formation, and neuronal migration [114••, 115–119, 120•, 121, 122] docannabinoid system in the rapidly changing brain, as is the case in adolescence, may have far-reaching consequences. This may be particularly true in the setting of already abnormal neurodevelopmental processes, as would likely be the case in individuals at risk for psychosis.

Window of Exposure

An emerging finding is that earlier exposure to cannabis is associated with a higher risk for psychosis outcome and that the risk declines when exposure is after late adolescence. Thus, those who begin using cannabis at a young age are at particularly high risk of developing schizophrenia [94•, 103, 123]. One study reported that the association between cannabis and psychotic disorders was only significant when cannabis use began before age 14 years [103]. Another study found that, compared with cannabis users with onset after age 17 years, those who began use before age 17 years had a significantly greater risk of positive symptoms (adjusted OR 9.5, p=0.0001), and a greater risk of auditory hallucinations (adjusted OR 8.5, p=0.003) [123]. One interpretation of these findings is that cannabis exposure during critical periods of brain development may lead to long-lasting consequences such as psychosis. Indeed, this hypothesis has received some support in animal studies showing that exposure to cannabinoids in adolescence has more deleterious effects than exposure in adulthood [124–128].

Alternatively, Stefanis et al. found a consistent lag of 7–8 years between age of onset of cannabis use and the age of onset of psychosis in a retrospective study of 997 individuals (ages 12–19 years at time of onset of cannabis). This suggests that cumulative exposure to cannabis may be more relevant than age at onset of cannabis, with earlier cannabis use resulting in greater cumulative exposure [129].

Another important theme is that cannabis use is associated with an earlier age of onset of psychosis—by 2.7 years in one meta-analysis [109••]. This association appears to be somewhat specific, since tobacco use, which is also highly prevalent in psychotic disorders, is not associated with an earlier onset of psychosis [130].

Cannabis and Cognitive and Negative Symptoms

Cognitive Symptoms

Cognitive deficits, a core feature of schizophrenia [131], include deficits in memory, attention, executive functioning vocabulary, visuospatial skills, and learning [132]. There are several parallels between the cognitive deficits observed in schizophrenia and the cognitive deficits associated with cannabis exposure.

In controlled laboratory experiments, cannabis and cannabinoids have been shown to produce transient, dose-related cognitive deficits (reviewed in Warnock [28]), including impairments in working memory, short-term memory, and attention. These cognitive deficits bear some resemblance to the cognitive deficits of schizophrenia. Whether chronic exposure to cannabis is associated with persistent cognitive deficits remains controversial (reviewed in Fried et al. [134]). In chronic cannabis users, one study found no persistent cognitive deficits after 28 days of confirmed abstinence [133••], while other studies have shown that the time to full recovery ranges from weeks to months of abstinence [133••, 134]. Another study found persistent deficits despite almost 2 years of abstinence [85, 135]. In a recent review [136], among studies in which cognitive testing was performed 3 weeks or later after the last use of cannabis, there was considerable variability in whether deficits were found on measures of attention/concentration [133••, 135, 137–142], decision making/risk taking [143], response inhibition [133••, 137–139, 142], working memory [141], and verbal memory [133••, 138, 139]. Most studies found impairment on reasoning/problem-solving task ([133••, 137–139, 142]).

Recently, a number of important studies have contributed to the evidence for an association between cannabis use and persistent cognitive impairment. One notable study was a follow-up from the Dunedin cohort, where cannabis use was assessed via interviews at 18, 21, 26, 32, and 38 years of age and neuropsychological testing was performed at ages 13 and 38 years. Neurocognitive decline in numerous domains, including processing speed, memory, executive functioning, and verbal comprehension was shown in cannabis users. Deficits were most notable among those who began use in adolescence and heavy users. Overall, the study estimated a loss of 8 IQ points attributable to cannabis use, which did not reverse even after cessation of cannabis [144••].

In another recent study, Fontes et al. investigated the neurocognitive performance of chronic cannabis users (n=104) and healthy controls (n=44). Cannabis users who began using before age 15 performed worse than controls in measures of sustained attention, impulse control, and executive functioning [145]. Importantly, this study did not account for the possibility of residual effects of acute cannabis intoxication from subjects' last use of cannabis.

Negative Symptoms

Cannabis use, especially when chronic and heavy, has been associated with an "amotivational syndrome," [85, 146–149] which is characterized by numerous negative symptoms, including a lack of motivation, a loss of arousal, apathy, lethargy, and impaired social functioning [77]. Most of the existing

literature describing this phenomenon is decades old. Symptoms of the cannabis-associated "amotivational syndrome" bear resemblance to the negative symptoms of schizophrenia (amotivation, apathy, social withdrawal, disinterest in blunted affect, etc.). However, earlier studies have suggested that confounding variables—such as other substance abuse, poverty, or other psychiatric disorders—may explain this "amotivational syndrome" [150].

In contrast, some studies suggest that schizophrenia patients who use cannabis have fewer negative symptoms than those who do not [151, 152]. This evidence, however, is limited due to the cross-sectional design of these studies.

In conclusion, while considerable research has focused on an association between cannabis exposure and positive symptoms, there is some evidence to suggest that cannabis exposure is also associated with negative symptoms, which, like positive symptoms and cognitive deficits, represent the three main domains of symptoms of schizophrenia.

Genetic and Other Studies

A number of candidate genes have been studied as interacting with cannabis exposure to confer a higher risk for schizophrenia (see Table 2). Catechol-*O*-methyltransferase (COMT) is an enzyme that metabolizes dopamine in the prefrontal cortex; individuals with the Val/Val genotype at locus 158/108 have a higher metabolic activity of this enzyme (and thus lower level of prefrontal cortical dopamine) relative to those with the Met/Met polymorphism [153]. Early reports [154••] suggested that individuals with the Val/Val [154••] *COMT* genotype were ten times more likely to develop psychosis than those with the Met/Met genotype. Subsequent data, however, have yielded mixed results [155, 156, 157••], with a recent 2-year longitudinal study showing no differences in the risk for developing psychosis among *COMT* polymorphisms (see Table 2) [158]. Likewise, Estrada et al. found no overall greater risk for psychosis in association with cannabis among all genotypes of *COMT* [159]. However, this study did find that the Val/Val genotype is associated with the earliest age of onset of psychosis (see Table 2). Finally, Costas et al. showed that schizophrenia patients who were Met homozygotes had higher rates of lifetime cannabis use relative to Val homozygotes [160]. These data were in contrast to the earliest report of a *COMT* gene by cannabis exposure interaction reported by Caspi et al. [154••].

While recent studies of the *COMT* genotype moderating the psychosis–cannabis association have been mixed, there has been a surge of interest in AKT1, which codes for a phosphorylating enzyme that has been shown to be activated by cannabinoid receptors [161]. In a sample of psychotic patients, their unaffected siblings, and unrelated controls, Van Winkel found a twofold higher incidence of C/C genotype in patients with daily cannabis use history. Furthermore, individuals with a C/C genotype had a higher chance of being diagnosed with psychotic disorder relative to siblings and unrelated controls (see Table 2) [157••]. Daily cannabis users with the C/C genotype have been found to be at significantly higher risk of being diagnosed with psychotic disorder relative to T/T genotypes (OR 7.23). Also, individuals with the C/C genotypes who used cannabis had a higher risk of psychotic disorder than individuals who did not use cannabis (OR 2.18) [162••]. Other investigators [163••] have shown that those with the C/C AKT1 genotype who use cannabis showed poorer sustained attention than those with the T/T genotype. This was true even when cannabis use was remote (>12 months prior to testing). Recently, preliminary evidence has shown that another single-nucleotide polymorphism (SNP) of the *AKT1* gene (SNP rs1130233) may moderate the acute psychosis–cannabis interaction [164].

Recent studies have identified other candidate genes as playing a role in moderating the association between cannabis use and psychosis, including *BDNF* [165] and *DAT1* [164], which codes for a dopamine transporter that removes synaptic dopamine in striatal regions. In conclusion, there is emerging, but not robust, evidence of specific genetic polymorphisms interacting with cannabis exposure to confer a higher risk for the development of schizophrenia.

An emerging literature suggests that a history of childhood abuse may confer a higher risk of psychosis in individuals who use cannabis [166, 167]. In a longitudinal study, Konings and colleagues showed an interactive effect of history of childhood abuse and cannabis use in the development of psychosis [168]. Importantly, this study did not demonstrate that individuals with a prior history of child abuse were more likely to subsequently use cannabis. An interactive effect between childhood abuse and cannabis use on the development of psychosis was not supported in a recent study of a large set of individuals (N=1,923) followed longitudinally [169]. Vinkers et al. showed a three-way interaction between cannabis use, *COMT* genotype, and childhood abuse in moderating the risk for psychosis. Those who had Val/Val genotype were more likely to develop psychotic experiences when they had a history of cannabis use and childhood abuse than individuals with the Met/Met genotype [170]; a replication sample showed similar results but did not reach statistical significance. In a cross-sectional study, Alemany et al. similarly reported that individuals who had the Val/Val genotype and who had been exposed to childhood abuse were vulnerable to the psychosis-inducing effects of cannabis [171].

In summary, the specific genes *COMT* and *AKT1*, as well as a history of childhood abuse, may moderate the interaction between cannabis and psychosis. However, more research, especially of a prospective and longitudinal nature, is needed to better characterize the roles that these factors may play.

Table 2 Studies of the genetic–cannabis interaction

Gene/locus	Study	Study design	Sample size	Follow-up	Results
COMT/rs4680	Caspi et al., 2005 [154••]	Longitudinal, prospective (Dunedin cohort)	803	26 years	OR of developing psychotic disorder: 10.9 (95 % CI 2.2–54.1) for Val/Val genotype 2.5 (95 % CI 0.78–8.2) for Val/Met allele 1.1 (95 % CI 0.21–5.4) for Met/Met allele
COMT/rs4680	Zammit et al., 2011 [158]	Longitudinal (Avon cohort)	2,630	2 years	OR of psychosis in cannabis users: 1.56 (95 % CI 1.05–2.31) with Met/Met genotype 1.47(95 % CI 0.85–2.26) with Val/Val genotype 1.68 (95 % CI 1.23–-2.28) with Met/Val genotype OR 1.0 (95 % CI 0.73–1.36) of cannabis–COMT interaction
COMT/rs4680	Costas et al., 2011 [160]	Case-only, cross-sectional analysis	748	NA	OR 2.07 (95 % CI 1.27–3.26) of history of cannabis use in schizophrenia patients with Met/Met genotype vs. Val/Val genotype
COMT/rs4680	Estrada et al., 2011 [159]	Case–control, cross-sectional analysis	80 inpatients with schizophrenia 77 inpatients with non-psychotic psychiatric illness	NA	No difference in genotypes between diagnosis groups or between cannabis users and non-users AOP was 15.46 (SD 1.09) for Val/Val cannabis users AOP was 17.12 (SD 2.9) for Val/Met cannabis users AOP was 18.78 (4.01) for Met/Met cannabis users For effect of genotype on AOP, beta=1.66, SE=0.78, $p=0.04$
AKT1/rs2494732	van Winkel, 2011 [157••]	Cross-sectional analysis	801 subjects with psychosis 740 unaffected siblings 419 controls	NA	RR 1.90 ($p<0.01$) of C/C genotype in daily cannabis users: case-only analysis OR 1.96 (95 % CI 1.09–3.53) of being diagnosed with psychotic disorder in C/C allele subjects: case-sibling analysis OR 2.08 (95 % CI 0.92–4.67) of being diagnosed with psychotic disorder in C/C allele subjects: case–control analysis
AKT1/rs2494732	DiForte et al., 2012	Case–control, cross-sectional analysis	489 subjects 278 controls	NA	OR 7.23 (95 % CI 1.37–38.12) of psychotic disorder in C/C genotype subjects with daily cannabis use vs. T/T genotype OR 2.18 (95 % CI 1.12–4.31) of psychotic disorder in C/C genotype subjects with history of cannabis use

AOP age of onset of psychosis, *CI* confidence interval, *NA* not applicable, *OR* odds ratio, *RR* relative risk, *SD* standard deviation, *SE* standard error

Conclusions

In summary, exposure to cannabis is associated with a number of distinct syndromes, including (1) acute psychosis associated with cannabis intoxication; (2) acute psychosis that lasts beyond the period of acute intoxication; and (3) persistent psychotic disorders. Given the changing legal status of cannabis in the USA and elsewhere, research on the association of cannabis and psychosis (especially persistent psychotic disorders) has profound implications for public health and policy. As evidenced above, the cannabis–psychosis relationship fulfills many but not all of the traditional criteria for causality. The strength of association is modest but consistent; the relationship is biologically plausible, exhibits a dose–response effect, and, in most studies, persistent psychosis is preceded by cannabis use (though few studies have taken into account the time of onset of negative symptoms).

Similar to tobacco use and lung cancer, not everyone who has been exposed to cannabis develops a persistent psychotic disorder such as schizophrenia and not everyone diagnosed with schizophrenia has been exposed to cannabis. Therefore, cannabis exposure is neither necessary nor sufficient to "cause" a persistent psychotic disorder such as schizophrenia. More likely, cannabis may be a component cause that, in concert with known (specific genetic polymorphisms or history of childhood abuse) and unknown factors, contributes to the risk of schizophrenia.

As the pathophysiology of schizophrenia remains poorly understood, the role of cannabinoid exposure in contributing to the development of this disorder is significant and warrants further study. Additionally, further work is necessary to identify the factors that moderate cannabis-associated psychosis, especially with respect to persistent psychosis. Such research will lead to greater understanding of the biological mechanisms underlying individual vulnerability. The cumulative literature to date indicates that individuals with a family history of schizophrenia, individuals with prodromal symptoms, and individuals who have experienced discreet episodes of psychosis related to cannabis should be discouraged from using cannabis and cannabinoids.

Compliance with Ethics Guidelines

Conflict of Interest Deepak Cyril D'Souza, Rajiv Radhakrishnan, and Samuel T. Wilkinson have nothing to disclose.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Devane WA, Dysarz 3rd FA, Johnson MR, Melvin LS, Howlett AC. Determination and characterization of a cannabinoid receptor in rat brain. Mol Pharmacol. 1988;34(5):605–13.
2. Schatz AR, Lee M, Condie RB, Pulaski JT, Kaminski NE. Cannabinoid receptors CB1 and CB2: a characterization of expression and adenylate cyclase modulation within the immune system. Toxicol Appl Pharmacol. 1997;142(2):278–87.
3. Freund TF, Katona I, Piomelli D. Role of endogenous cannabinoids in synaptic signaling. Physiol Rev. 2003;83(3):1017–66.
4. Twitchell W, Brown S, Mackie K. Cannabinoids inhibit N- and P/Q-type calcium channels in cultured rat hippocampal neurons. J Neurophysiol. 1997;78(1):43–50.
5. Farkas I, Kallo I, Deli L, Vida B, Hrabovszky E, Fekete C, et al. Retrograde endocannabinoid signaling reduces GABAergic synaptic transmission to gonadotropin-releasing hormone neurons. Endocrinology. 2010;151(12):5818–29.
6. Bacci A, Huguenard JR, Prince DA. Long-lasting self-inhibition of neocortical interneurons mediated by endocannabinoids. Nature. 2004;431(7006):312–6.
7. Bodor AL, Katona I, Nyiri G, Mackie K, Ledent C, Hajos N, et al. Endocannabinoid signaling in rat somatosensory cortex: laminar differences and involvement of specific interneuron types. J Neurosci. 2005;25(29):6845–56.
8. Eggan SM, Melchitzky DS, Sesack SR, Fish KN, Lewis DA. Relationship of cannabinoid CB1 receptor and cholecystokinin immunoreactivity in monkey dorsolateral prefrontal cortex. Neuroscience. 2010;169(4):1651–61.
9. Hill EL, Gallopin T, Ferezou I, Cauli B, Rossier J, Schweitzer P, et al. Functional CB1 receptors are broadly expressed in neocortical GABAergic and glutamatergic neurons. J Neurophysiol. 2007;97(4):2580–9.
10. •• 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. *Study detailing the distribution of cannabinoid receptors in the brain*.
11. Katona I, Sperlagh B, Magloczky Z, Santha E, Kofalvi A, Czirjak S, et al. GABAergic interneurons are the targets of cannabinoid actions in the human hippocampus. Neuroscience. 2000;100(4):797–804.
12. Ali AB, Todorova M. Asynchronous release of GABA via tonic cannabinoid receptor activation at identified interneuron synapses in rat CA1. Eur J Neurosci. 2010;31(7):1196–207.
13. Foldy C, Neu A, Jones MV, Soltesz I. Presynaptic, activity-dependent modulation of cannabinoid type 1 receptor-mediated inhibition of GABA release. J Neurosci. 2006;26(5):1465–9.
14. Mechoulam R. Plant cannabinoids: a neglected pharmacological treasure trove. Br J Pharmacol. 2005;146(7):913–5.
15. Elsohly MA, Slade D. Chemical constituents of marijuana: The complex mixture of natural cannabinoids. Life Sci. 2005;78(5):539–48.
16. Russo EB. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. Br J Pharmacol. 2011;163(7):1344–64.
17. Compton DR, Johnson MR, Melvin LS, Martin BR. Pharmacological profile of a series of bicyclic cannabinoid analogs: classification as cannabimimetic agents. J Pharmacol Exp Ther. 1992;260(1):201–9.

18. Schubart CD, Sommer IE, Fusar-Poli P, de Witte L, Kahn RS, Boks MP. Cannabidiol as a potential treatment for psychosis. Eur Neuropsychopharmacol. 2014;24(1):51–64.
19. Morgan CJ, Curran HV. Effects of cannabidiol on schizophrenia-like symptoms in people who use cannabis. Br J Psychiatry. 2008;192(4):306–7.
20. Mechoulam, Hanus. In: Castle D, Murray R, editors. Marijuana and Madness. Cambridge: Cambridge University Press; 1994. p. 1–18: .
21. Solomons K, Neppe VM, Kuyl JM. Toxic cannabis psychosis is a valid entity. S Afr Med J. 1990;78(8):476–81.
22. Di Forti M, Morgan C, Dazzan P, Pariante C, Mondelli V, Marques TR, et al. High-potency cannabis and the risk of psychosis. Br J Psychiatry. 2009;195(6):488–91.
23. Rottanburg D, Robins AH, Ben-Arie O, Teggin A, Elk R. Cannabis-associated psychosis with hypomanic features. Lancet. 1982;2(8312):1364–6.
24. Solomons K, Neppe VM. Cannabis–its clinical effects. S Afr Med J. 1989;76(3):102–4.
25.•• D'Souza DC, Perry E, MacDougall L, Ammerman Y, Cooper T, Wu YT, et al. The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. Neuropsychopharmacology. 2004;29(8):1558–72. *A randomized, double-blind, placebo-controlled, crossover study showing that THC can induce a range of positive, negative, and cognitive symptoms in healthy individuals that bear some resemblance to the symptoms of schizophrenia.*
26. Englund A, Morrison PD, Nottage J, Hague D, Kane F, Bonaccorso S, et al. Cannabidiol inhibits THC-elicited paranoid symptoms and hippocampal-dependent memory impairment. J Psychopharmacol. 2013;27(1):19–27.
27. Sherrica T, Fantegrossi WE. Synthetic Cannabinoids: Pharmacology, Behavioral Effects and Abuse Potential. Curr Addict Rep. In Press
28. Warnock J. Insanity from hasheesh. J Mental Sci. 1903;49:96–110.
29.•• Radhakrishnan R AP, Sewell RA, Skosnik PD, Ranganathan M, D'Souza DC. Cannabis, Cannabinoids and the link with psychosis. In: Madras B, Kuhar MJ, editors. The Effects of Drug Abuse on the Human Nervous System. San Diego,CA: Academic Press (Elsevier); 2014. p. 423–74. *Comprehensive review of the association between cannabis use and psychosis*.
30. Green B, Kavanagh D, Young R. Being stoned: a review of self-reported cannabis effects. Drug Alcohol Rev. 2003;22(4):453–60.
31. 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.
32. Brewer TL, Collins M. A review of clinical manifestations in adolescent and young adults after use of synthetic cannabinoids. J Spec Pediatr Nurs. Epub 2013 Dec 10.
33. Spaderna M, Addy PH, D'Souza DC. Spicing things up: synthetic cannabinoids. Psychopharmacology (Berl). 2013;228(4):525–40.
34. Morrison PD, Zois V, McKeown DA, Lee TD, Holt DW, Powell JF, et al. The acute effects of synthetic intravenous Delta9-tetrahydrocannabinol on psychosis, mood and cognitive functioning. Psychol Med. 2009;39(10):1607–16.
35. 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.
36. 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. 1999;142(3):230–5.
37. Sewell RA, Schnakenberg A, Elander J, Radhakrishnan R, Williams A, Skosnik PD, et al. Acute effects of THC on time perception in frequent and infrequent cannabis users. Psychopharmacology (Berl). 2013;226(2):401–13.
38.•• D'Souza DC, Abi-Saab WM, Madonick S, Forselius-Bielen K, Doersch A, Braley G, et al. Delta-9-tetrahydrocannabinol effects in schizophrenia: implications for cognition, psychosis, and addiction. Biol Psychiatry. 2005;57(6):594–608. *The only randomized, double-blind, placebo-controlled, crossover study showing that THC exacerbates symptoms in chronic, stable, medicated schizophrenia patients and that schizophrenia patients are more vulnerable to the effects of THC.*
39. 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.
40. Roser P, Juckel G, Rentzsch J, Nadulski T, Gallinat J, Stadelmann AM. Effects of acute oral Delta(9)-tetrahydrocannabinol and standardized cannabis extract on the auditory P300 event-related potential in healthy volunteers. Eur Neuropsychopharmacol. 2008;18(8):569–77.
41. D'Souza DC, Fridberg DJ, Skosnik PD, Williams A, Roach B, Singh N, et al. Dose-Related Modulation of Event-Related Potentials to Novel and Target Stimuli by Intravenous Delta(9)-THC in Humans. Neuropsychopharmacology. 2012;37(7):1632–46.
42. van der Meer L, de Vos AE, Stiekema AP, Pijnenborg GH, van Tol MJ, Nolen WA, et al. Insight in schizophrenia: involvement of self-reflection networks? Schizophr Bull. 2013;39(6):1288–95.
43. Spronk D, Dumont GJ, Verkes RJ, de Bruijn ER. Acute effects of delta-9-tetrahydrocannabinol on performance monitoring in healthy volunteers. Front Behav Neurosci. 2011;5:59.
44. Uhlhaas PJ, Singer W. Abnormal neural oscillations and synchrony in schizophrenia. Nat Rev Neurosci. 2010;11(2):100–13.
45. Singer W. Neuronal synchrony: a versatile code for the definition of relations? Neuron. 1999;24(1):49–65. *111–25*.
46. Whittington MA, Faulkner HJ, Doheny HC, Traub RD. Neuronal fast oscillations as a target site for psychoactive drugs. Pharmacol Ther. 2000;86(2):171–90.
47. Melloni L, Molina C, Pena M, Torres D, Singer W, Rodriguez E. Synchronization of neural activity across cortical areas correlates with conscious perception. J Neurosci. 2007;27(11):2858–65.
48. Uhlhaas PJ, Pipa G, Lima B, Melloni L, Neuenschwander S, Nikolic D, et al. Neural synchrony in cortical networks: history, concept and current status. Front Integr Neurosci. 2009;3:17.
49. Wang XJ. Neurophysiological and computational principles of cortical rhythms in cognition. Physiol Rev. 2010;90(3):1195–268.
50. Katona I, Sperlagh B, Sik A, Kafalvi A, Vizi ES, Mackie K, et al. Presynaptically located CB1 cannabinoid receptors regulate GABA release from axon terminals of specific hippocampal interneurons. J Neurosci. 1999;19(11):4544–58.
51. Hajos N, Katona I, Naiem SS, MacKie K, Ledent C, Mody I, et al. Cannabinoids inhibit hippocampal GABAergic transmission and network oscillations. Eur J Neurosci. 2000;12(9):3239–49.
52. Morgan NH, Stanford IM, Woodhall GL. Modulation of network oscillatory activity and GABAergic synaptic transmission by CB1 cannabinoid receptors in the rat medial entorhinal cortex. Neural Plasticity. 2008;2008:808564.
53. Robbe D, Montgomery SM, Thome A, Rueda-Orozco PE, McNaughton BL, Buzsaki G. Cannabinoids reveal importance of spike timing coordination in hippocampal function. Nat Neurosci. 2006;9(12):1526–33.
54. Reich CG, Karson MA, Karnup SV, Jones LM, Alger BE. Regulation of IPSP theta rhythm by muscarinic receptors and endocannabinoids in hippocampus. J Neurophysiol. 2005;94(6):4290–9.
55. 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.

56. Sales-Carbonell C, Rueda-Orozco PE, Soria-Gomez E, Buzsaki G, Marsicano G, Robbe D. Striatal GABAergic and cortical glutamatergic neurons mediate contrasting effects of cannabinoids on cortical network synchrony. Proc Natl Acad Sci USA. 2013;110(2):719–24.
57. Bocker KB, Hunault CC, Gerritsen J, Kruidenier M, Mensinga TT, Kenemans JL. Cannabinoid modulations of resting state EEG theta power and working memory are correlated in humans. J Cogn Neurosci. 2010;22(9):1906–16.
58. Bhattacharyya S, Morrison PD, Fusar-Poli P, Martin-Santos R, Borgwardt S, Winton-Brown T, et al. Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. Neuropsychopharmacology. 2010;35(3):764–74.
59. Bossong MG, Jansma JM, Bhattacharyya S, Ramsey NF. Role of the endocannabinoid system in brain functions relevant for schizophrenia: An overview of human challenge studies with cannabis or 9-tetrahydrocannabinol (THC). Prog Neuropsychopharmacol Biol Psychiatry. Epub 2013 Dec 29.
60.• Bhattacharyya S, Crippa JA, Allen P, Martin-Santos R, Borgwardt S, Fusar-Poli P, et al. Induction of psychosis by Delta9-tetrahydrocannabinol reflects modulation of prefrontal and striatal function during attentional salience processing. Arch Gen Psychiatry. 2012;69(1):27–36. *Controlled laboratory imaging study showing the brain activation patterns associated with the psychotomimetic effects of THC.*
61. Atakan Z, Bhattacharyya S, Allen P, Martin-Santos R, Crippa JA, Borgwardt SJ, et al. Cannabis affects people differently: inter-subject variation in the psychotogenic effects of Delta9-tetrahydrocannabinol: a functional magnetic resonance imaging study with healthy volunteers. Psychol Med. 2013;43(6):1255.
62. Kuepper R, Ceccarini J, Lataster J, van Os J, van Kroonenburgh M, van Gerven JM, et al. Delta-9-tetrahydrocannabinol-induced dopamine release as a function of psychosis risk: 18 F-fallypride positron emission tomography study. PloS One. 2013;8(7):e70378.
63. Laruelle M. Schizophrenia: from dopaminergic to glutamatergic interventions. Curr Opin Pharmacol. 2014;14c:97–102.
64. Bossong MG, van Berckel BN, Boellaard R, Zuurman L, Schuit RC, Windhorst AD, et al. Delta 9-tetrahydrocannabinol induces dopamine release in the human striatum. Neuropsychopharmacology. 2009;34(3):759–66.
65. Barkus E, Morrison PD, Vuletic D, Dickson JC, Ell PJ, Pilowsky LS, et al. Does intravenous Delta9-tetrahydrocannabinol increase dopamine release? A SPET study. J Psychopharmacol. 2011;25(11):1462–8.
66. Stokes PR, Mehta MA, Curran HV, Breen G, Grasby PM. Can recreational doses of THC produce significant dopamine release in the human striatum? NeuroImage. 2009;48(1):186–90.
67. D'Souza DC, Braley G, Blaise R, Vendetti M, Oliver S, Pittman B, et al. Effects of haloperidol on the behavioral, subjective, cognitive, motor, and neuroendocrine effects of Delta-9-tetrahydrocannabinol in humans. Psychopharmacology (Berl). 2008;198(4):587–603.
68. Liem-Moolenaar M, te Beek ET, de Kam ML, Franson KL, Kahn RS, Hijman R, et al. Central nervous system effects of haloperidol on THC in healthy male volunteers. J Psychopharmacol. 2010;24(11):1697–708.
69. Kleinloog D, Liem-Moolenaar M, Jacobs G, Klaassen E, de Kam M, Hijman R, et al. Does olanzapine inhibit the psychomimetic effects of Delta(9)-tetrahydrocannabinol? J Psychopharmacol. 2012;26(10):1307–16.
70.•• Arendt M, Rosenberg R, Foldager L, Perto G, Munk-Jorgensen P. Cannabis-induced psychosis and subsequent schizophrenia-spectrum disorders: follow-up study of 535 incident cases. Br J Psychiatry. 2005;187:510–5. *A retrospective review and follow-up of patients initially diagnosed with cannabis-induced psychosis who converted to schizophrenia.*
71. Bernhardson G, Gunne LM. Forty-six cases of psychosis in cannabis abusers. Int J Addict. 1972;7(1):9–16.
72. Harding T, Knight F. Marihuana-modified mania. Arch Gen Psychiatry. 1973;29(5):635–7.
73. Mathers DC, Ghodse AH, Caan AW, Scott SA. Cannabis use in a large sample of acute psychiatric admissions. Br J Addict. 1991;86(6):779–84.
74. Carney MW, Bacelle L, Robinson B. Psychosis after cannabis abuse. Br Med J (Clin Res Ed). 1984;288(6423):1047.
75. Talbott JA, Teague JW. Marihuana psychosis: Acute toxic psychosis associated with the use of cannabis derivatives. JAMA. 1969;210:299–302.
76. Tennant FS, Groesbeck CJ. Psychiatric effects of hashish. Arch Gen Psychiatry. 1972;27:133–6.
77. Wylie AS, Scott RT, Burnett SJ. Psychosis due to "skunk". BMJ. 1995;311(6997):125.
78. Basu D, Malhotra A, Bhagat A, Varma VK. Cannabis psychosis and acute schizophrenia. A case–control study from India. Eur Addict Res. 1999;5(2):71–3.
79. Chaudry HR, Moss HB, Bashir A, Suliman T. Cannabis psychosis following bhang ingestion. Br J Addict. 1991;86(9):1075–81.
80. Cohen SI. Cannabis consumption and schizophrenia. Br J Psychiatry. 1994;165(3):410–1.
81. Thacore VR. Bhang psychosis. Br J Psychiatry. 1973;123(573):225–9.
82. Thacore VR, Shukla SR. Cannabis psychosis and paranoid schizophrenia. Arch Gen Psychiatry. 1976;33(3):383–6.
83. Talbott JA, Teague JW. Marihuana psychosis. Acute toxic psychosis associated with the use of Cannabis derivatives JAMA. 1969;210(2):299–302.
84. Kolansky H, Moore WT. Effects of marihuana on adolescents and young adults. JAMA. 1971;216(3):486–92.
85. Hall W, Solowij N. Adverse effects of cannabis. Lancet. 1998;352(9140):1611–6.
86. Aggarwal M, Banerjee A, Singh SM, Mattoo SK, Basu D. Substance-induced psychotic disorders: 13-year data from a de-addiction centre and their clinical implications. Asian J Psychiatr. 2012;5(3):220–4.
87. Niemi-Pynttari JA, Sund R, Putkonen H, Vorma H, Wahlbeck K, Pirkola SP. Substance-induced psychoses converting into schizophrenia: a register-based study of 18,478 Finnish inpatient cases. J Clin Psychiatry. 2013;74(1):e94–9.
88. Pihlajamaa J, Suvisaari J, Henriksson M, Heila H, Karjalainen E, Koskela J, et al. The validity of schizophrenia diagnosis in the Finnish Hospital Discharge Register: findings from a 10-year birth cohort sample. Nord J Psychiatry. 2008;62(3):198–203.
89. Rounsaville BJ. DSM-V research agenda: substance abuse/psychosis comorbidity. Schizophr Bull. 2007;33(4):947–52.
90.• D'Souza DC. Cannabinoids and psychosis. Int Rev Neurobiol. 2007;78:289–326. *Review of epidemiological and neurobiological evidence for the association of cannabis and psychosis, including a possible causal role.*
91.•• Andreasson S, Allebeck P, Engstrom A, Rydberg U. Cannabis and schizophrenia. A longitudinal study of Swedish conscripts. Lancet. 1987;2(8574):1483–6. *One of the first epidemiological studies (N > 50,000) showing an association between cannabis exposure and risk of psychosis.*
92.•• 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. *A follow-up of the Swedish military cohort (N > 50,000), in response to hypotheses that the cannabis–psychosis association could be explained by other drugs or personality traits.*

93.•• Manrique-Garcia E, Zammit S, Dalman C, Hemmingsson T, Andreasson S, Allebeck P. Cannabis, schizophrenia and other non-affective psychoses: 35 years of follow-up of a population-based cohort. Psychol Med. 2012;42(6):1321–8. *Additional follow-up at 35 years of the Swedish military cohort, confirming an increased risk of psychosis for early and heavy cannabis users.*

94.• 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. *One of the first prospective cohort studies showing an association between early cannabis exposure and risk for psychosis.*

95. 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.

96. Kuepper R, van Os J, Lieb R, Wittchen HU, Hofler M, Henquet C. Continued cannabis use and risk of incidence and persistence of psychotic symptoms: 10 year follow-up cohort study. BMJ (Clin Res Ed). 2011;342:d738.

97. Fergusson DM, Horwood LJ, Ridder EM. Tests of causal linkages between cannabis use and psychotic symptoms. Addiction (Abingdon, England). 2005;100(3):354–66.

98. Arseneault L, Cannon M, Witton J, Murray RM. Causal association between cannabis and psychosis: examination of the evidence.[see comment]. Br J Psychiatry. 2004;184:110–7.

99.•• Moore TH, Zammit S, Lingford-Hughes A, Barnes TR, Jones PB, Burke M, et al. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. Lancet. 2007;370(9584):319–28. *A systematic review of the association between cannabis and psychosis and cannabis and affective disorders.*

100. 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.

101.•• Gage SH, Zammit S, Hickman M. Stronger evidence is needed before accepting that cannabis plays an important role in the aetiology of schizophrenia in the population. F1000 Med Rep. 2013;5(2). Brief review suggesting that, while important neurobiologically, there is still much unkown with regards to the cannabis–schizophrenia connection.

102. Dragt S, Nieman DH, Schultze-Lutter F, van der Meer F, Becker H, de Haan L, et al. Cannabis use and age at onset of symptoms in subjects at clinical high risk for psychosis. Acta Psychiatr Scand. 2012;125(1):45–53.

103. Schimmelmann BG, Conus P, Cotton SM, Kupferschmid S, Karow A, Schultze-Lutter F, et al. Cannabis use disorder and age at onset of psychosis–a study in first-episode patients. Schizophr Res. 2011;129(1):52–6.

104. Cunha PJ, Rosa PG, Ayres Ade M, Duran FL, Santos LC, Scazufca M, et al. Cannabis use, cognition and brain structure in first-episode psychosis. Schizophr Res. 2013;147(2–3):209–15.

105. Allebeck P, Adamsson C, Engstrom A, Rydberg U. Cannabis and schizophrenia: a longitudinal study of cases treated in Stockholm County [erratum appears in Acta Psychiatr Scand 1993 Oct;88(4):304]. Acta Psychiatr Scand. 1993;88(1):21–4.

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

107. Hambrecht M, Hafner H. Substance abuse and the onset of schizophrenia. Biological Psychiatry. 1996;40(11):1155–63.

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

109.•• Large M, Sharma S, Compton MT, Slade T, Nielssen O. Cannabis use and earlier onset of psychosis: a systematic meta-analysis. Arch Gen psychiatry. 2011;68(6):555–61. *Systematic meta-analysis evaluating 83 studies that investigate the association with cannabis use on the age of onset of psychosis.*

110. Gonzalez-Pinto A, Alberich S, Barbeito S, Gutierrez M, Vega P, Ibanez B, et al. Cannabis and first-episode psychosis: different long-term outcomes depending on continued or discontinued use. Schizophr Bull. 2011;37(3):631–9.

111. Griffith-Lendering MF, Wigman JT. Prince van Leeuwen A, Huijbregts SC, Huizink AC, Ormel J, et al. Cannabis use and vulnerability for psychosis in early adolescence–a TRAILS study. Addiction. 2013;108(4):733–40.

112. Davis GP, Compton MT, Wang S, Levin FR, Blanco C. Association between cannabis use, psychosis, and schizotypal personality disorder: findings from the National Epidemiologic Survey on Alcohol and Related Conditions. Schizophr Res. 2013;151(1–3):197–202.

113. Crews F, He J, Hodge C. Adolescent cortical development: a critical period of vulnerability for addiction. Pharmacol Biochem Behav. 2007;86(2):189–99.

114.•• Galve-Roperh I, Aguado T, Palazuelos J, Guzman M. The endocannabinoid system and neurogenesis in health and disease. Neuroscientist. 2007;13(2):109–14. *Concise review on the neurobiological role of the endocannabinoid system*.

115. Mulder J, Aguado T, Keimpema E, Barabas K, Ballester Rosado CJ, Nguyen L, et al. Endocannabinoid signaling controls pyramidal cell specification and long-range axon patterning. Proc Natl Acad Sci U S A. 2008;105(25):8760–5.

116. Watson S, Chambers D, Hobbs C, Doherty P, Graham A. The endocannabinoid receptor, CB1, is required for normal axonal growth and fasciculation. Mol Cell Neurosci. 2008;38(1):89–97.

117. Berghuis P, Dobszay MB, Wang X, Spano S, Ledda F, Sousa KM, et al. Endocannabinoids regulate interneuron migration and morphogenesis by transactivating the TrkB receptor. Proc Natl Acad Sci U S A. 2005;102(52):19115–20.

118. Berghuis P, Rajnicek AM, Morozov YM, Ross RA, Mulder J, Urban GM, et al. Hardwiring the brain: endocannabinoids shape neuronal connectivity. Science. 2007;316(5828):1212–6.

119. Aguado T, Palazuelos J, Monory K, Stella N, Cravatt B, Lutz B, et al. The endocannabinoid system promotes astroglial differentiation by acting on neural progenitor cells. J Neurosci. 2006;26(5):1551–61.

120.• Harkany T, Guzman M, Galve-Roperh I, Berghuis P, Devi LA, Mackie K. The emerging functions of endocannabinoid signaling during CNS development. Trends Pharmacol Sci. 2007;28(2):83–92. *A review of the role that the endocannabinoid system plays in brain development.*

121. Fernandez-Ruiz J, Berrendero F, Hernandez ML, Ramos JA. The endogenous cannabinoid system and brain development. Trends Neurosci. 2000;23(1):14–20.

122. Jin K, Xie L, Kim SH, Parmentier-Batteur S, Sun Y, Mao XO, et al. Defective adult neurogenesis in CB1 cannabinoid receptor knockout mice. Mol Pharmacol. 2004;66(2):204–8.

123. Ruiz-Veguilla M, Barrigon ML, Hernandez L, Rubio JL, Gurpegui M, Sarramea F, et al. Dose–response effect between cannabis use and psychosis liability in a non-clinical population: evidence from a snowball sample. J Psychiatr Res. 2013;47(8):1036–43.

124. O'Shea M, Singh ME, McGregor IS, Mallet PE. Chronic cannabinoid exposure produces lasting memory impairment and increased anxiety in adolescent but not adult rats. J Psychopharmacol. 2004;18(4):502–8.

125. Quinn HR, Matsumoto I, Callaghan PD, Long LE, Arnold JC, Gunasekaran N, et al. Adolescent rats find repeated Delta(9)-THC less aversive than adult rats but display greater residual cognitive deficits and changes in hippocampal protein

expression following exposure. Neuropsychopharmacology. 2008;33(5):1113–26.
126. Cha YM, White AM, Kuhn CM, Wilson WA, Swartzwelder HS. Differential effects of delta9-THC on learning in adolescent and adult rats. Pharmacol Biochem Behav. 2006;83(3):448–55.
127. Schneider M, Schomig E, Leweke FM. Acute and chronic cannabinoid treatment differentially affects recognition memory and social behavior in pubertal and adult rats. Addict Biol. 2008;13(3–4):345–57.
128. Schneider M. Puberty as a highly vulnerable developmental period for the consequences of cannabis exposure. Addict Biol. 2008;13(2):253–63.
129. Stefanis NC, Dragovic M, Power BD, Jablensky A, Castle D, Morgan VA. Age at initiation of cannabis use predicts age at onset of psychosis: the 7- to 8-year trend. Schizophr Bull. 2013;39(2):251–4.
130. Myles N, Newall H, Compton MT, Curtis J, Nielssen O, Large M. The age at onset of psychosis and tobacco use: a systematic meta-analysis. Soc Psychiatry Psychiatr Epidemiol. 2012;47(8):1243–50.
131. Pope Jr HG, Gruber AJ, Yurgelun-Todd D. Residual neuropsychologic effects of cannabis. Curr Psychiatry Rep. 2001;3(6):507–12.
132. 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. 2006;185(3):358–68.
133.•• Pope Jr HG, Gruber AJ, Hudson JI, Huestis MA, Yurgelun-Todd D. Neuropsychological performance in long-term cannabis users. Arch Gen Psychiatry. 2001;58(10):909–15. *One of the first studies showing the resolution of cognitive deficits with abstinence from cannnabis.*
134. Fried PA, Watkinson B, Gray R. Neurocognitive consequences of marihuana–a comparison with pre-drug performance. Neurotoxicol Teratol. 2005;27(2):231–9.
135. Solowij N. Do cognitive impairments recover following cessation of cannabis use? Life Sci. 1995;56(23–24):2119–26.
136. Crean RD, Crane NA, Mason BJ. An evidence based review of acute and long-term effects of cannabis use on executive cognitive functions. J Addict Med. 2011;5(1):1–8.
137. Lyons MJ, Bar JL, Panizzon MS, Toomey R, Eisen S, Xian H, et al. Neuropsychological consequences of regular marijuana use: a twin study. Psychol Med. 2004;34(7):1239–50.
138. Pope Jr HG, Gruber AJ, Hudson JI, Cohane G, Huestis MA, Yurgelun-Todd D. Early-onset cannabis use and cognitive deficits: what is the nature of the association? Drug Alcohol Depend. 2003;69(3):303–10.
139. Pope Jr HG, Gruber AJ, Hudson JI, Huestis MA, Yurgelun-Todd D. Cognitive measures in long-term cannabis users. J Clin Pharmacol. 2002;42(11 Suppl):41S–7S.
140. Pope Jr HG. Cannabis, cognition, and residual confounding. JAMA. 2002;287(9):1172–4.
141. Verdejo-Garcia AJ, Lopez-Torrecillas F. Aguilar de Arcos F, Perez-Garcia M. Differential effects of MDMA, cocaine, and cannabis use severity on distinctive components of the executive functions in polysubstance users: a multiple regression analysis. Addict Behav. 2005;30(1):89–101.
142. Bolla KI, Brown K, Eldreth D, Tate K, Cadet JL. Dose-related neurocognitive effects of marijuana use. Neurology. 2002;59(9):1337–43.
143. Verdejo-Garcia A, Bechara A, Recknor EC, Perez-Garcia M. Executive dysfunction in substance dependent individuals during drug use and abstinence: an examination of the behavioral, cognitive and emotional correlates of addiction. J Int Neuropsychol Soc. 2006;12(3):405–15.
144.•• Meier MH, Caspi A, Ambler A, Harrington H, Houts R, Keefe RS, et al. Persistent cannabis users show neuropsychological decline from childhood to midlife. Proc Nat Acad Sci U S A. 2012;109(40):E2657–64. *A longitudinal, prospective population-based sample investigating the association of cannabis use and IQ.*
145. Fontes MA, Bolla KI, Cunha PJ, Almeida PP, Jungerman F, Laranjeira RR, et al. Cannabis use before age 15 and subsequent executive functioning. Br J Psychiatry. 2011;198(6):442–7.
146. Millman RB, Sbriglio R. Patterns of use and psychopathology in chronic marijuana users. Psychiatr Clin North Am. 1986;9(3):533–45.
147. Halikas J, Weller R, Morse C. Effects of regular marijuana use on sexual performance. J Psychoactive Drugs. 1982;14(1–2):59–70.
148. Kolansky H, Moore WT. Effects of marihuana on adolescents and young adults. J Psychiatr Nurs Ment Health Serv. 1971;9(6):9–16.
149. Rovai L, Maremmani AG, Pacini M, Pani PP, Rugani F, Lamanna F, et al. Negative dimension in psychiatry. Amotivational syndrome as a paradigm of negative symptoms in substance abuse. Riv Psichiatr. 2013;48(1):1–9.
150. Hollister LE. Cannabis–1988. Acta Psychiatr Scand Suppl. 1988;345:108–18.
151. Bersani G, Orlandi V, Kotzalidis G, Pancheri P. Cannabis and schizophrenia: impact on onset, course, psychopathology and outcomes. Eur Arch Psychiatry Clin Neurosci. 2002;252(2):86–92.
152. Compton MT, Furman AC, Kaslow NJ. Lower negative symptom scores among cannabis-dependent patients with schizophrenia-spectrum disorders: preliminary evidence from an African American first-episode sample. Schizophr Res. 2004;71(1):61–4.
153. Tunbridge EM, Harrison PJ, Weinberger DR. Catechol-*o*-Methyltransferase, Cognition, and Psychosis: Val^{158} Met and Beyond. Biologic Psychiatry. 2006;60(2):141–51.
154.•• Caspi A, Moffitt TE, Cannon M, McClay J, Murray R, Harrington H, et al. 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. Biologic Psychiatry. 2005;57(10):1117–27. *The first study investigating the gene COMT as a possible moderator of the cannabis–psychosis association; a prospective population-based cohort.*
155. Zammit S, Spurlock G, Williams H, Norton N, Williams N, O'Donovan MC, et al. Genotype effects of CHRNA7, CNR1 and COMT in schizophrenia: interactions with tobacco and cannabis use. Br J Psychiatry. 2007;191:402–7.
156. Kantrowitz JT, Nolan KA, Sen S, Simen AA, Lachman HM, Bowers Jr MB. Adolescent cannabis use, psychosis and catechol-O-methyltransferase genotype in African Americans and Caucasians. Psychiatr Q. 2009;80(4):213–8.
157.•• van Winkel R. Family-based analysis of genetic variation underlying psychosis-inducing effects of cannabis: sibling analysis and proband follow-up. Arch Gen Psychiatry. 2011;68(2):148–57. *The first study suggesting a role for AKT1 in moderating the risk of psychosis associated with cannabis use.*
158. Zammit S, Owen MJ, Evans J, Heron J, Lewis G. Cannabis, COMT and psychotic experiences. Br J Psychiatry. 2011;199(5):380–5.
159. Estrada G, Fatjo-Vilas M, Munoz MJ, Pulido G, Minano MJ, Toledo E, et al. Cannabis use and age at onset of psychosis: further evidence of interaction with COMT Val158Met polymorphism. Acta Psychiatr Scand. 2011;123(6):485–92.
160. Costas J, Sanjuan J, Ramos-Rios R, Paz E, Agra S, Tolosa A, et al. Interaction between COMT haplotypes and cannabis in schizophrenia: a case-only study in two samples from Spain. Schizophr Res. 2011;127(1–3):22–7.
161. Sánchez MG. Ruiz-Llorente L, Sánchez AM, Díaz-Laviada I. Activation of phosphoinositide 3-kinase/PKB pathway by CB_1 and CB_2 cannabinoid receptors expressed in prostate PC-3 cells. Involvement in Raf-1 stimulation and NGF induction. Cellular signalling. 2003;15(9):851–9.

162.•• Di Forti M, Iyegbe C, Sallis H, Kolliakou A, Falcone MA, Paparelli A, et al. Confirmation that the AKT1 (rs2494732) genotype influences the risk of psychosis in cannabis users. Biological psychiatry. 2012;72(10):811–6. *A case–control study confirming a possible role for the gene AKT1 as a moderator of the cannabis–psychosis interaction.*

163.•• van Winkel R, van Beveren NJ, Simons C. AKT1 moderation of cannabis-induced cognitive alterations in psychotic disorder. Neuropsychopharmacology. 2011;36(12):2529–37. *A case–control study suggesting a role for AKT1 polymorphisms in conferring vulnerability to cannabis-associated risk of psychotic disorder.*

164. Bhattacharyya S, Atakan Z, Martin-Santos R, Crippa JA, Kambeitz J, Prata D, et al. Preliminary report of biological basis of sensitivity to the effects of cannabis on psychosis: AKT1 and DAT1 genotype modulates the effects of delta-9-tetrahydrocannabinol on midbrain and striatal function. Mol Psychiatry. 2012;17(12):1152–5.

165. Decoster J, van Os J, Kenis G, Henquet C, Peuskens J, De Hert M, et al. Age at onset of psychotic disorder: cannabis, BDNF Val66Met, and sex-specific models of gene-environment interaction. Am J Med Genet B Neuropsychiatr Genet. 2011;156B(3):363–9.

166. Houston JE, Murphy J, Adamson G, Stringer M, Shevlin M. Childhood sexual abuse, early cannabis use, and psychosis: testing an interaction model based on the National Comorbidity Survey. Schizophr Bull. 2008;34(3):580–5.

167. Harley M, Kelleher I, Clarke M, Lynch F, Arseneault L, Connor D, et al. Cannabis use and childhood trauma interact additively to increase the risk of psychotic symptoms in adolescence. Psychol Med. 2010;40(10):1627–34.

168. Konings M, Stefanis N, Kuepper R, de Graaf R, ten Have M, van Os J, et al. Replication in two independent population-based samples that childhood maltreatment and cannabis use synergistically impact on psychosis risk. Psychol Med. 2012;42(1):149–59.

169. Kuepper R, Henquet C, Lieb R, Wittchen HU, van Os J. Non-replication of interaction between cannabis use and trauma in predicting psychosis. Schizophr Res. 2011;131(1–3):262–3.

170. Vinkers CH, Van Gastel WA, Schubart CD, Van Eijk KR, Luykx JJ, Van Winkel R, et al. The effect of childhood maltreatment and cannabis use on adult psychotic symptoms is modified by the COMT Val^{158}Met polymorphism. Schizophr Res. 2013;150(1):303–11.

171. Alemany S, Arias B, Fatjo-Vilas M, Villa H, Moya J, Ibanez MI, et al. Psychosis-inducing effects of cannabis are related to both childhood abuse and COMT genotypes. Acta Psychiatr Scand. 2014;129(1):54–62.