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Invited review

# Cannabis-associated psychosis: Neural substrate and clinical impact

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ABSTRACT

Prospective epidemiological studies have consistently demonstrated that cannabis use is associated with an increased subsequent risk of both psychotic symptoms and schizophrenia-like psychoses. Early onset of use, daily use of high-potency cannabis, and synthetic cannabinoids carry the greatest risk. The risk-increasing effects are not explained by shared genetic predisposition between schizophrenia and cannabis use. Experimental studies in healthy humans show that cannabis and its active ingredient, delta-9-tetrahydrocannabinol (THC), can produce transient, dose-dependent, psychotic symptoms, as well as an array of psychosis-relevant behavioral, cognitive and psychophysiological effects; the psychotogenic effects can be ameliorated by cannabidiol (CBD). Findings from structural imaging studies in cannabis users have been inconsistent but functional MRI studies have linked the psychotomimetic and cognitive effects of THC to activation in brain regions implicated in psychosis. Human PET studies have shown that acute administration of THC weakly releases dopamine in the striatum but that chronic users are characterised by low striatal dopamine. We are beginning to understand how cannabis use impacts on the endocannabinoid system but there is much still to learn about the biological mechanisms underlying how cannabis increases risk of psychosis.

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**Contents**



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## 1. Introduction

In this review, we will consider the relationship between cannabis and psychosis. We will commence with epidemiological evidence concerning whether cannabis use can induce schizophrenia-like psychosis and then proceed to consider human laboratory studies exploring the acute psychotogenic effects of cannabinoids. Then we will discuss if there are structural, neurochemical or functional brain changes associated with cannabis use and with cannabis-associated psychosis. Finally, we will consider the status of the endogenous cannabinoid system in schizophrenia and how it may be affected by exogenous cannabinoids.

At the outset, it is important to distinguish between psychotic symptoms and a clinical psychotic disorder. Psychotic symptoms include disorganized thinking and speech, delusions, and hallucinations. A psychotic disorder is a clinical condition characterized by more persistent psychotic symptoms and often accompanied by other deficits. The symptoms of schizophrenia, the most severe of the psychotic disorders, include not just positive psychotic symptoms, but often also negative symptoms (amotivation, social withdrawal, and emotional blunting) and cognitive deficits (impairments in memory, attention and executive function). By definition people diagnosed as having clinical psychotic disorders, necessarily show psychotic symptoms. Psychotic symptoms can also present in a variety of other disorders e.g. Alzheimer's Disease or depression, and not uncommonly occur in the absence of a clinical disorder.

## 2. Cannabis use and persistent psychotic disorder

### 2.1. Epidemiological evidence

The literature concerning whether use of cannabis increases the risk of persistent psychosis is extensive. As there have been several recent reviews of the epidemiological studies (Gage et al., 2016; Murray and Di Forti, 2016; Murray et al., 2016), we will provide just a short discussion, focusing on new and controversial issues.

The first study to prospectively examine whether cannabis plays a causal role in psychosis was carried out among conscripts to the Swedish Military (Andréasson et al., 1987). Now there have been 13 such longitudinal studies (Table 1). Ten found that cannabis use was associated with a significantly increased risk of the subsequent development of psychotic symptoms or psychotic illness (Arseneault et al., 2002; van Os et al., 2002; Weiser et al., 2002; Zammit et al., 2002; Fergusson et al., 2003; Ferdinand et al., 2005; Henquet et al., 2005; Manrique-Garcia et al., 2012; Rognli et al., 2015; Tien and Anthony, 1990; Bechtold et al., 2016); the other three showed a trend in the same direction (Wiles et al., 2006; Rössler et al., 2012; Gage et al., 2014).

Marconi et al. (2016) carried out a meta-analysis to quantify the magnitude of the effect. There was a dose-response relationship with the risk increasing with the more cannabis consumed; the odds ratio for risk of psychosis-related outcomes reached almost four among the heaviest users compared to the non-users.

Psychotic patients who use cannabis have an earlier illness onset than those who do not (Large et al., 2011). They are also have higher IQ than non-users (Arnold et al., 2015; Løberg et al., 2014) as well as higher premorbid IQ and better premorbid social function (Ferraro et al., 2013); cannabis using patients are less likely to show neurological soft signs (Ruiz-Veguilla et al., 2012) than non-using patients. A possible explanation is that many non-drug-using schizophrenic patients show neurodevelopmental impairment with poor premorbid cognition and social function. In contrast, the cannabis users are often initially clever and sociable; introduced to cannabis by their friends, they are sufficiently socially adept to be able to conceal their drug habit.

Among psychotic patients, continued use of cannabis harbours a bad outcome. A meta-analysis demonstrated that those who continue cannabis use have higher relapse rates, longer hospital admissions, and more severe positive symptoms than either former users who discontinued cannabis or never-users (Schoeler et al., 2016a,b).

In recent years the potency of the street cannabis available in many Western countries has increased. In the 1960s, herbal cannabis (marijuana) and resin (hashish) commonly contained 3% or less THC, the principal psychoactive component of cannabis. However, by the early years of the 21st century, the mean THC had risen to 16 and 20% in England and Holland respectively (Hardwick, 2008; Pijlman et al., 2005). Similarly Australia saw high-potency cannabis taking increasing market share, with mean THC around 15% (Swift et al., 2013), while in the US potency reached an average of 12% by 2014 (ElSohly et al., 2016).

Higher potency types of cannabis carry more risk than traditional forms. A case-controlled study showed that people using high-potency cannabis on a daily basis were five times more likely than non-users to suffer from a psychotic disorder (Di Forti et al., 2015). Surprisingly, use of traditional hashish did not increase risk of psychosis, probably because its lower THC content was combined with the presence of cannabidiol (CBD) (Di Forti et al., 2013, 2015); as we shall show later, CBD ameliorates the psychotogenic effects of THC in experimental studies. A survey of 2000 cannabis users in Holland reported that those who used cannabis with the highest CBD content had experienced fewer psychotic-like experiences (Schubart et al., 2011). A study testing hair for cannabinoids, showed that users with both detectable THC and CBD had fewer psychotic symptoms than those in whom only THC could be detected (Morgan and Curran, 2008).

Novel ways of extracting THC from the plant have produced a

**Table 1**
Longitudinal studies concerning the role of cannabis as a risk factor for psychosis.

| Study | Country | Design | No. Participants | Follow-up (years) | OR (95% CI) (adjusted risk) |
|---|---|---|---|---|---|
| Tien & Anthony | US | Population based | 4494 | 1 | 2.4 (1.2–7.1) |
| Zammit et al. | Sweden | Conscript cohort | 50,053 | 27 | 3.1 (1.7–5.5) |
| Manrique-Garcia et al. | | | | 35 | 1.8 (1.3–2.3) |
| van Os et al. | The Netherlands | Population based | 4045 | 3 | 2.8 (1.2–6.5) |
| Weiser et al. | Israel | Population based | 9724 | 4–15 | 2.0 (1.3–3.1) |
| Fergusson et al. | New Zealand | Birth cohort | 1265 | 3 | 1.8 (1.2–2.6) |
| Arseneault et al. | New Zealand | Birth cohort | 1034 | 15 | 4.5 (1.1–18.2) |
| Ferdinand et al. | The Netherlands | Population based | 1580 | 14 | 2.8 (1.79–4.43) |
| Henquet et al. | Germany | Population based | 2437 | 4 | 1.7 (1.1–1.5) |
| Wiles et al. | UK | Population based | 8580 | 1.5 | 1.5 (0.55–3.94) |
| Rössler et al. | Switzerland | Community Survey | 591 | 30 | 1.8 (0.96–3.2) |
| Gage et al. | UK | Birth cohort | 1756 | 2 | 1.1 (0.76–1.65) |
| Rognli et al. | Sweden | Cohort of discharged prisoners | 6217 | 5 | 2.6 (1.40–5.0) |
| Bechtold et al. | USA | Adolescent boys | 1009 | 5 | 1.51 (1.08–2.11) |

range of new products from “edibles” to resin oil and “wax dabs” with up to 75% THC content (Raber et al., 2015). Reports have begun to emerge of cases of psychosis following the use of such types of cannabis (Pierre et al., 2016).

Since 2008, the recreational use of synthetic cannabinoids, sometimes termed spice or K2, has increased dramatically. While THC is a partial agonist with weak affinity for the CB1 receptor, synthetic cannabinoids are full agonists and generally have higher affinity for the receptor. Not surprisingly, they pose a greater health risk compared to plant cannabis (Spaderna et al., 2013; Tait et al., 2015; Winstock et al., 2015; EMCDDA, 2016). Psychotic reactions are increasingly being reported consequent upon use of synthetic cannabinoids (Castaneto et al., 2014; Papanti et al., 2013), and mounting evidence suggests that more chronic psychotic disorders can also occur (Fattore, 2016).

### 2.2. Skeptics

Although the vast bulk of the literature indicates that cannabis is a contributory cause of schizophrenia, some remain skeptical (Haney and Evins, 2016; Hill, 2015; Ksir and Hart, 2016). We will now review the main arguments.

A common idea has been that those cannabis users who develop psychosis have also been using other drugs. However, a number of studies have addressed this issue and not found the effects sufficient to negate the effects of cannabis (e.g. Arseneault et al., 2002), even when use of tobacco was accounted for (Di Forti et al., 2009, 2015).

Could those who use cannabis be more psychologically deviant than those who do not? Two recent iterations of the Swedish Military Study controlled for ‘disturbed behaviour’ (truancy, contact with police/childcare authority, running away from home) and still found that cannabis use significantly increased risk of schizophrenia (Zammit et al., 2002; Manrique-Garcia et al., 2012). Similarly, the Dunedin study controlled for psychotic symptoms at age 11, and still found that cannabis use increased risk of later psychotic symptoms (Arseneault et al., 2002).

Might some people be taking cannabis in an attempt to self-medicate symptoms of psychosis or its precursors? There is little evidence for this. A study from Christchurch showed that once psychotic symptoms developed, people tended to smoke less cannabis (Fergusson et al., 2003, 2015). In the only laboratory study conducted, THC worsened core psychotic symptoms (D'Souza et al., 2005). There have been suggestions that prodromal or indeed psychotic patients may use cannabis to counteract negative symptoms (Gill et al., 2015; Archie et al., 2013) but as yet there are few empirical data to support this notion. Indeed, when psychotic patients are asked why they use cannabis, they report the same hedonic reasons as the rest of the population, i.e., for enjoyment (Bianconi et al., 2016).

Another argument states that as cannabis use became more common in the latter part of the 20th century, there ought to have been an increase in the incidence of schizophrenia. Sadly, there is little reliable information on temporal trends in the incidence of schizophrenia, so it is difficult to examine this question. One study using the same diagnostic criteria for schizophrenia reported that the incidence in South London doubled between 1965 and 1999 (Boydell et al., 2006). Preliminary data from a large European study (the EU-GEI study) has shown fivefold variation in the incidence of psychosis across 16 centres; the highest rates were found in London and Amsterdam which also reported the greatest use of high potency cannabis (Di Forti M, Presented at the International Congress for Schizophrenia Research, San Diego, March 2017).

A final argument, which suggests that the genes that predispose to schizophrenia also predispose to cannabis use, will be discussed later.

## 3. Human laboratory studies (HLS) of cannabinoids

HLS have been used to study the acute, transient psychosis-like phenomena time-locked to the administration of cannabinoids (Table 2). HLS allow for causal inferences to be made with confidence because of the precise temporal relationship between cause (drug administration) and effect (psychosis), and the dose and administration of the drug can be carefully controlled. Furthermore, the individual and interactive effects of the different constituents of cannabis (e.g., delta-9- tetrahydrocannabinol [THC] and cannabidiol [CBD]) can be isolated.

### 3.1. HLS of cannabinoids in healthy subjects

HLS have been carried out using various cannabinoids, including THC, the synthetic THC analog Nabilone, and CBD, a non-intoxicating constituent of cannabis.

Cannabis, extracts of cannabis, as well as THC by itself, induce positive psychotic symptoms including suspiciousness, paranoid delusions, disorders of thought processes, as well as perceptual alterations. These changes are dose dependent, and their time course depends on the route of administration (peak effect within 30 min for inhaled and intravenous, 1–2 h for oral).

One of the earliest experimental studies was conducted in 1944; at doses of about 30–50 mg oral and 8–30 mg smoked cannabis, 12.5% of subjects experienced psychotic reactions (Mayor’s Committee on Marihuana, 1944). The following decade, after oral

**Table 2**
Psychosis relevant humans laboratory studies with cannabinoids in humans.

| Author | Dose and Route of Cannabinoid Agonist | Route | Outcome | Other drugs |
|---|---|---|---|---|
| (Atakan et al., 2013) | THC: 10 mg | PO | PANSS, *f*MRI (BOLD) | |
| (Barkus et al., 2011) | THC: 2.5 mg | IV | PANSS, *in vivo* DA release | |
| (Bhattacharyya et al., 2012a,b) | THC: 10 mg | PO | PANSS | CBD 600 mg – PO |
| (Bhattacharyya et al., 2009a) | THC: 10 mg | PO | PANSS, *f*MRI (BOLD) | CBD 600 mg - PO |
| (Bhattacharyya et al., 2010a) | THC: 1.25 mg | PO | PANSS, *f*MRI (BOLD) | CBD 5 mg - PO |
| (Bhattacharyya et al., 2012a,b) | THC: 10 mg | PO | *f*MRI (BOLD) | |
| (Martin-Santos et al., 2012) | THC: 10 mg | PO | *f*MRI (BOLD) | CBD 600 mg - PO |
| (Bhattacharyya et al., 2015) | THC: 10 mg | PO | *f*MRI (BOLD) | CBD 600 mg - PO |
| (Bhattacharyya et al., 2015a) | THC: 10 mg | PO | PANSS, *f*MRI (BOLD) | |
| (Borgwardt et al., 2008b) | THC: 10 mg | PO | PANSS, *f*MRI (BOLD) | CBD 600 mg – PO |
| (Bossong et al., 2009) | THC: 8 mg | Inh | VAS, BPRS, *in vivo* DA release | |
| (Bossong et al., 2012) | THC: 6 mg + 1 mg (X3) | Inh | VAS, *f*MRI (BOLD) | |
| (Bossong et al., 2012a,b) | THC: 6 mg + 1 mg (X3) | Inh | VAS, *f*MRI (BOLD) | |
| (Bossong et al., 2013a) | THC: 6 mg + 1 mg (X3) | Inh | VAS, *f*MRI (BOLD) | |
| (Bossong et al., 2013b) | THC: 6 mg + 1 mg (X3) | Inh | VAS, *f*MRI (BOLD) | |
| (Bossong et al., 2015) | THC: 10 mg | PO | *in vivo* DA release | |
| | THC: 8 mg | Inh | | |
| (Böcker et al., 2010) | THC: 29.3, 49.1, or 69.4 mg | Inh | EEG | |
| (Cortes-Briones et al., 2015a,b) | THC: 0.015, 0.03 mg/kg | IV | EEG, PANSS | |
| (Cortes-Briones et al., 2015a,b) | THC: 0.015, 0.03 mg/kg | IV | EEG, PANSS | |
| (D'Souza et al., 2004) | THC: 2.5, 5 mg | IV | PANSS, CADSS | |
| (D'Souza et al., 2005) | THC: 2.5, 5 mg | IV | PANSS, CADSS | |
| (D'Souza et al., 2008a,b) | THC: 2.5, 5 mg | IV | PANSS, CADSS | |
| (D'Souza et al., 2008a,b) | THC: 0.0286 mg/kg | IV | PANSS, CADSS | Haloperidol 0.057 mg/kg PO |
| (D'Souza et al., 2012) | THC: 0.015, 0.03 mg/kg | IV | PANSS, CADSS, ERPS | |
| (Emrich et al., 1991) | THC: 3–4 mg/kg Cannabis resin | PO | BDI | |
| (Englund et al., 2013) | THC: 1.5 mg | IV | PANSS | CBD 600 mg - PO |
| (Englund et al., 2016) | THC: 1 mg | IV | CAPE | THCV 10 mg/day for 5 days - PO |
| (Fusar-Poli et al., 2010) | THC: 10 mg | PO | PANSS, *f*MRI (BOLD) | CBD 600 mg - PO |
| (Hallak et al., 2010) | N/A | | PANSS, BPRS | CBD 300, 600 mg – PO |
| (Henquet et al., 2006) | THC: 300 μg/kg in tobacco cigarettes | Inh | CAPE | |
| (Ilan et al., 2005) | THC: low:1.8%; High:3.6% | Inh | EEG | CBD Low: 0.1–0.4%; High: >1%; CBC: Low: 0.1–0.2%; high: >5% -smoking |
| (Jansma et al., 2013) | THC: 6 mg + 1 mg (X3) | Inh | VAS, *f*MRI (BOLD) | |
| (Juckel et al., 2007) | THC: 10 mg | PO | ERPs | Cannabis extract: THC: 10 mg + CBD: 5.4 mg - PO |
| (Kaufmann et al., 2010) | THC: 20 mg cannabis extract | PO | BPRS | Diazepam 5 mg |
| (Kleinloog et al., 2012) | THC: 2, 4, 6 mg | Inh | PANSS | Olanzapine 10 mg of PO; Diphenhydramine 15 mg PO (X2) |
| (Kleinloog et al., 2015) | THC 2, 4, 6 mg (1.5 h apart) (reported in Klumpers et al., 2012) | Inh | VAS, *f*MRI (BOLD) | Compared with ketamine, ethanol, morphine |
| (Klumpers et al., 2012) | THC: 2, 6, & 6 mg (1.5 h apart) | Inh | VAS, *f*MRI (BOLD) | |
| (Klumpers et al., 2013a,b) | THC: 5 mg (4 times) | Inh | VAS | Rimonabant 60 mg – PO; TM38837 (peripheral CB1R antagonist) 100 mg or 500 mg – PO |
| (Klumpers et al., 2013a,b) | THC: 2, 4, 6, & 9 mg (1 h apart) | Inh | VAS | Surinabant 5, 20, or 60 mg – PO |
| (Koethe et al., 2006) | THC: 120 μg/kg | PO | BPRS, BDI | |
| (Kopell et al., 1972) | THC: 0.35 mg/kg | PO | EEG | 0.7 ml/kg of 95% ethanol |
| (Kuepper et al., 2013b) | THC: 8 mg | Inh | VAS, *in vivo* DA release | |
| (Leweke et al., 1998) | THC: 10 mg | PO | ERPs | |
| (Leweke et al., 2000) | Nabilone: 1 mg | PO | BDI | CBD 200 mg - PO |
| (Liem-Moolenaar et al., 2010) | THC: 2, 4, 6 mg | Inh | VAS, PANSS, EEG | Haloperidol 3 mg PO |
| (Morrison and Stone, 2011) | THC: 2.5 mg | IV | PANSS | |
| (Morrison et al., 2009b) | THC: 2.5 mg | IV | PANSS, CAPE | |
| (Morrison et al., 2011) | THC: 1.25 mg | IV | PANSS, EEG | |
| (Nottage et al., 2015) | THC: 1.25 mg | IV | PANSS, EEG | |
| (Radhakrishnan et al., 2015) | THC: 0.015 mg/kg | IV | CADSS, ERPs | Iomazenil 3.7 μg/kg - IV |
| (Ranganathan et al., 2012) | THC: 0.0286 mg/kg | IV | PANSS, CADSS | Naltrexone 25 mg - PO |
| (Roser et al., 2008) | THC: 10 mg | PO | ERPs | Cannabis extract: THC: 10 mg + CBD: 5.4 mg - PO |
| (Stadelmann et al., 2011) | THC: 10 mg | PO | ERPs | Cannabis extract: THC: 10 mg + CBD: 5.4 mg - PO |
| (Stokes et al., 2009) | THC: 10 mg | PO | PSI, *In vivo* DA release | |
| (Winton-Brown et al., 2011) | THC: 10 mg | PO | PANSS, *f*MRI (BOLD) | CBD 600 mg - PO |
| (Zuurman et al., 2008) | THC: 2, 4, 6, & 8 mg (1.5 h apart) | Inh | VAS, EEG | |

**Abbreviations**BDI: Binocular Depth Inversion; BOLD; Blood oxygen level dependent; BPRS: Brief Psychiatric Rating Scale; CADSS: Clinician Administered Dissociative Symptoms Scale; CAPE: Community Assessment of Psychic Experience; CBD: Cannabidiol; EEG: Electroencephalography; ERPs: Event Related Potentials; HLS: Human Laboratory Studies; Inh: Inhaled; IV: intravenous; PANSS: Positive and Negative Syndrome Scale; PET: Positron Emission Tomography; PO: per oral; PSI: Psychotomimetic States Inventory; SPET: Single Photon Emission Tomography; THC: Delta-9-Tetrahydrocannabinol; VAS: Visual Analog Scale.

doses of cannabis extract (~50–70 mg THC), 12 subjects reported fragmented thinking, disturbed temporal and spatial perception, illusions and hallucinations, derealization and depersonalization, and memory deficits (Ames, 1958). Other quasi-experimental studies reported dose-related psychotic symptoms following cannabis (Isbell et al., 1967; Isbell and Jasinski, 1969; Renault et al., 1974).

More tightly controlled laboratory studies have been carried out in recent years (reviewed in Sherif et al., 2016). D'Souza et al. (2004) characterized the effects of intravenous THC (0 mg, 2.5 mg, and 5 mg), in a double blind, randomized, placebo-controlled study of healthy research participants (n = 22). Studies of this kind have

clearly confirmed that THC and nabilone can produce transient positive symptoms as well as conceptual disorganization, depersonalization and derealization, distorted sensory perceptions, and extreme slowing of time (Bhattacharyya et al., 2010a, 2012a, 2015a; D'Souza et al., 2004, 2008a,b, 2012; Freeman et al., 2015; Koethe et al., 2006; Leweke et al., 1999a,b; Leweke et al., 2000; Morrison et al., 2009b). There is high inter-individual variability of these symptoms, which occur in 35–50% of participants at high doses (D'Souza et al., 2004; Morrison et al., 2009a; Englund et al., 2016).

THC can also induce effects which are similar to negative symptoms; D'Souza et al. (2004) reported blunted affect, lack of spontaneity, and being internally preoccupied; such symptoms are not related to sedation (Morrison and Stone, 2011). Of note, an amotivational syndrome similar to negative symptoms has been reported with chronic use of marijuana (Rovai et al., 2013).

Cannabinoids produce acute transient dose-related deficits in memory, executive function, abstract ability, decision making, and attention (Hart et al., 2001; Heishman et al., 1990; Hooker and Jones, 1987; Leweke et al., 1998; Marks and MacAvoy, 1989; Miller et al., 1977; Ranganathan et al., 2006). Consistent with studies in rodents and non-human primates (reviewed in Lichtman et al., 2002; Wilson and Nicoll, 2002), the most robust effects of cannabinoids in humans target memory and attention (Hart et al., 2001; Heishman et al., 1990; Hooker and Jones, 1987; M. Leweke et al., 1998; Marks and MacAvoy, 1989; Miller et al., 1977; Ranganathan et al., 2006). Several groups have demonstrated that THC produces dose-related impairments in both immediate and delayed (30-min) verbal recall (D'Souza et al., 2004, 2005; Morrison et al., 2009b). Importantly, the profile of cognitive deficits induced by cannabinoids bears some resemblance to those observed in schizophrenia (Heinrichs and Zakzanis, 1998): in both cases, working and verbal memory are most affected (Ranganathan et al., 2006).

EEG measures of information processing (e.g. P50) show that the ability of the brain to modulate its sensitivity to incoming sensory information (sensory gating) is impaired in psychotic disorders (Bramon et al., 2004; de Wilde et al., 2007; Patterson et al., 2008; Rentzsch et al., 2007; Solowij and Michie, 2007). Skosnik et al. (unpublished) found that acute THC induced P50 gating deficits in healthy subjects, and that chronic cannabis users exhibit reduced P50 gating (Edwards et al., 2009).

Neural oscillations in the gamma (ɣ) band (30–80 Hz) are critically involved in perception, attention, and working memory (e.g. Lisman and Buzsáki, 2008), processes that are altered in psychosis. Patients with psychotic disorder show attenuated γ-band (~40 Hz) responses (Krishnan et al., 2009; Kwon et al., 1999; Light et al., 2006; Spencer et al., 2008). Cortes-Briones et al. (2015a,b) reported that THC administration disrupted γ- band neural oscillations, and that THC induced disruptions in γ-band neural oscillations correlated with psychotomimetic symptoms. Neural noise is also known to be high in psychotic disorders (Winterer et al., 2004; Winterer and Weinberger, 2003; Yang et al., 2014). Cortes-Briones et al. (2015a,b) found that acute THC administration increased neural noise in healthy volunteers and the increase in THC-induced cortical noise strongly correlated with increase in positive symptoms.

CBD, a non-psychoactive cannabinoid constituent of cannabis shows an interesting pattern of interaction with THC. Pretreatment with CBD attenuated the psychotomimetic effects of THC (Bhattacharyya et al., 2010a; Englund et al., 2013).

### 3.2. HLS in individuals with schizophrenia

There have been a few studies in people with schizophrenia. In 1934, Lindeman and Malamud administered hashish to a group of schizophrenia patients, who experienced an exacerbation of their symptoms. Seven decades later, D'Souza et al. (2005) carried out a three-day, double-blind, randomized, placebo-controlled crossover study in which the effects of 0 mg (placebo), and two active doses (2.5 mg, and 5 mg intravenous THC) were characterized in 13 stable, antipsychotic-treated schizophrenia patients. THC transiently increased positive and negative symptoms, with a significant effect of dose. Most of the schizophrenia patients but only a minority of control subjects had a clinically significant increase in psychosis in response to 2.5 mg THC. Schizophrenia patients were also more sensitive to the memory impairing effects of THC. The study failed to observe any "beneficial" effects of cannabinoid agonists in individuals with schizophrenia – challenging the cannabis self-medication hypothesis in schizophrenia (D'Souza et al., 2005).

## 4. Brain imaging

### 4.1. Structural MRI

There have been over 30 Structural MRI studies comparing grey and white matter volume or density in regular cannabis users relative to non-users.

Some, but not, all have reported that regular cannabis use is associated with lower grey matter volumes in regions that have also been implicated in psychosis, including the hippocampus (Ashtari et al., 2011; Demirakca et al., 2011; Lorenzetti et al., 2015; Matochik et al., 2005; Yücel et al., 2008), amygdala (Schacht et al., 2012; Yücel et al., 2008), putamen (Yip et al., 2014), and prefrontal cortex (Battistella et al., 2014; Churchwell et al., 2010; Filbey et al., 2014; Price et al., 2015).

However, other studies have not detected any significant differences (Batalla et al., 2013; Block et al., 2000; Medina et al., 2009; Tzilos et al., 2005). A recent study in a larger sample of 466 individuals aged 22–35 (Orr et al., 2016) found no relationship between cannabis use and grey matter volume in any region. However, age of onset of use was related the shape of the nucleus accumbens, and total lifetime use was related to the shape of the amygdala and hippocampus (See Table 3).

In view of the latter finding, it is interesting that the two MRI studies that examined the greatest cumulative exposure to cannabis (62,000 joints and 20 years of use, respectively) both found smaller amygdala and hippocampal volumes in users than controls (Lorenzetti et al., 2015; Yücel et al., 2008); reduction in hippocampal volume was correlated with cumulative exposure over ten years and with subclinical psychotic symptoms.

Two longitudinal MRI studies of heavy users and non-users, failed to find between-group longitudinal volumetric differences (Cousijn et al., 2012; Koenders et al., 2016). However, within the user group, at both cross-sectional time points, increased severity of dependence and weekly amount of use were associated with smaller amygdala and hippocampal volumes, respectively.

### 4.2. Diffusion tensor imaging

Diffusion tensor imaging (DTI) provides an indication of the integrity of white matter tracts (Beaulieu, 2002). The most common DTI measure reported in the cannabis literature is fractional anisotropy (FA). Compared to controls, cannabis users have been reported to show reduced FA in tracts that are also sites of reduced FA in psychosis, including the superior longitudinal (Becker et al., 2015; Yücel et al., 2010) and uncinate fasciculi (Shollenbarger et al., 2015), the callosum (Filbey et al., 2014; Gruber et al., 2014; Shollenbarger et al., 2015; Zalesky et al., 2012), the fornix (Zalesky et al., 2012) and the thalamic radiation (Becker et al., 2015).

Few studies have considered the potency of the cannabis used.

**Table 3**
Selective overview of structural MRI studies in cannabis users vs non-users.

| Author(s) | Year | Cannabis users, N. (mean age or range) | Non-using controls, N. (mean age or range) | Cannabis use exposure/duration (CU: cannabis users. NU: non-using controls) | Volume/density findings |
|---|---|---|---|---|---|
| (Orr et al., 2016) | 2016 | 466 (22-35y) Confirmatory analysis: 247 (22-35y) | Confirmatory analysis: 392 (22-35y) | Parametric number of uses: 0, 1–5, 6–10, 11–100, 101–999, >1000. CU: first use <age 18, >100 lifetime uses. | VBM: No differences in 15 prefrontal cortical regions, NuAcc, hipp, cerebellum cortex and white matter, thalamus, and amygdala. No differences in categorical analysis of users vs non-user group in any region. |
| (Koenders et al., 2016) - *3 year follow-up* (Cousijn et al., 2012) | 2016 | 20 (21y) | 22 (22y) | CU: using for > 2years, >10days/month. NU: <30 lifetime uses, none in past year. | VBM: No whole brain differences longitudinally, at baseline or 3 year follow-up. No GM volume difference in any ROI: orbitofrontal cortex, ACC, insula, striatum, thalamus, amygdala, hippocampus and cerebellum. No interaction between group and time. |
| (Price et al., 2015) | 2015 | 27 (21y) | 32 (21y) | CU: mean joints in past year = 291, lifetime = 1944, age first use = 17. | Users showed: ↓ medial orbitofrontal volume. No differences in lateral orbitofrontal, superior frontal, rostral middle frontal, or inferior parietal regions. |
| (Lorenzetti et al., 2015) | 2015 | 15 (40y) | 15 (36y) | CU: mean duration = 21 years regular use, lifetime smoking episodes = 62,000, current rate = 28 days/month use. | Users showed: ↓ hippocampus and amygdala volumes, no difference in orbitofrontal cortex, ACC, or pituitary. |
| (Weiland et al., 2015) | 2015 | 29 adults (27y) 50 adolescents (17y) | 29 adults (28y) 50 adolescents (17y) | CU: all using daily. | VBM: No difference in whole brain GM volume/density or ROIs in nucleus accumbens, amygdala, hippocampi, or cerebellum. |
| (Pagliaccio et al., 2015) | 2015 | 262 (29y) Sibling/twin pairs concordant or discordant for cannabis use (241 pairs). | 221 (29y) | CU: *ever*-users, 49% used < age 17, 18% dependent, 36% used in past year. NU: never used. | Users showed: ↓ L amygdala and R ventral striatum volume (but within normal range of variation). No difference in hippocampus or WBV. Non-users from discordant pairs had similar ↓ amygdala volume (no different from their using counterpart). |
| (French et al., 2015) | 2015 | 1577 (12-21y) Healthy individuals across 3 cohorts with a high vs low polygenic risk score (PGRS) for schizophrenia. | | CU: ever used. NU: never used. | Cortical thickness: negative association between cannabis use in early adolescence and cortical thickness in males with high PGRS. No such association in females or low-PGRS males. In a male-only cohort, most frequent users (>61 uses) had ↓ cortical thickness relative to never-users. |
| | | 486 | 1091 | | |
| (Filbey et al., 2014) | 2014 | 48 (28y) | 62 (30y) | CU: mean age first use = 18, years of use = 10, all used >4 times/week. | VBM, users showed: ↓ bilateral orbitofrontal gyri GM volume |
| (Battistella et al., 2014) | 2014 | 25 (23y median) | 22 (25y median) | CU: regular users, minimum 10 joints/month. NU: occasional users, between 1 joint/month, maximum <1/week. | VBM, regular users showed: ↓ GM volume in medial temporal cortex, temporal pole, parahippocampal gyrus, insula & orbitofrontal cortex, but ↑ cerebellar volume |
| (Yip et al., 2014) | 2014 | 20 (27y) | 20 (29y) | CU: all cannabis dependent, mean duration of use = 12years. | ROI analysis, users showed: ↓ L and R putamen volumes. No differences in caudate volume. |
| (Batalla et al., 2014) | 2013 | 29 (21y) | 28 (22y) | CU: first use <16 years, duration = 6 years, mean of 2.5 joints/day. NU: <5 lifetime uses. | No differences in GM/WM/ICV/CSF volume. No GM differences in PFC, ACC or hippocampus-amygdala complex. |
| (Schacht et al., 2012) | 2012 | 37 (28y) | 37 (27y) | CU: duration = 10years, heavy users, minimum 4 uses/week over past 6months. NU: never regularly used. | Users showed: ↓ bilateral hippocampal and L amygdala volume. No difference in ICV or R amygdala. |
| (Cousijn et al., 2012) | 2012 | 33 (21y) | 43 (22y) | CU: used >10 days in last month, >240 days in last 2 years, duration heavy use = 2.5 years. NU: <50 joints lifetime, none in last year. | VBM ROI, users showed: ↑ GM in cerebellum, no differences in any other ROI: orbitofrontal cortex, ACC, striatum, amygdala, hippocampus, or in WM. |
| (Ashtari et al., 2011) | 2011 | 14 (19y) | 14 (19y) | CU: treatment-seeking, 6 joints/day, tested after 7months abstinence. NU: <5 lifetime uses of any illicit drug. | ROI, users showed: ↓ bilateral hippocampus volume. No difference in amygdala. |
| (Demirakca et al., 2011) | 2011 | 11 (22y) | 13 (23y) | CU: age first use = 17, frequency = 25 days past month, 300 days past year. NU: <1 lifetime use. | VBM (ROI), users showed: ↓ GM volume in R anterior hippocampus, but no difference in composition or concentration of GM in whole-brain or hippocampal ROI. |
| (Churchwell et al., 2010) | 2010 | 18 (18y) | 18 (17y) | CU: cannabis abusers, age first use = 15, frequency of weekly uses = 9. | ROI analysis, users showed: ↓ medial orbital prefrontal cortex (moPFC) volume. No differences in lateral oPFC, total loPFC, or left moPFC, total moPFC, or total oPFC. |
| (Medina et al., 2009; Medina et al., 2007) | 2009 | 16 (18y) | 16 (18y) | CU: lifetime uses = 476, duration = 3.4years, tested after 1 month abstinence. NU: <1 lifetime use. | No difference in overall WM volume or ICV or any measure of GM/WM volume in multiple PFC ROIs. No difference in R or L hippocampal volume. |
| (Yücel et al., 2008) | 2008 | 15 (40y) | 16 (36y) | CU: mean duration regular use = 20 years, age first use = 20, lifetime episodes of use = 62,000. NU: mean lifetime episodes = 11. | Users showed: ↓ bilateral hippocampal and amygdala volume. No difference in ICV or whole brain GM + WM. |

**Table 3** (*continued*)

| Author(s) | Year | Cannabis users, N. (mean age or range) | Non-using controls, N. (mean age or range) | Cannabis use exposure/duration (CU: cannabis users. NU: non-using controls) | Volume/density findings |
|---|---|---|---|---|---|
| (Matochik et al., 2005) | 2005 | 11 (25y) | 8 (30y) | CU: heavy use, mean = 34 joints/week, mean duration = 7.5 years, age of onset = 15.7. | VBM, users showed: ↑ GM density bilateral precentral gyrus & R thalamus, ↓ GM density in R PHG, and also hippocampus (after small volume correction) |
| (Tzilos et al., 2005) | 2005 | 22 (38y) | 26 (30y) | CU: mean episodes of smoking = 20140, age of onset = 16, duration = 23 years, history of dependence. NU: never met dependence criteria. | No differences in mean GM, WM, CSF or total brain volume. No differences in R/L hippocampal volume or ratio of volume. |
| (Block et al., 2000) | 2000 | 18 (22) | 13 (23y) | CU: current mean use = 18 times/week for duration of 4 years. NU: <2 lifetime uses. | No difference in GM or WM in: frontal, temporal, parietal or occipital lobes, or the cerebellum, subcortical regions or hippocampal volume. Ventricular CSF volumes were *lower* than controls. |

CU: cannabis using group, NU: non-using controls, y: years, ↓: decrease, ↑: increase, >: more than, <: less than, ROI: region of interest, VBM: voxel-based morphometry, GM: grey matter, WM: white matter, WBV: whole brain volume, ICV: intracranial volume, CSF: cerebrospinal fluid, R: right, L: left, RL: bilateral (right + left), prefixes (d: dorsal, m: medial, v: ventral, l: lateral), ACC: anterior cingulate cortex, OFC: orbitofrontal cortex, PHG: parahippocampal gyrus, PFC: prefrontal cortex.

However, Rigucci et al. (2016) investigated corpus callosal microstructure in patients with their first onset of psychosis and controls; users of high potency cannabis had higher total mean diffusivity and axial diffusivity in the corpus callosum than both low potency users and non-users.

### 4.3. Functional MRI studies

#### 4.3.1. Response inhibition

Using a go/no-go task, two studies found that THC attenuated activation in the inferior frontal, anterior cingulate and precuneal cortex, and augmented activation in the medial temporal cortex and caudate (Bhattacharyya et al., 2015a; Borgwardt et al., 2008a,b). These results are consistent with altered frontal activation in cannabis users during inhibition and cognitive control tasks (Eldreth et al., 2004; Gruber and Yurgelun-Todd, 2005; Tapert et al., 2007). This mirrors the altered prefrontal and striatal activation evident during inhibition tasks in patients with psychosis (Kaladjian et al., 2007; Rubia et al., 2001).

#### 4.3.2. Learning & memory

As we noted earlier, acute cannabis intoxication is associated with robust impairments of learning and memory. Whether cannabis use can cause enduring deficits has been less clear (Grant et al., 2003). However, a recent meta-analysis reported modest non-acute impairments across a number of memory domains, particularly prospective and verbal memory (Schoeler et al., 2016). The key neural substrates for learning and memory, such as the prefrontal cortex and hippocampal formation, are rich in CB1 receptors (Burns et al., 2007), and patients with psychosis show altered activation in these regions during memory tasks (Achim and Lepage, 2005; Allen et al., 2012; Weiss and Heckers, 2001).

Bhattacharyya et al. (2009a) assessed the effects of THC on 15 healthy males during a verbal paired associates learning task. THC altered medial temporal activation during encoding such that the normal linear task response was abolished and the correlation with recall scores was lost. THC also attenuated striatal activation during recall, and this was correlated with the level of positive psychotic symptoms it induced.

Similar results have been reported in cannabis users, with attenuated prefrontal activation (Nestor et al., 2008), augmented activation in para/hippocampal regions (Jacobsen et al., 2004; Nestor et al., 2008) and more diffuse patterns of activation relative to comparator groups (Kanayama et al., 2004). However, some studies have tested individuals after only short periods (<24 h) of abstinence, and so residual effects of intoxication cannot be ruled out (Curran et al., 2002).

#### 4.3.3. Salience processing

The subjective effects of acute cannabis intoxication include alterations in the perceived profoundness and meaning of conversation and stimuli (Tart, 1970), which could be secondary to the modulation of salience processing. The attribution of salience is altered in psychosis (Kapur, 2003), and this accompanied by altered activation in the striatum (Diaconescu et al., 2011; Jensen et al., 2008; Roiser et al., 2012). In chronic cannabis users, performance in salience tasks is largely unimpaired, but the underlying neural responses differ significantly from controls (Wijayendran et al., 2016).

In an fMRI study of processing oddball (salient) relative to standard stimuli in volunteers, THC augmented prefrontal activation and attenuated it in the caudate. The effect of THC on caudate activation was inversely related to the severity of psychotic symptoms it induced (Bhattacharyya et al., 2012a,b).

#### 4.3.4. Emotion processing

THC can attenuate the amygdala response to threat-related faces (Phan et al., 2008) and may increase functional connectivity between amygdala subnuclei and frontal regions (Gorka et al., 2015). THC has also been found to attenuate amygdala, hippocampal, parietal and prefrontal activation to fearful faces, and augment activation of these regions to happy faces (Bossong et al., 2013a).

Other work has found that THC attenuated activation in the middle frontal gyri and posterior cingulate cortex, and augmented activation in the precuneus and sensorimotor cortex, in association with induction of anxiety (Fusar-Poli, 2009). Conversely, CBD attenuated activation in the amygdala and the parahippocampal and cingulate cortex, and the effect on amygdala activation was associated with a decrease in skin conductance, consistent with an anxiolytic effect of CBD (Crippa et al., 2004). In addition, CBD (but not THC) reduced effective connectivity between the cingulate and amygdala during processing of fearful faces (Fusar-Poli et al., 2010).

### 4.4. Neurochemical imaging

Most of the work examining the effects of cannabis use on neurochemical indices in the brain *in vivo* has focused on dopamine related measures.

#### 4.4.1. PET and SPECT

Since CB1 activation in rodents stimulates neuronal firing of mesolimbic dopamine neurons and elevates striatal dopamine levels (Cheer et al., 2004), imaging studies examined acute release of dopamine in response to cannabis administration (Bossong et al., 2015; Voruganti et al., 2001). However, studies of oral (Stokes et al., 2009) and intravenous THC (Barkus et al., 2011), both failed to show significant dopamine release, although the latter used SPECT which may have been inadequate to detect an effect. Pooling of two cohorts, where subjects were administered inhaled or oral THC, in order to achieve higher power, did indicate a small but significant displacement of [$^{11}$C]raclopride in the ventral striatum.

Kuepper et al. (2013a) studied striatal dopamine release following vaporized THC (8 mg) and placebo in 9 healthy cannabis users, 8 patients with psychotic disorder, and 7 unrelated first-degree relatives. Relative to healthy controls, both patients and relatives showed significant displacement of the ligand ([F-18] fallypride) in striatal sub- regions, indicative of dopamine release. This was most pronounced in caudate nucleus.

Initial studies in chronic cannabis users showed normal levels of D2 receptors and dopamine release (Albrecht et al., 2012; Sevy et al., 2008; Stokes et al., 2010; Urban et al., 2012). More recent studies using [$^{11}$C]PHNO, a radiotracer that is more sensitive to the effects of a dopamine enhancing pharmacological challenge by virtue of being an agonist, showed deficits in dopamine release or re-uptake (van de Giessen et al., 2017; Volkow et al., 2014).

Bloomfield et al. (2014) examining [$^{18}$F]-DOPA in cannabis users indicated that long-term cannabis use was correlated with a dose-dependent decrease in dopamine synthesis capacity in the striatum especially in subjects meeting criteria for cannabis abuse or dependence. Dopamine synthesis capacity was negatively associated with magnitude of cannabis use and positively associated with age of onset of cannabis use but not with cannabis-induced psychotic-like symptoms.

Striatal and extrastriatal dopamine transporter (DAT) were measured using the PET tracer [$^{11}$C]PE2I (Leroy et al., 2012). DAT availability was significantly reduced in the drug using groups, compared to controls. As participants were also nicotine smokers, the effects of cannabis alone cannot be determined from this study.

Thus, unlike findings in other addictions of major deficits in dopamine release and reuptake (Martinez and Narendran, 2010), studies in cannabis dependence show deficits only in severe daily users. These deficits are more prominent in the early abstinence phase and easier to measure using agonist D2 radiotracers, such as [$^{11}$C]PHNO. Severity and duration of use may both contribute to this deficit in dopamine transmission.

How this deficit is linked to the propensity of cannabis to increase psychosis risk is not certain. It is likely that the deficit in the chronic stage reflects the long term effects of repeated episodes of enhanced dopamine signaling states secondary to acute self administration. An intriguing pattern noted across many studies (Thompson et al., 2013; Urban et al., 2012; van de Giessen et al., 2017) is that dopaminergic alterations preferentially affect the caudate, and the putamen to a lesser extent, more so than the ventral striatum, corresponding to the pattern of expression of mRNA for the CB1 receptor in the adult brain, which is higher in dorsal compared to ventral striatum (Wang et al., 2003). The rostral caudate is a site of integration across functional domains within the cortico-basal ganglia circuits in the brain, and the striatal subdivision where abnormal release is most prominent in schizophrenia. Furthermore, excess dopamine release in the associative striatum predicts conversion from a prodromal state to frank psychosis (Howes et al., 2009) and relates to the magnitude of psychotic symptoms (Howes et al., 2009; Thompson et al., 2013). It is clear that more studies are needed to further characterize reliably the differences across striatal subdivisions.

In addition to dopamine, a few studies have examined the endocannabinoid (CB1) receptor. CB1 receptor was examined in cannabis users with the CB1 receptor-selective radioligand [$^{18}$F] FMPEP-d2. Chronic heavy users showed reduction of CB1 receptor binding in most brain regions that began to reverse after 4 weeks of abstinence (Hirvonen et al., 2012). This was replicated using a different radiotracer [$^{11}$C]OMAR showing rapid reversal within days of the downregulation of CB1 receptors (D'Souza et al., 2016).

#### 4.4.2. MRS

Proton magnetic Resonance Imaging ($^{1}$H-MRS) has been used to examine adults and adolescents dependent on cannabis. These studies (reviewed by Sneider et al., 2013) suggested decreases in NAA, myo-inositol, and other measures related to neuronal viability in various cortical regions. One study measuring glutamate in the striatum and hippocampus in the same subjects who underwent PET imaging (van de Giessen et al., 2017) showed no abnormalities. In general, there is a paucity of MRS data in cannabis users to allow definitive conclusions.

## 5. Age of initiation of cannabis use

In the Dunedin cohort study, those who started to use cannabis at age 18 or later showed only a small, non-significant increase in the risk of schizophrenia-like psychosis by age 26, but the risk increased fourfold among those starting at age 15 or earlier (Arseneault et al., 2002). A possible explanation for this and similar reports is that the brain is still developing when teenagers start cannabis. Exposing the juvenile brain to the drug might permanently impair the endocannabinoid system, and impact adversely on brain and neurotransmitter function (Volkow et al., 2016).

There is, indeed, some evidence that when cannabis use is initiated before 16–17 years, it is associated with a global reduction in grey matter volume, particularly in the frontal lobes (Wilson et al., 2000), and reduced fractional anisotropy in several white matter tracts (Gruber et al., 2014; Orr et al., 2016; Zalesky et al., 2012). In addition, reduced parahippocampal volume has been associated with recreational use initiated during early adolescence (Battistella et al., 2014) as have greater white matter alterations (Gruber et al., 2014; Orr et al., 2016; Zalesky et al., 2012).

Neurochemical studies have also reported a significant association between dopamine release and age of onset of drug use in cannabis users (Urban et al., 2012): the earlier participants started using cannabis, the lower was their dopamine release, especially in the associative striatum (AST). This association with age of use has been independently replicated (Bloomfield et al., 2014).

The capacity of cannabis to increase dopamine release acutely in the associative striatum, combined with its use in adolescence, during maturation of the brain circuits subserved by the associative striatum, may offer a potential explanation for its propensity to induce psychosis.

## 6. Can genetics provide clarification?

### 6.1. Are individuals genetically predisposed to schizophrenia more likely to smoke cannabis?

A popular explanation for the association between cannabis use and psychosis is shared genetic vulnerability (Hill, 2015; Ksir et al., 2016; Ksir and Hart, 2016). In recent years it has become possible to derive a polygenic risk score for schizophrenia (PRS-SCZ) which reflects genetic predisposition to the illness; the PRS-SCZ is the sum of schizophrenia associated alleles across many genetic loci, typically weighted by the effect sizes from the large PGC2 GWAS study

of cases and controls (Ripke et al., 2014).

Power et al. (2014) examined the relationship between predisposition to schizophrenia, as measured by the PRS-SCZ, and cannabis use in healthy Australians: the PRS-SCZ predicted about 5% of variance in whether individuals had ever used cannabis. Subsequently, Verweij et al. (2017) showed that the PRS-SCZ explained a similar small proportion of the variance in lifetime cannabis use in just under 7000 individuals. An Icelandic study examined the relationship between the PRS-SCZ and a range of addictive disorders (Reginsson et al., 2017). Again the PRS-SCZ explained about 5% of variance in cannabis use disorder (as well as in alcohol and opioid use disorders), but a slightly greater proportion of amphetamine use and sedative use disorders.

However, a trans-European study which had more detailed cannabis data on nearly 900 first episode cases of psychosis and some 1200 normal controls found no effect of the PRS-SCZ on patterns of cannabis use in either psychotic patients or controls (Di Forti et al., Presented at the International Congress for Schizophrenia Research, San Diego, March 2017).

Thus, although the literature is not wholly consistent, it may be that people with a genetic predisposition to schizophrenia may be slightly more likely to use a range of drugs. However, it seems unlikely that this can explain much of the association between cannabis use and psychosis since a) at best only a small proportion of the variance is explained by the PRS-SCZ, and b) it explains a similar proportion of variance in substance use disorders which are not associated with increased risk of psychosis.

Vaucher and colleagues (2017) adopted the opposite approach by examining whether genetic predisposition to cannabis use increased risk of schizophrenia. They used ten genetic variants previously found to associate with cannabis use, in a Mendelian Randomisation (MR) analysis of the association of genetically determined cannabis use on risk of schizophrenia in 34,241 cases and 45,604 controls. They concluded “these findings strongly support a causal association between genetically determined use of cannabis and risk of schizophrenia”. Another MR study on the same dataset explored both forward and reverse causation and found evidence for both (forward OR 1.04, reverse OR 1.10), although with much smaller effects (Gage et al., 2017).

### 6.2. Interaction between genetic risk and cannabis use

Perhaps some individuals are more vulnerable to the psychotogenic effects of cannabis than others. No published study has yet examined a possible interaction between the PRS-SCZ and cannabis use in causing psychosis. However, the PRS-SCZ was examined in relation to structural brain imaging in three cohorts of adolescents (total n = 1577). Cannabis use before age 16 was associated with reduced global cortical thickness, but only in males with a high PRS-SCZ score (French et al., 2015). Genetic risk for psychosis may thus interact with cannabis exposure to alter cortical morphometry.

Other work has examined candidate genes, in particular Catechol- Methyl-Transferase (COMT), which plays an important role in the metabolism of dopamine in the prefrontal cortex. Caspi et al (2005) reported that the Val-Met functional polymorphism of the COMT gene appeared to moderate liability to cannabis- associated psychosis, but attempted replications have been inconsistent (e,g. Zammit et al., 2011).

Nevertheless, Henquet et al. (2006) conducted a double-blind, placebo-controlled cross-over study in patients with a psychotic disorder, relatives of such patients, and healthy controls. Subjects received THC or placebo in tobacco cigarettes. THC was not associated with a significant increase in positive symptoms and no significant condition x genotype interaction was observed on psychotic symptoms. However, the authors reported a significant three-way condition x genotype x CAPE-trait interaction which suggested that pre-existing psychosis liability influenced the genetic moderation of THC-induced expression of psychosis. The analysis is perhaps too complex to be wholly convincing.

However, in the same study, THC exposure caused significantly greater impairment on a delayed recognition task in subjects with the Val-Val genotype than in those with the Val-Met or the Met-Met genotypes. Another study found that those with the Val- Val genotype performed worse on the digit span backwards task under the effect of intravenous THC than those with other genotypes (Tunbridge et al., 2015), while there was no difference in the positive psychotic symptoms induced by THC.

Two case-control studies have found that a variant of AKT1 increases risk of psychotic illness among cannabis users, and a third has shown that those who carry this variant show a greater psychotogenic response to smoked cannabis (Di Forti et al., 2012; Morgan et al., 2016; van Winkel et al., 2011). A variant in the D2 receptor gene may also increase psychosis risk, and the risk is even greater in carriers of both this variant and the AKT1 risk allele (Colizzi et al., 2015).

## 7. The endocannabinoid system and schizophrenia

In the brain, the primary endocannabinoids are anandamide and 2-arachidonylglycerol (2-AG) (Katona and Freund, 2012). Anandamide, a partial cannabinoid 1 receptor (CB1R) agonist, shows relatively low concentrations in brain (Katona and Freund, 2012; Pertwee et al., 2010), whereas 2-AG, a full CB1R agonist, is present at much higher concentrations (Stella et al., 1997).

### 7.1. Studies of schizophrenia

Much of what we know about the neurochemistry of schizophrenia has its origins in studies of drug-induced psychoses (Paparelli et al., 2011). Not surprisingly, the finding that exogenous cannabinoids can induce psychosis has led on to the question of whether the endogenous endocannabioid system may be abnormal in schizophrenia.

Levels of anandamide were reported to be eight-fold higher in the cerebrospinal fluid (CSF) in first-episode, antipsychotic-naive schizophrenia subjects (Giuffrida et al., 2004) as well as individuals with prodomal psychotic symptoms (Koethe et al., 2009). Furthermore, blood levels of anandamide were three-fold higher in schizophrenia subjects off antipsychotic medications (De Marchi et al., 2003). However, CSF studies have not detected quantifiable levels of 2-AG (F. M. Leweke et al., 1999a,b). Thus, how levels of endocannabinoids measured in the CSF and peripheral blood relate to endocannabinoid signaling in the brain remains unclear. Unfortunately, attempts to quantify 2-AG directly in postmortem human studies have not been successful due to a marked effect of postmortem delay on 2-AG (Palkovits et al., 2008).

For the synthesizing and metabolizing enzymes for 2-AG, cortical levels of the mRNAs for DAGL$\alpha$, DAGL$\beta$, MGL and FAAH (fatty acid amide hydrolase, which hydrolyzes anandamide but not 2-AG) did not differ between schizophrenia patients and healthy subjects (Volk et al., 2010). However, ABHD6 mRNA levels were elevated in the prefrontal cortex of schizophrenia subjects who were younger and had a shorter illness duration (Volk et al., 2013). Because of the co-localization of ABHD6 with DAGL in the dendritic spines of dorsolateral prefrontal cortex pyramidal neurons (Ludányi et al., 2011; Marrs et al., 2010; Yoshida et al., 2006), higher ABHD6 mRNA levels in the earlier stages of the illness may lead to higher metabolism of 2-AG directly at the source of 2-AG production in dendritic spines, which could in turn lead to lower 2-AG levels available for binding to CB1Rs.

Higher CB1R binding in the cerebral cortex of schizophrenia subjects has been consistently reported in postmortem studies (Dalton et al., 2011; Dean et al., 2001; Jenko et al., 2012; Newell et al., 2006; Zavitsanou et al., 2004). However, studies of CB1R mRNA and protein levels have produced conflicting results. For example, two studies found no differences between schizophrenia and unaffected comparison subjects in prefrontal cortical CB1R mRNA levels (Dalton et al., 2011; Urigüen et al., 2009). In contrast, prefrontal CB1R mRNA and protein levels were reported to be lower in schizophrenia (Eggan et al., 2008, 2010).

Interpreting the above conflicting findings is difficult. However, in the same schizophrenia subjects in whom lower CB1R mRNA and protein levels were found (Volk et al., 2014), a receptor binding study reported higher levels of [3H]-OMAR binding to CB1R, and a negative correlation between [3H]-OMAR receptor binding and CB1R mRNA levels in adjacent tissue sections (Volk et al., 2014). This combination of lower CB1R mRNA and protein levels and higher CB1R receptor binding in the prefrontal cortex of the same schizophrenia subjects suggests several possible interpretations of the nature of endocannabinoid system dysfunction in schizophrenia (Volk and Lewis, 2016).

One possibility is that the number of CB1Rs accessible to ligand binding in the membrane of CCK-containing axon terminals is increased in schizophrenia, while the total amount of intracellular CB1R is reduced, as suggested by the findings of lower CB1R mRNA and protein immunoreactivity levels. In contrast to most G-protein coupled receptors, which are found in the plasma membrane, CB1Rs are largely localized intracellularly (Rozenfeld, 2011). Thus, altered trafficking of the CB1R in schizophrenia could give rise to higher levels of membrane-bound CB1Rs even in the face of less transcription and lower intracellular levels of the receptor. A second option is that the higher levels of CB1R binding reflect greater receptor affinity. Unfortunately, CB1R receptor affinity has not been adequately quantified in schizophrenia (Jenko et al., 2012). However, higher CB1R affinity might be related to higher ABHD6 levels in schizophrenia as prefrontal ABHD6 mRNA and CB1R binding levels were positively correlated in the illness (Volk et al., 2013). Because ABHD6 and DAGL are co-localized in the dendritic spines of cortical pyramidal neurons (Ludányi et al., 2011; Marrs et al., 2010; Yoshida et al., 2006), greater expression of ABHD6 mRNA could lead to higher metabolism of 2-AG directly at the source of 2-AG production in dendritic spines, which would in turn lower 2-AG activity at CB1Rs. Lower 2-AG signaling could then lead to a compensatory up-regulation in membrane localization through either altered trafficking or higher affinity of the affected CB1R in that location (Volk and Lewis, 2016).

### *7.2. Impact of cannabis use on the endocannabinoid system in schizophrenia*

Under normal physiological conditions, activation of CB1Rs suppresses GABA release only from the CB1R-containing terminals that synapse onto the pyramidal cells whose activity stimulates endocannabinoid signaling. In contrast, exogenous cannabinoids affect all CB1R terminals, suppressing GABA release onto pyramidal cells without selectivity. The adverse consequences of this indiscriminate activation of CB1Rs may be exacerbated in schizophrenia due to the presence of higher membrane-bound levels of CB1R or higher levels of CB1R affinity (Dalton et al., 2011; Dean et al., 2001; Jenko et al., 2012; Newell et al., 2006; Volk et al., 2014; Zavitsanou et al., 2004).

In addition, lower mRNA and protein expression of the GABA synthesizing enzyme GAD67, one of the most consistently reported findings in postmortem studies of schizophrenia (Akbarian et al., 1995; Curley et al., 2011; Duncan et al., 2010; Guidotti et al., 2000; Straub et al., 2007; Volk et al., 2000), could lead to deficits in GABA synthesis. Such a deficit might be partially compensated by a reduction in 2-AG-mediated suppression of GABA release from CB1R-containing axon terminals due to the greater expression of ABHD6 in the early stages of schizophrenia (Volk et al., 2013). This hypothesis suggests that the adverse effects of cannabis use in individuals with schizophrenia might be due to the cannabis-mediated activation of CB1Rs counteracting the compensatory effect of lower 2-AG signaling, at least in the earlier stages of the illness. Consistent with this interpretation, the deleterious effects of cannabis use appear to be most prominent in younger individuals (Casadio et al., 2011; Compton et al., 2009; Galvez-Buccollini et al., 2012).

## 8. Conclusions

In our opinion, the epidemiological evidence clearly demonstrates that heavy cannabis use, particularly of high potency types, or of synthetic cannabinoids, increases the risk of psychosis, especially in those who start their use in their early teens (Murray and Di Forti, 2016). Gage et al. (2016), who extensively reviewed epidemiological studies concerning cannabis use and psychosis for possible confounding, bias, misclassification, and reverse causation, concluded that “epidemiologic studies provide strong enough evidence to warrant a public health message that cannabis use can increase the risk of psychotic disorders”. However, argument continues over the proportion of psychosis that could be prevented if nobody used cannabis; estimates range from 6.2 to 24% in different countries (Di Forti et al., 2015; Henquet et al., 2005).

Genetic predisposition to schizophrenia does not explain more than a small proportion of cannabis use in the general population or in patients; this undermines the argument that those individuals who develop psychosis following cannabis use were destined to develop schizophrenia anyway and their cannabis use was simply an epiphenomenon of this predisposition or in patients.

Preliminary evidence from candidate gene studies has suggested that certain individuals are especially vulnerable to cannabis-induced psychosis by virtue of possessing risk alleles in DRD2 and AKT1 genes. These genes are involved in postsynapic dopamine signalling so these findings are compatible with the idea that chronic cannabis use induces postsynaptic supersensitivity in the associative striatum; this supersensitivity could explain the occurrence of psychosis in cannabis users in the face of low striatal dopamine (Murray et al., 2014).

Human laboratory studies have conclusively demonstrated that THC and other cannabinoids can induce transient positive and negative psychotic symptoms and mimic some of the cognitive and neurophysiological abnormalities found in schizophrenia. However, to what extent findings from these experimental studies can be extrapolated to chronic recurrent psychotic disorders is uncertain.

Structural brain imaging studies examining effects of cannabis use are highly inconsistent. It is very likely that much of this is related to small sample sizes, a problem that has plagued brain imaging studies in general (David et al., 2013). Furthermore, much of this literature is limited by inadequate matching of potential confounders between the cannabis and control groups. For example, cannabis and alcohol use are highly correlated (Fergusson et al., 1994), and alcohol use is robustly associated with reduced grey matter volumes (Fein et al., 2002; Jernigan et al., 1991; Makris et al., 2008; Paul et al., 2008). Simply covarying for alcohol use can lead to spurious results (Miller and Chapman, 2001; Weiland et al., 2015). In a study that tightly controlled for potential confounders, users and non-users were matched for age and alcohol problem (AUDIT) scores (Weiland et al., 2015), daily cannabis use had no effect on any MRI measure.

Functional imaging has produced more interesting findings. For example, THC can reduce ability to regulate inhibitory control over impulses, thoughts, emotions and behaviours as exemplified by its ability to attenuatuate inferior frontal activation during response inhibition tasks. THC's well-known effects on learning are reflected in altered medial temporal activation during encoding. THC also attenuates striatal activation during recall, and this has been correlated with the level of positive psychotic symptoms it induced. THC also appears to modulate the neural substrate of salience processing, providing another mechanism by which cannabis could induce or exacerbate psychotic symptoms (D'Souza et al., 2004, 2005). These findings although plausible require replication in larger samples.

It has been more difficult to demonstrate the acute effects of THC on dopamine in humans than animals but it seems likely that it does release dopamine in the striatum though to a smaller extent than for example amphetamine; one, as yet unreplicated, study suggested a great effect in psychotic patients and their relatives, raising the possibility of genetic vulnerability. Chronic users of cannabis show decreased striatal dopamine synthesis, which contrasts with the usual findings in acutely psychotic patients.

Growing understanding of the impact of exogenous cannabioids on the endocannabinoid system, and of the components of the system that are disturbed in schizophrenia, provide plausible molecular explanations for the association between cannabis and psychosis. However, the precise mechanism/s by which cannabinoids induce psychosis in humans remains elusive; understanding these mechanisms is important not just for cannabis-associated psychosis but may also inform our understanding of psychosis in general.

## References


Achim, A.M., Lepage, M., 2005. Episodic memory-related activation in schizophrenia: meta-analysis. Br. J. Psychiatry 187 (6), 500–509.

Akbarian, S., Kim, J.J., Potkin, S.G., Hagman, J.O., Tafazzoli, A., Bunney, W.E., Jones, E.G., 1995. Gene expression for glutamic acid decarboxylase is reduced without loss of neurons in prefrontal cortex of schizophrenics. Archives General Psychiatry 52 (4), 258–266.

Albrecht, D.S., Skosnik, P.D., Vollmer, J.M., Brumbaugh, M.S., Perry, K.M., Mock, B.H., Yoder, K.K., 2012. Striatal D(2)/D(3) receptor availability is inversely correlated with cannabis consumption in chronic marijuana users. Drug Alcohol Depend. 2013 (128), 52–57.

Allen, P., Chaddock, C. a., Howes, O.D., Egerton, A., Seal, M.L., Fusar-Poli, P., McGuire, P.K., 2012. Abnormal relationship between medial temporal lobe and subcortical dopamine function in people with an ultra high risk for psychosis. Schizophr. Bull. 38 (5), 1040–1049.

Ames, F., 1958. A clinical and metabolic study of acute intoxication with cannabis sativa and its role in the model psychoses. Br. J. Psychiatry 104 (437), 972–999.

Andréasson, S., Engström, A., Allebeck, P., Rydberg, U., 1987. Cannabis and schizophrenia a longitudinal study of Swedish conscripts. Lancet 330 (8574), 1483–1486.

Archie, S., Boydell, K.M., Stasiulis, E., et al., 2013. Reflections of young people who have had a first episode of psychosis: what attracted them to use alcohol and illicit drugs? Early Interv. Psychiatry 7, 193–199.

Arnold, C., Allott, K., Farhall, J., Killackey, E., Cotton, S., 2015. Neurocognitive and social cognitive predictors of cannabis use in first-episode psychosis. Schizophr. Res. 168 (1), 231–237.

Arseneault, L., Cannon, M., Poulton, R., Murray, R., Caspi, A., Moffitt, T.E., 2002. Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. BMJ 325 (7374), 1212–1213, 4/1212.

Ashtari, M., Avants, B., Cyckowski, L., Cervellione, K.L., Roofeh, D., Cook, P., Kumra, S., 2011. Medial temporal structures and memory functions in adolescents with heavy cannabis use. J. Psychiatric Res. 45 (8), 1055–1066.

Atakan, Z., Bhattacharyya, S., Allen, P., Martín-Santos, R., Crippa, J. a, Borgwardt, S.J., McGuire, P., 2013. Cannabis affects people differently: inter-subject variation in the psychotogenic effects of Δ9-tetrahydrocannabinol: a functional magnetic resonance imaging study with healthy volunteers. Psychol. Med. 43 (6), 1255–1267.

Barkus, E., Morrison, P.D., Vuletic, D., Dickson, J.C., Ell, P.J., Pilowsky, L.S., Murray, R.M., 2011. Does intravenous Δ9-tetrahydrocannabinol increase dopamine release? A SPET study. J. Psychopharmacol. (Oxf. Engl.) 25 (11), 1462–1468.

Batalla, A., Bhattacharyya, S., Yücel, M., Fusar-Poli, P., Crippa, J.A., Nogué, S., Martin-Santos, R., 2013. Structural and functional imaging studies in chronic cannabis users: a systematic review of adolescent and adult findings. PLoS One 8 (2), e55821.

Batalla, A., Soriano-Mas, C., Lõpez-Solà, M., Torrens, M., Crippa, J.A., Bhattacharyya, S., Martín-Santos, R., 2014. Modulation of brain structure by catechol-O- methyltransferase Val 158Met polymorphism in chronic cannabis users. Addict. Biol. 19 (4), 722–732.

Battistella, G., Fornari, E., Annoni, J.-M., Chtioui, H., Dao, K., Fabritius, M., Giroud, C., 2014. Long-term effects of cannabis on brain structure. Neuropsychopharmacol. Offic. Publ. Am. Coll. Neuropsychopharmacol. (Febr.) 1–8.

Beaulieu, C., 2002. The basis of anisotropic water diffusion in the nervous system - a technical review. NMR Biomed. 15 (7–8), 435–455.

Bechtold, J., Hipwell, A., Lewis, D.A., Loeber, R., Pardini, D., 2016. 2016 Concurrent and sustained cumulative effects of adolescent marijuana use on subclinical psychotic symptoms. Am. J. Psychiatry 173 (8), 781–789.

Becker, M.P., Collins, P.F., Lim, K.O., Muetzel, R.L., Luciana, M., 2015. Longitudinal changes in white matter microstructure after heavy cannabis use. Dev. Cogn. Neurosci. 16, 23–35.

Bhattacharyya, S., Atakan, Z., Martin-Santos, R., Crippa, J.A., Kambeitz, J., Malhi, S., McGuire, P.K., 2015a. Impairment of inhibitory control processing related to acute psychotomimetic effects of cannabis. Eur. Neuropsychopharmacol. 25 (1), 26–37.

Bhattacharyya, S., Atakan, Z., Martin-Santos, R., Crippa, J.A., Kambeitz, J., Prata, D., McGuire, P.K., 2012a. Preliminary report of biological basis of sensitivity to the effects of cannabis on psychosis: AKT1 and DAT1 genotype modulates the effects of δ-9-tetrahydrocannabinol on midbrain and striatal function. Mol. Psychiatry 17 (12), 1152–1155.

Bhattacharyya, S., Crippa, J.A., Allen, P., Martin-Santos, R., Borgwardt, S., Fusar-Poli, P., McGuire, P.K., 2012b. Induction of psychosis by Δ9-tetrahydrocannabinol reflects modulation of prefrontal and striatal function during attentional salience processing. Archives General Psychiatry 69 (1), 27–36.

Bhattacharyya, S., Falkenberg, I., Martin-Santos, R., Atakan, Z., Crippa, J.A., Giampietro, V., McGuire, P., 2015. Cannabinoid modulation of functional connectivity within regions processing attentional salience. Neuropsychopharmacology 40 (6), 1343–1352.

Bhattacharyya, S., Fusar-Poli, P., Borgwardt, S., Martin-Santos, R., Nosarti, C., O'Carroll, C., McGuire, P., 2009a. Modulation of mediotemporal and ventrostriatal function in humans by Delta9-tetrahydrocannabinol: a neural basis for the effects of Cannabis sativa on learning and psychosis. Archives General Psychiatry 66 (4), 442–451.

Bhattacharyya, S., Morrison, P.D., Fusar-Poli, P., Martin-Santos, R., Borgwardt, S., Winton-Brown, T., McGuire, P.K., 2010a. Opposite effects of delta-9- tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. Neuropsychopharmacol. Offic. Publ. Am. Coll. Neuropsychopharmacol. 35 (3), 764–774.

Bianconi, F., Bonomo, M., Marconi, A., Kolliakou, A., Stilo, S.A., Iyegbe, C., Di Forti, M., 2016. Differences in cannabis-related experiences between patients with a first episode of psychosis and controls. Psychol. Med. 46 (5), 995–1003.

Block, R.I., O'Leary, D.S., Ehrhardt, J.C., Augustinack, J.C., Ghoneim, M., Arndt, S., Hall, J.A., 2000. Effects of frequent marijuana use on brain tissue volume and composition. Neuroreport 11 (3), 491–496.

Bloomfield, M. a P., Morgan, C. J. a, Egerton, A., Kapur, S., Curran, H.V., Howes, O.D., 2014. Dopaminergic function in cannabis users and its relationship to cannabis-induced psychotic symptoms. Biol. Psychiatry 75 (6), 470–478.

Böcker, K.B.E., Hunault, C.C., Gerritsen, J., Kruidenier, M., Mensinga, T.T., Kenemans, J.L., 2010. Cannabinoid modulations of resting state EEG θ power and working memory are correlated in humans. J. Cognitive Neurosci. 22 (9), 1906–1916.

Borgwardt, S.J., Allen, P., Bhattacharyya, S., Fusar-Poli, P., Crippa, J.A., Seal, M.L., McGuire, P.K., 2008a. Neural basis of ??-9-Tetrahydrocannabinol and cannabidiol: effects during response inhibition. Biol. Psychiatry 64 (11), 966–973.

Borgwardt, S.J., Allen, P., Bhattacharyya, S., Fusar-Poli, P., Crippa, J.A., Seal, M.L., McGuire, P.K., 2008b. Neural basis of Δ-9-tetrahydrocannabinol and cannabidiol: effects during response inhibition. Biol. Psychiatry 64 (11), 966–973.

Bossong, M.G., Jager, G., van Hell, H.H., Zuurman, L., Jansma, J.M., Mehta, M. a., Ramsey, N.F., 2012a. Effects of Δ9-tetrahydrocannabinol administration on human encoding and recall memory function: a pharmacological fMRI study. J. Cognitive Neurosci. 24 (3), 588–599.

Bossong, M.G., Jansma, J.M., Van Hell, H.H., Jager, G., Oudman, E., Saliasi, E., Ramsey, N.F., 2012b. Effects of Δ9-tetrahydrocannabinol on human working memory function. Biol. Psychiatry 71 (8), 693–699.

Bossong, M.G., Mehta, M.A., van Berckel, B.N.M., Howes, O.D., Kahn, R.S., Stokes, P.R.A., 2015. Further human evidence for striatal dopamine release induced by administration of Δ9-tetrahydrocannabinol (THC): selectivity to limbic striatum. Psychopharmacology 232 (15), 2723–2729.

Bossong, M.G., van Berckel, B.N.M., Boellaard, R., Zuurman, L., Schuit, R.C., Windhorst, A.D., Kahn, R.S., 2009. Delta 9-tetrahydrocannabinol induces dopamine release in the human striatum. Neuropsychopharmacology. Offic. Publ. Am. Coll. Neuropsychopharmacol. 34 (3), 759–766.

Bossong, M.G., van Hell, H.H., Jager, G., Kahn, R.S., Ramsey, N.F., Jansma, J.M., 2013a. The endocannabinoid system and emotional processing: a pharmacological fMRI study with {increment}9-tetrahydrocannabinol. Eur. Neuropsychopharmacol. 23, 1687–1697.

Bossong, M.G., van Hell, H.H., Jager, G., Kahn, R.S., Ramsey, N.F., Jansma, J.M., 2013b. The endocannabinoid system and emotional processing: a pharmacological

fMRI study with Δ9-tetrahydrocannabinol. Eur. Neuropsychopharmacol. J. Eur. Coll. Neuropsychopharmacol. 23 (12), 1687–1697.
Boydell, J., van Os, J., Caspi, A., Kennedy, N., Giouroukou, E., Fearon, P., Murray, R.M., 2006. Trends in cannabis use prior to first presentation with schizophrenia, in South-East London between 1965 and 1999. Psychol. Med. 36 (10), 1441–1446.
Bramon, E., Rabe-Hesketh, S., Sham, P., Murray, R.M., Frangou, S., 2004. Meta-analysis of the P300 and P50 waveforms in schizophrenia. Schizophr. Res. 70 (2–3), 315–329.
Burns, H.D., Van Laere, K., Sanabria-Bohórquez, S., Hamill, T.G., Bormans, G., Eng, W., Hargreaves, R.J., 2007. [18F]MK-9470, a positron emission tomography (PET) tracer for in vivo human PET brain imaging of the cannabinoid-1 receptor. Proc. Natl. Acad. Sci. U. S. A. 104 (23), 9800–9805.
Casadio, P., Fernandes, C., Murray, R.M., Di Forti, M., 2011. Cannabis use in young people: the risk for schizophrenia. Neurosci. Biobehav. Rev. 35 (8), 1779–1787.
Caspi, A., Moffitt, T.E., Cannon, M., McClay, J., Murray, R., Harrington, H., Craig, I.W., 2005. Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene X environment interaction. Biol. Psychiatry 57 (10), 1117–1127.
Castaneto, M.S., Gorelick, D.A., Desrosiers, N.A., Hartman, R.L., Pirard, S., Huestis, M.A., 2014. Synthetic cannabinoids: epidemiology, pharmacodynamics, and clinical implications. Drug Alcohol Depend. 144, 12–41.
Cheer, J.F., Wassum, K.M., Heien, M.L.A.V., Phillips, P.E.M., Wightman, R.M., 2004. Cannabinoids enhance subsecond dopamine release in the nucleus accumbens of awake rats. J. Neurosci. 24 (18), 4394–4400.
Churchwell, J.C., Lopez-Larson, M., Yurgelun-Todd, D.A., 2010. Altered frontal cortical volume and decision making in adolescent cannabis users. Front. Psychol. 1, 225.
Colizzi, M., Iyegbe, C., Powell, J., Blasi, G., Bertolino, A., Murray, R.M., Di Forti, M., 2015. Interaction between DRD2 and AKT1 genetic variations on risk of psychosis in cannabis users: a case-control study. NPJ Schizophr. 1, 15025.
Compton, M.T., Kelley, M.E., Ramsay, C.E., Pringle, M., Goulding, S.M., Esterberg, M.L., Walker, E.F., 2009. Association of pre-onset cannabis, alcohol, and tobacco use with age at onset of prodrome and age at onset of psychosis in first-episode patients. Am. J. Psychiatry 166 (11), 1251–1257.
Cortes-Briones, J.A., Cahill, J.D., Skosnik, P.D., Mathalon, D.H., Williams, A., Sewell, R.A., D'Souza, D.C., 2015a. The psychosis-like effects of Δ9-tetrahydrocannabinol are associated with increased cortical noise in healthy humans. Biol. Psychiatry 78 (11), 805–813.
Cortes-Briones, J., Skosnik, P.D., Mathalon, D., Cahill, J., Pittman, B., Williams, A., D'Souza, D.C., 2015b. Δ9-THC disrupts gamma (γ)–Band neural oscillations in humans. Neuropsychopharmacology 40 (9), 2124–2134.
Cousijn, J., Wiers, R.W., Ridderinkhof, K.R., Brink, W. Van Den, Veltman, D.J., Goudriaan, A.E., 2012. NeuroImage Grey matter alterations associated with cannabis use : results of a VBM study in heavy cannabis users and healthy controls. NeuroImage 59 (4), 3845–3851.
Crippa, J. A. de S., Zuardi, A.W., Garrido, G.E.J., Wichert-Ana, L., Guarnieri, R., Ferrari, L., Busatto, G.F., 2004. Effects of cannabidiol (CBD) on regional cerebral blood flow. Neuropsychopharmacology 29 (2), 417–426.
Curley, A.A., Arion, D., Volk, D.W., Asafu-Adjei, J.K., Sampson, A.R., Fish, K.N., Lewis, D.A., 2011. Cortical deficits of glutamic acid decarboxylase 67 expression in schizophrenia: clinical, protein, and cell type-specific features. Am. J. Psychiatry 168 (9), 921–929.
Curran, V.H., Brignell, C., Fletcher, S., Middleton, P., Henry, J., 2002. Cognitive and subjective dose-response effects of acute oral Δ9-tetrahydrocannabinol (THC) in infrequent cannabis users. Psychopharmacology 164 (1), 61–70.
D'Souza, D.C., Abi-Saab, W.M., Madonick, S., Forselius-Bielen, K., Doersch, A., Braley, G., Krystal, J.H., 2005. Delta-9-tetrahydrocannabinol effects in schizophrenia: implications for cognition, psychosis, and addiction. Biol. Psychiatry 57 (6), 594–608.
D'Souza, D.C., Braley, G., Blaise, R., Vendetti, M., Oliver, S., Pittman, B., Perry, E., 2008a. Effects of haloperidol on the behavioral, subjective, cognitive, motor, and neuroendocrine effects of Delta-9-tetrahydrocannabinol in humans. Psychopharmacology 198 (4), 587–603.
D'Souza, D.C., Cortes-Briones, J.A., Ranganathan, M., Thurnauer, H., Creatura, G., Surti, T., Skosnik, P.D., 2016. Rapid changes in CB1 receptor availability in cannabis dependent males after abstinence from cannabis. Biol. Psychiatry 1, 60–67.
D'Souza, D.C., Fridberg, D.J., Skosnik, P.D., Williams, A., Roach, B., Singh, N., Mathalon, D., 2012. Dose-related modulation of event-related potentials to novel and target stimuli by intravenous $\Delta^9$-THC in humans. Neuropsychopharmacology. Offic. Publ. Am. Coll. Neuropsychopharmacol. 37 (7), 1632–1646.
D'Souza, D.C., Perry, E., MacDougall, L., Ammerman, Y., Cooper, T., Wu, Y., Krystal, J.H., 2004. The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. Neuropsychopharmacology 29 (8), 1558–1572.
D'Souza, D.C., Ranganathan, M., Braley, G., Gueorguieva, R., Zimolo, Z., Cooper, T., Krystal, J., 2008b. Blunted psychotomimetic and amnestic effects of delta-9-tetrahydrocannabinol in frequent users of cannabis. Neuropsychopharmacol. Offic. Publ. Am. Coll. Neuropsychopharmacol. 33 (10), 2505–2516.
Dalton, V.S., Long, L.E., Weickert, C.S., Zavitsanou, K., 2011. Paranoid schizophrenia is characterized by increased CB1 receptor binding in the dorsolateral prefrontal cortex. Neuropsychopharmacology 36 (8), 1620–1630.
David, S.P., Ware, J.J., Chu, I.M., Loftus, P.D., Fusar-Poli, P., Radua, J., Munafò, M.R., Ioannidis, J.P., 2013 Jul 25. Potential reporting bias in fMRI studies of the brain. PLoS One 8 (7), e70104. http://dx.doi.org/10.1371/journal.pone.0070104. Print 2013.
De Marchi, N., De Petrocellis, L., Orlando, P., Daniele, F., Fezza, F., Di Marzo, V., 2003. Endocannabinoid signalling in the blood of patients with schizophrenia. Lipids Health Dis. 2 (1), 5.
Dean, B., Sundram, S., Bradbury, R., Scarr, E., Copolov, D., 2001. Studies on [3H]CP-55940 binding in the human central nervous system: regional specific changes in density of cannabinoid-1 receptors associated with schizophrenia and cannabis use. Neuroscience 103 (1), 9–15.
de Wilde, O.M., Bour, L.J., Dingemans, P.M., Koelman, J.H.T.M., Linszen, D.H., 2007. A meta-analysis of P50 studies in patients with schizophrenia and relatives: differences in methodology between research groups. Schizophr. Res. 97 (1–3), 137–151.
Demirakca, T., Sartorius, A., Ende, G., Meyer, N., Welzel, H., Skopp, G., Hermann, D., 2011. Diminished gray matter in the hippocampus of cannabis users : possible protective effects of cannabidiol. Drug Alcohol Depend. 114 (2–3), 242–245.
Diaconescu, A.O., Jensen, J., Wang, H., Willeit, M., Menon, M., Kapur, S., McIntosh, A.R., 2011. Aberrant effective connectivity in schizophrenia patients during appetitive conditioning. Front. Hum. Neurosci. 4 (January), 239.
Di Forti, M., Iyegbe, C., Sallis, H., Kolliakou, A., Falcone, M.A., Paparelli, A., Murray, R.M., 2012. Confirmation that the AKT1 (rs2494732) genotype influences the risk of psychosis in cannabis users. Biol. Psychiatry 72 (10), 811–816.
Di Forti, M., Marconi, A., Carra, E., Fraietta, S., Trotta, A., Bonomo, M., Murray, R.M., 2015. Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: a case-control study. Lancet Psychiatry 2 (3), 233–238.
Di Forti, M., Morgan, C., Dazzan, P., Pariante, C., Mondelli, V., Marques, T.R., Murray, R.M., 2009. High-potency cannabis and the risk of psychosis. Br. J. Psychiatry J. Ment. Sci. 195 (6), 488–491.
Di Forti, M., Sallis, H., Allegri, F., Trotta, A., Ferraro, L., Stilo, S. a, Murray, R.M., 2013. Daily use, especially of high-potency cannabis, drives the earlier onset of psychosis in cannabis users. Schizophr. Bull. 1–9.
Duncan, C.E., Webster, M.J., Rothmond, D.A., Bahn, S., Elashoff, M., Shannon Weickert, C., 2010. Prefrontal GABAA receptor α-subunit expression in normal postnatal human development and schizophrenia. J. Psychiatric Res. 44 (10), 673–681.
Edwards, C.R., Skosnik, P.D., Steinmetz, A.B., O'Donnell, B.F., Hetrick, W.P., 2009. Sensory gating impairments in heavy cannabis users are associated with altered neural oscillations. Behav. Neurosci. 123 (4), 894–904.
Eggan, S.M., Hashimoto, T., Lewis, D.A., 2008. Reduced cortical cannabinoid 1 receptor messenger RNA and protein expression in schizophrenia. Archives General Psychiatry 65 (7), 772–784.
Eggan, S.M., Stoyak, S.R., Verrico, C.D., Lewis, D.A., 2010. Cannabinoid CB1 receptor immunoreactivity in the prefrontal cortex: comparison of schizophrenia and major depressive disorder. Neuropsychopharmacol. Offic. Publ. Am. Coll. Neuropsychopharmacol. 35 (10), 2060–2071.
Eldreth, D.A., Matochik, J.A., Cadet, J.L., Bolla, K.I., 2004. Abnormal brain activity in prefrontal brain regions in abstinent marijuana users. NeuroImage 23 (3), 914–920.
ElSohly, M.A., Mehmedic, Z., Foster, S., Gon, C., Chandra, S., Church, J.C., 2016. Changes in cannabis potency over the last 2 decades (1995–2014): analysis of current data in the United States. Biol. Psychiatry 79 (7), 613–619.
EMCDDA, 2016. European Drug Report 2016. European Monitoring of Drugs and Drugs Addiction. Lisbon.
Emrich, H.M., Weber, M.M., Wendl, A., Zihl, J., von Meyer, L., Hanisch, W., 1991. Reduced binocular depth inversion as an indicator of cannabis-induced censorship impairment. Pharmacol. Biochem. Behav. 40 (3), 689–690. Retrieved from.
Englund, A., Atakan, Z., Kralj, A., Tunstall, N., Murray, R., Morrison, P., 2016. The effect of five day dosing with THCV on THC-induced cognitive, psychological and physiological effects in healthy male human volunteers: a placebo-controlled, double- blind, crossover pilot trial. J. Psychopharmacol. 30 (2).
Englund, A., Morrison, P.D., Nottage, J., Hague, D., Kane, F., Bonaccorso, S., Kapur, S., 2013. Cannabidiol inhibits THC-elicited paranoid symptoms and hippocampal-dependent memory impairment. J. Psychopharmacol. 27 (1).
Fattore, L., 2016. Synthetic cannabinoids—further evidence supporting the relationship between cannabinoids and psychosis. Biol. Psychiatry 79 (7), 539–548.
Fein, G., Di Sclafani, V., Cardenas, V.A., Goldmann, H., Tolou-Shams, M., Meyerhoff, D.J., 2002. Cortical gray matter loss in treatment-naive alcohol dependent individuals. Alcohol Clin. Exp. Res. 26 (4), 558–564.
Ferdinand, R.F., Sondeijker, F., van der Ende, J., Selten, J.-P., Huizink, A., Verhulst, F.C., 2005. Cannabis use predicts future psychotic symptoms, and vice versa. Addict. (Abingdon, Engl. 100 (5), 612–618.
Fergusson, D.M., Boden, J.M., Horwood, L.J., 2015. Psychosocial sequelae of cannabis use and implications for policy: findings from the Christchurch Health and Development Study. Soc. Psychiatry Psychiatric Epidemiol. 50 (9), 1317–1326.
Fergusson, D.M., Horwood, L.J., Swain-Campbell, N.R., 2003. Cannabis dependence and psychotic symptoms in young people. Psychol. Med. 33 (1), 15–21. Retrieved from.
Fergusson, D.M., Lynskey, M.T., Horwood, L.J., 1994. Alcohol consumption and associated problems in a birth cohort of 15 year olds. N. Z. Med. J. 107 (977), 167–170. Retrieved from.
Ferraro, L., Russo, M., O'Connor, J., Wiffen, B.D.R., Falcone, M.A., Sideli, L., Di Forti, M.,

2013. Cannabis users have higher premorbid IQ than other patients with first onset psychosis. Schizophr. Res. 150 (1), 129–135.
Filbey, F.M., Aslan, S., Calhoun, V.D., Spence, J.S., Damaraju, E., Caprihan, A., Carter, C., 2014. Long-term effects of marijuana use on the brain. Proc. Natl. Acad. Sci. 111 (47), 16913–16918.
Freeman, D., Dunn, G., Murray, R.M., Evans, N., Lister, R., Antley, A., Morrison, P.D., 2015. How cannabis causes paranoia: using the intravenous administration of Δ9- tetrahydrocannabinol (THC) to identify key cognitive mechanisms leading to paranoia. Schizophr. Bull. 41 (2), 391–399.
French, L., Gray, C., Leonard, G., Perron, M., Pike, G.B., Richer, L., Paus, T., 2015. Early cannabis use, polygenic risk score for schizophrenia and brain maturation in adolescence. JAMA Psychiatry 72 (10), 1002–1011.
Fusar-Poli, P., 2009. Distinct effects of Δ9-tetrahydrocannabinol and cannabidiol on neural activation during emotional processing. Archives General Psychiatry 66 (1), 95.
Fusar-Poli, P., Allen, P., Bhattacharyya, S., Crippa, J.A., Mechelli, A., Borgwardt, S., McGuire, P., 2010. Modulation of effective connectivity during emotional processing by Delta 9-tetrahydrocannabinol and cannabidiol. Int. J. Neuropsychopharmacol./Offic. Sci. J. Coll. Int. Neuropsychopharmacol. (CINP) 13 (4), 421–432.
Gage, S.H., Hickman, M., Heron, J., Munafò, M.R., Lewis, G., Macleod, J., Zammit, S., 2014. Associations of cannabis and cigarette use with psychotic experiences at age 18: findings from the Avon Longitudinal Study of Parents and Children. Psychol. Med. 44 (16), 3435–3444.
Gage, S.H., Hickman, M., Zammit, S., 2016. Association between cannabis and psychosis: epidemiologic evidence. Biol. Psychiatry 79 (7), 549–556.
Gage, S.H., Jones, H.J., Burgess, S., Bowden, J., Davey Smith, G., Zammit, S., Munafò, M.R., 2017. Assessing causality in associations between cannabis use and schizophrenia risk: a two-sample Mendelian randomization study. Psychol. Med. 47 (5), 971–980.
Galvez-Buccollini, J.A., Proal, A.C., Tomaselli, V., Trachtenberg, M., Coconcea, C., Chun, J., Delisi, L.E., 2012. Association between age at onset of psychosis and age at onset of cannabis use in non-affective psychosis. Schizophr. Res. 139 (1–3), 157–160.
Gill, K.E., Poe, L., Azimov, N., et al., 2015. Reasons for cannabis use among youths at ultra high risk for psychosis. Early Interv. Psychiatry 9, 207–210.
Giuffrida, A., Leweke, F.M., Gerth, C.W., Schreiber, D., Koethe, D., Faulhaber, J., Piomelli, D., 2004. Cerebrospinal anandamide levels are elevated in acute schizophrenia and are inversely correlated with psychotic symptoms. Neuropsychopharmacology. Offic. Publ. Am. Coll. Neuropsychopharmacol. 29 (11), 2108–2114.
Gorka, S.M., Fitzgerald, D.A., de Wit, H., Phan, K.L., 2015. Cannabinoid modulation of amygdala subregion functional connectivity to social signals of threat. Int. J. Neuropsychopharmacol./Offic. Sci. J. Coll. Int. Neuropsychopharmacol. (CINP) 18 (3), 104.
Grant, I., Gonzalez, R., Carey, C.L., Natarajan, L., Wolfson, T., 2003. Non-acute (residual) neurocognitive effects of cannabis use: a meta-analytic study. J. Int. Neuropsychol. Soc. 9 (5), 679–689.
Gruber, S.A., Dahlgren, M.K., Sagar, K.A., Gönenç, A., Lukas, S.E., 2014. Worth the wait: effects of age of onset of marijuana use on white matter and impulsivity. Psychopharmacology 231 (8), 1455–1465.
Gruber, S.A., Yurgelun-Todd, D.A., 2005. Neuroimaging of marijuana smokers during inhibitory processing: a pilot investigation. Cognitive Brain Res. 23 (1), 107–118.
Guidotti, A., Auta, J., Davis, J.M., Di-Giorgi-Gerevini, V., Dwivedi, Y., Grayson, D.R., DiGiorgi Gerevini, V., 2000. Decrease in reelin and glutamic acid decarboxylase67 (GAD67) expression in schizophrenia and bipolar disorder: a postmortem brain study. Archives General Psychiatry 57 (11), 1061–1069. Retrieved from.
Hallak, J.E.C., Machado-de-Sousa, J.P., Crippa, J.A.S., Sanches, R.F., Trzesniak, C., Chaves, C., Zuardi, A.W., 2010. Performance of schizophrenic patients in the Stroop Color Word Test and electrodermal responsiveness after acute administration of cannabidiol (CBD). Revista Brasileira de Psiquiatria (São Paulo, Brazil : 1999) 32 (1), 56–61. Retrieved from.
Haney, M., Evins, A.E., 2016. Does cannabis cause, exacerbate or ameliorate psychiatric Disorders? An oversimplified debate discussed. Neuropsychopharmacology 41 (2), 393–401.
Hardwick, S., 2008. Home Office Cannabis Potency Study 2008. Home Office. Retrieved from http://www.dldocs.stir.ac.uk/documents/potency.pdf.
Hart, C.L., van Gorp, W., Haney, M., Foltin, R.W., Fischman, M.W., 2001. Effects of acute smoked marijuana on complex cognitive performance. Neuropsychopharmacol. Offic. Publ. Am. Coll. Neuropsychopharmacol. 25 (5), 757–765.
Heinrichs, R.W., Zakzanis, K.K., 1998. Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. Neuropsychology 12 (3), 426–445. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9673998.
Heishman, S.J., Huestis, M.A., Henningfield, J.E., Cone, E.J., 1990. Acute and residual effects of marijuana: profiles of plasma THC levels, physiological, subjective, and performance measures. Pharmacol. Biochem. Behav. 37 (3), 561–565. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1965045.
Henquet, C., Krabbendam, L., Spauwen, J., Kaplan, C., Lieb, R., Wittchen, H.-U., van Os, J., 2005. Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. BMJ 330 (7481), 11–20.
Henquet, C., Rosa, A., Krabbendam, L., Papiol, S., Fananás, L., Drukker, M., van Os, J., 2006. An experimental study of catechol-o-methyltransferase Val158Met moderation of delta-9-tetrahydrocannabinol-induced effects on psychosis and cognition. Neuropsychopharmacol. Offic. Publ. Am. Coll. Neuropsychopharmacol. 31 (12).
Hill, M., 2015. Perspective: Be clear about the real risks. Nature 525 (7570), S14.
Hirvonen, J., Goodwin, R.S., Li, C.-T., Terry, G.E., Zoghbi, S.S., Morse, C., Innis, R.B., 2012. Reversible and regionally selective downregulation of brain cannabinoid CB1 receptors in chronic daily cannabis smokers. Mol. Psychiatry 17 (6), 642–649.
Hooker, W.D., Jones, R.T., 1987. Increased susceptibility to memory intrusions and the Stroop interference effect during acute marijuana intoxication. Psychopharmacology 91 (1), 20–24. Retrieved from.
Howes, O.D., Montgomery, A.J., Asselin, M.-C., Murray, R.M., Valli, I., Tabraham, P., Grasby, P.M., 2009. Elevated striatal dopamine function linked to prodromal signs of schizophrenia. Archives General Psychiatry 66 (1), 13.
Ilan, A.B., Gevins, A., Coleman, M., ElSohly, M.A., de Wit, H., 2005. Neurophysiological and subjective profile of marijuana with varying concentrations of cannabinoids. Behav. Pharmacol. 16 (5–6), 487–496. Retrieved from.
Isbell, H., Gorodetzsky, C.W., Jasinski, D., Claussen, U., von Spulak, F., Korte, F., 1967. Effects of (−)delta-9-trans-tetrahydrocannabinol in man. Psychopharmacologia 11 (2), 184–188.
Isbell, H., Jasinski, D.R., 1969. A comparison of LSD-25 with (-)-delta-9-trans-tetrahydrocannabinol (THC) and attempted cross tolerance between LSD and THC. Psychopharmacologia 14 (2), 115–123.
Jacobsen, L.K., Mencl, W.E., Westerveld, M., Pugh, K.R., 2004. Impact of cannabis use on brain function in adolescents. Ann. N. Y. Acad. Sci. 1021, 384–390.
Jansma, J.M., van Hell, H.H., Vanderschuren, L.J.M.J., Bossong, M.G., Jager, G., Kahn, R.S., Ramsey, N.F., 2013. THC reduces the anticipatory nucleus accumbens response to reward in subjects with a nicotine addiction. Transl. Psychiatry 3 (2), e234.
Jenko, K.J., Hirvonen, J., Henter, I.D., Anderson, K.B., Zoghbi, S.S., Hyde, T.M., Kleinman, J.E., 2012. Binding of a tritiated inverse agonist to cannabinoid CB1 receptors is increased in patients with schizophrenia. Schizophr. Res. 141 (2–3), 185–188.
Jensen, J., Willeit, M., Zipursky, R.B., Savina, I., Smith, A.J., Menon, M., Kapur, S., 2008. The formation of abnormal associations in schizophrenia: neural and behavioral evidence. Neuropsychopharmacology 33 (3), 473–479.
Jernigan, T.L., Butters, N., DiTraglia, G., Schafer, K., Smith, T., Irwin, M., Cermak, L.S., 1991. Reduced cerebral grey matter observed in alcoholics using magnetic resonance imaging. Alcohol. Clin. Exp. Res. 15 (3), 418–427.
Juckel, G., Roser, P., Nadulski, T., Stadelmann, A.M., Gallinat, J., 2007. Acute effects of Delta9-tetrahydrocannabinol and standardized cannabis extract on the auditory evoked mismatch negativity. Schizophr. Res. 97 (1–3), 109–117. http://doi.org/10.1016/j.schres.2007.08.015.
Kaladjian, A., Jeanningros, R., Azorin, J.M., Grimault, S., Anton, J.L., Mazzola-Pomietto, P., 2007. Blunted activation in right ventrolateral prefrontal cortex during motor response inhibition in schizophrenia. Schizophr. Res. 97 (1–3), 184–193.
Kanayama, G., Rogowska, J., Pope, H.G., Gruber, S.A., Yurgelun-Todd, D.A., 2004. Spatial working memory in heavy cannabis users: a functional magnetic resonance imaging study. Psychopharmacology 176 (3–4), 239–247.
Kapur, S., 2003. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. Am. J. Psychiatry 160 (1), 13–23.
Katona, I., Freund, T.F., 2012. Multiple functions of endocannabinoid signaling in the brain. Annu. Rev. Neurosci. 35, 529–558. http://doi.org/10.1146/annurev-neuro-062111-150420.
Kaufmann, R.M., Kraft, B., Frey, R., Winkler, D., Weiszenbichler, S., Bäcker, C., Kress, H.G., 2010. Acute psychotropic effects of oral cannabis extract with a defined content of Δ $^{9}$ -tetrahydrocannabinol (THC) in healthy volunteers. Pharmacopsychiatry 43 (1), 24–32.
Kleinloog, D., Liem-Moolenaar, M., Jacobs, G., Klaassen, E., de Kam, M., Hijman, R., van Gerven, J., 2012. Does olanzapine inhibit the psychomimetic effects of $\Delta^{9}$-tetrahydrocannabinol? J. Psychopharmacol. (Oxf. Engl. 26 (10), 1307–1316.
Kleinloog, D., Rombouts, S., Zoethout, R., Klumpers, L., Niesters, M., Khalili-Mahani, N., van Gerven, J., 2015. Subjective effects of ethanol, morphine, Δ 9-tetrahydrocannabinol, and ketamine following a pharmacological challenge are related to functional brain connectivity. Brain Connect. 5 (10) brain.2014.0314.
Klumpers, L.E., Cole, D.M., Khalili-Mahani, N., Soeter, R.P., te Beek, E.T., Rombouts, S.A.R.B., van Gerven, J.M.A., 2012. Manipulating brain connectivity with D-9- tetrahydrocannabinol: a pharmacological resting state FMRI study. NeuroImage 63 (3), 1701–1711.
Klumpers, L.E., Fridberg, M., de Kam, M.L., Little, P.B., Jensen, N.O., Kleinloog, H.D., van Gerven, J.M.A., 2013a. Peripheral selectivity of the novel cannabinoid receptor antagonist TM38837 in healthy subjects. Br. J. Clin. Pharmacol. 76 (6), 846–857.
Klumpers, L.E., Roy, C., Ferron, G., Turpault, S., Poitiers, F., Pinquier, J.-L., van Gerven, J.M.A., 2013b. Surinabant, a selective cannabinoid receptor type 1 antagonist, inhibits Δ $^{9}$ -tetrahydrocannabinol-induced central nervous system and heart rate effects in humans. Br. J. Clin. Pharmacol. 76 (1), 65–77.
Koenders, L., Cousijn, J., Vingerhoets, W.A.M., Van Den Brink, W., Wiers, R.W., Meijer, C.J., De Haan, L., 2016. Grey matter changes associated with heavy cannabis use: a longitudinal sMRI study. PLoS One 11 (5), 1–13.
Koethe, D., Gerth, C.W., Neatby, M.A., Haensel, A., Thies, M., Schneider, U., Leweke, F.M., 2006. Disturbances of visual information processing in early states of psychosis and experimental delta-9-tetrahydrocannabinol altered

states of consciousness. Schizophr. Res. 88 (1–3), 142–150.
Koethe, D., Giuffrida, A., Schreiber, D., Hellmich, M., Schultze-lutter, F., Ruhrmann, S., Leweke, F.M., 2009. Anandamide Elevation in Cerebrospinal Fluid in Initial Prodromal States of Psychosis, pp. 371–372.
Kopell, B.S., Tinklenberg, J.R., Hollister, L.E., 1972. Contingent negative variation amplitudes. Archives General Psychiatry 27 (6), 809.
Krishnan, G.P., Hetrick, W.P., Brenner, C.A., Shekhar, A., Steffen, A.N., O'Donnell, B.F., 2009. Steady state and induced auditory gamma deficits in schizophrenia. NeuroImage 47 (4), 1711–1719.
Ksir, C., Hart, C.L., 2016. Cannabis and psychosis: a critical overview of the relationship. Curr. Psychiatry Rep. 18 (2), 12.
Ksir, C., Hart, C.L., Lawlor, E., Arendt, M., Nordentoft, M., 2016. Correlation still does not imply causation. Lancet Psychiatry 3 (5), 401.
Kuepper, R., Ceccarini, J., Lataster, J., van Os, J., van Kroonenburgh, M., van Gerven, J.M.A., Henquet, C., 2013a. Delta-9-tetrahydrocannabinol-induced dopamine release as a function of psychosis risk: 18F-fallypride positron emission tomography study. PloS One 8 (7), e70378.
Kuepper, R., Ceccarini, J., Lataster, J., van Os, J., van Kroonenburgh, M., van Gerven, J. M. a, Henquet, C., 2013b. Delta-9-tetrahydrocannabinol-induced dopamine release as a function of psychosis risk: 18F-fallypride positron emission tomography study. PloS One 8 (7), e70378.
Kwon, J.S., O'Donnell, B.F., Wallenstein, G.V., Greene, R.W., Hirayasu, Y., Nestor, P.G., McCarley, R.W., 1999. Gamma frequency-range abnormalities to auditory stimulation in schizophrenia. Archives General Psychiatry 56 (11), 1001–1005. Retrieved from.
Large, M., Sharma, S., Compton, M.T., Slade, T., Nielssen, O., 2011. Cannabis use and earlier onset of psychosis: a systematic meta-analysis. Archives General Psychiatry 68 (6), 555–561.
Leroy, C., Karila, L., Martinot, J.-L., Lukasiewicz, M., Duchesnay, E., Comtat, C., Trichard, C., 2012. Striatal and extrastriatal dopamine transporter in cannabis and tobacco addiction: a high-resolution PET study. Addict. Biol. 17 (6), 981–990.
Leweke, F.M., Giuffrida, A., Wurster, U., Emrich, H.M., Piomelli, D., 1999a. Elevated endogenous cannabinoids in schizophrenia. Neuroreport 10 (8), 1665–1669.
Leweke, F.M., Schneider, U., Radwan, M., Schmidt, E., Emrich, H.M., 2000. Different effects of nabilone and cannabidiol on binocular depth inversion in Man. Pharmacol. Biochem. Behav. 66 (1), 175–181.
Leweke, F.M., Schneider, U., Thies, M., Münte, T.F., Emrich, H.M., 1999b. Effects of synthetic delta9-tetrahydrocannabinol on binocular depth inversion of natural and artificial objects in man. Psychopharmacology 142 (3), 230–235.
Leweke, M., Kampmann, C., Radwan, M., Dietrich, D.E., Johannes, S., Emrich, H.M., Münte, T.F., 1998. The effects of tetrahydrocannabinol on the recognition of emotionally charged words: an analysis using event-related brain potentials. Neuropsychobiology 37 (2), 104–111.
Lichtman, a H., Varvel, S. a, Martin, B.R., 2002. Endocannabinoids in cognition and dependence. Prostagl. Leukot. Essent. Fat. Acids 66 (2–3), 269–285.
Liem-Moolenaar, M., te Beek, E.T., de Kam, M.L., Franson, K.L., Kahn, R.S., Hijman, R., van Gerven, J. M. a., 2010. Central nervous system effects of haloperidol on THC in healthy male volunteers. J. Psychopharmacol. (Oxf. Engl. 24 (11), 1697–1708.
Light, G.A., Hsu, J.L., Hsieh, M.H., Meyer-Gomes, K., Sprock, J., Swerdlow, N.R., Braff, D.L., 2006. Gamma band oscillations reveal neural network cortical coherence dysfunction in schizophrenia patients. Biol. Psychiatry 60 (11), 1231–1240.
Lindemann, E., Malamud, W., 1934. Experimental analysis of the psychopathological effects of intoxicating drug. Am. J. Psychiatry 90 (4), 853–881.
Lisman, J., Buzsáki, G., 2008. A neural coding scheme formed by the combined function of gamma and theta oscillations. Schizophr. Bull. 34 (5), 974–980.
Løberg, E.M., Helle, S., Nygard, M., Berle, J. øystein, Kroken, R.A., Johnsen, E., 2014. The cannabis pathway to non-affective psychosis may reflect less neurobiological vulnerability. Fron. Psychiatry 5, 159. http://dx.doi.org/10.3389/fpsyt.2014.00159. Published online 2014 Nov 18.
Lorenzetti, V., Solowij, N., Whittle, S., Fornito, A., Lubman, D.I., Pantelis, C., Yücel, M., 2015. Gross morphological brain changes with chronic, heavy cannabis use. Br. J. Psychiatry 206 (1), 77–78.
Ludányi, A., Hu, S.S.-J., Yamazaki, M., Tanimura, A., Piomelli, D., Watanabe, M., Katona, I., 2011. Complementary synaptic distribution of enzymes responsible for synthesis and inactivation of the endocannabinoid 2-arachidonoylglycerol in the human hippocampus. Neuroscience 174, 50–63.
Makris, N., Oscar-Berman, M., Jaffin, S.K., Hodge, S.M., Kennedy, D.N., Caviness, V.S., Harris, G.J., 2008. Decreased volume of the brain reward system in alcoholism. Biol. Psychiatry 64 (3), 192–202.
Manrique-Garcia, E., Zammit, S., Dalman, C., Hemmingsson, T., Andreasson, S., Allebeck, P., 2012. Cannabis, schizophrenia and other non-affective psychoses: 35 years of follow-up of a population-based cohort. Psychol. Med. 42 (6), 1321–1328.
Marconi, A., Di Forti, M., Lewis, C., Murray, R.M., Vassos, E., 2016. Meta-analysis of the association between the level of cannabis use and risk of psychosis. Schizophr. Bull. 42 (5), 1262–1269.
Marks, D.F., MacAvoy, M.G., 1989. Divided attention performance in cannabis users and non-users following alcohol and cannabis separately and in combination. Psychopharmacology 99 (3), 397–401.
Marrs, W.R., Blankman, J.L., Horne, E.A., Thomazeau, A., Lin, Y.H., Coy, J., Stella, N., 2010. The serine hydrolase ABHD6 controls the accumulation and efficacy of 2-AG at cannabinoid receptors. Nat. Neurosci. 13 (8), 951–957.
Martin-Santos, R., Crippa, J. a, Batalla, a, Bhattacharyya, S., Atakan, Z., Borgwardt, S., McGuire, P.K., 2012. Acute effects of a single, oral dose of d9- tetrahydrocannabinol (THC) and cannabidiol (CBD) administration in healthy volunteers. Curr. Pharm. Des. 18 (32), 4966–4979.
Martinez, D., Narendran, R., 2010. Imaging neurotransmitter release by drugs of abuse. In: Current Topics in Behavioral Neurosciences, vol. 3, pp. 219–245.
Matochik, J.A., Eldreth, D.A., Cadet, J.L., Bolla, K.I., 2005. Altered brain tissue composition in heavy marijuana users. Drug Alcohol Depend. 77 (1), 23–30.
Mayor's Committee on Marihuana, 1944. The Marihuana Problem in New York City. Jacques Cattell Press, Philadelphia.
Medina, K.L., McQueeny, T., Nagel, B.J., Hanson, K.L., Yang, T.T., Tapert, S.F., 2009. Prefrontal cortex morphometry in abstinent adolescent marijuana users: subtle gender effects. Addict. Biol. 14 (4), 457–468.
Medina, K.L., Nagel, B.J., Park, A., Mcqueeny, T., Tapert, S.F., 2007. Depressive symptoms in adolescents: associations with white matter volume and marijuana use. J. Child Psychol. Psychiatry Allied Discip. 48 (6), 592–600.
Miller, G.A., Chapman, J.P., 2001. Misunderstanding analysis of covariance. J. Abnorm. Psychol. 110 (1), 40–48.
Miller, L.L., McFarland, D., Cornett, T.L., Brightwell, D., 1977. Marijuana and memory impairment: effect on free recall and recognition memory. Pharmacol. Biochem. Behav. 7 (2), 99–103.
Morgan, C.J.A., Curran, H.V., 2008. Effects of cannabidiol on schizophrenia-like symptoms in people who use cannabis. Br. J. Psychiatry J. Ment. Sci. 192 (4), 306–307.
Morgan, C.J.A., Freeman, T.P., Powell, J., Curran, H.V., 2016. AKT1 genotype moderates the acute psychotomimetic effects of naturalistically smoked cannabis in young cannabis smokers. Transl. Psychiatry 6, e738.
Morrison, P.D., Nottage, J., Stone, J.M., Bhattacharyya, S., Tunstall, N., Brenneisen, R., Ffytche, D.H., 2011. Disruption of frontal θ coherence by Δ9-tetrahydrocannabinol is associated with positive psychotic symptoms. Neuropsychopharmacol. Offic. Publ. Am. Coll. Neuropsychopharmacol. 36 (4), 827–836.
Morrison, P.D., Stone, J.M., 2011. Synthetic delta-9-tetrahydrocannabinol elicits schizophrenia-like negative symptoms which are distinct from sedation. Hum. Psychopharmacol. 26 (1), 77–80.
Morrison, P.D., Zois, V., McKeown, D.A., Lee, T.D., Holt, D.W., Powell, J.F., Murray, R.M., 2009a. The acute effects of synthetic intravenous Delta9-tetrahydrocannabinol on psychosis, mood and cognitive functioning. Psychol. Med. 39 (10), 1607–1616.
Morrison, P.D., Zois, V., McKeown, D. a, Lee, T.D., Holt, D.W., Powell, J.F., Murray, R.M., 2009b. The acute effects of synthetic intravenous Delta9-tetrahydrocannabinol on psychosis, mood and cognitive functioning. Psychol. Med. 39 (10), 1607–1616.
Murray, R.M., Di Forti, M., 2016. Cannabis and Psychosis: what degree of proof do we require? Biol. Psychiatry 79 (7), 514–515.
Murray, R.M., Mehta, M., Di Forti, M., 2014. Different dopaminergic abnormalities underlie cannabis dependence and cannabis-induced psychosis. Biol. Psychiatry 75, 430–431.
Murray, R.M., Quigley, H., Quattrone, D., Englund, A., Di Forti, M., 2016. Traditional marijuana, high-potency cannabis and synthetic cannabinoids: increasing risk for psychosis. World Psychiatry 15 (3), 195–204.
Nestor, L., Roberts, G., Garavan, H., Hester, R., 2008. Deficits in learning and memory: parahippocampal hyperactivity and frontocortical hypoactivity in cannabis users. NeuroImage 40 (3), 1328–1339.
Newell, K.A., Deng, C., Huang, X.-F., 2006. Increased cannabinoid receptor density in the posterior cingulate cortex in schizophrenia. Exp. Brain Res. 172 (4), 556–560.
Nottage, J.F., Stone, J., Murray, R.M., Sumich, A., Bramon-Bosch, E., ffytche, D., Morrison, P.D., 2015. Delta-9-tetrahydrocannabinol, neural oscillations above 20 Hz and induced acute psychosis. Psychopharmacology 232 (3), 519–528.
Orr, J.M., Paschall, C.J., Banich, M.T., 2016. Recreational marijuana use impacts white matter integrity and subcortical (but not cortical) morphometry. NeuroImage Clin. 12, 47–56.
Pagliaccio, D., Barch, D.M., Bogdan, R., Wood, P.K., Lynskey, M.T., Heath, A.C., Agrawal, A., 2015. Shared predisposition in the association between cannabis use and subcortical brain structure. JAMA Psychiatry 72 (10), 994–1001.
Palkovits, M., Harvey-White, J., Liu, J., Kovacs, Z.S., Bobest, M., Lovas, G., Kunos, G., 2008. Regional distribution and effects of postmortal delay on endocannabinoid content of the human brain. Neuroscience 152 (4), 1032–1039.
Papanti, D., Schifano, F., Botteon, G., Bertossi, F., Mannix, J., Vidoni, D., Bonavigo, T., 2013. Spiceophrenia " : a Systematic Overview of " Spice " -related Psychopathological Issues and a Case Report, (November 2012), pp. 379–389.
Paparelli, A., Forti, M. Di, Morrison, P.D., Murray, R.M., 2011. Drug-induced psychosis: how to avoid star gazing in schizophrenia research by looking at more obvious sources of Light. Front. Behav. Neurosci. 5.
Patterson, J.V., Hetrick, W.P., Boutros, N.N., Jin, Y., Sandman, C., Stern, H., Bunney, W.E., 2008. P50 sensory gating ratios in schizophrenics and controls: a review and data analysis. Psychiatry Res. 158 (2), 226–247.
Paul, C.A., Au, R., Fredman, L., Massaro, J.M., Seshadri, S., Decarli, C., Wolf, P.A., 2008. Association of alcohol consumption with brain volume in the Framingham study. Arch. Neurol. 65 (10), 1363–1367.
Pertwee, R.G., Howlett, A.C., Abood, M.E., Alexander, S.P.H., Di Marzo, V., Elphick, M.R., Ross, R.A., 2010. International union of basic and clinical pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB1 and CB2. Pharmacol. Rev. 62 (4).
Phan, K.L., Angstadt, M., Golden, J., Onyewuenyi, I., Popovska, A., de Wit, H., 2008.

Cannabinoid modulation of amygdala reactivity to social signals of threat in humans. J. Neurosci. Offic. J. Soc. Neurosci. 28 (10), 2313–2319.
Pierre, J.M., Gandal, M., Son, M., 2016. Cannabis-induced psychosis associated with high potency "wax dabs". Schizophr. Res. 172 (1–3), 211–212.
Pijlman, F.T.A., Rigter, S.M., Hoek, J., Goldschmidt, H.M.J., Niesink, R.J.M., 2005. Strong increase in total delta-THC in cannabis preparations sold in Dutch coffee shops. Addict. Biol. 10 (2), 171–180.
Power, R.A., Verweij, K.J.H., Zuhair, M., Montgomery, G.W., Henders, A.K., Heath, A.C., Martin, N.G., 2014. Genetic predisposition to schizophrenia associated with increased use of cannabis. Mol. Psychiatry 19 (11), 1201–1204.
Price, J.S., McQueeny, T., Shollenbarger, S., Browning, E.L., Wieser, J., Lisdahl, K.M., 2015. Effects of marijuana use on prefrontal and parietal volumes and cognition in emerging adults. Psychopharmacology 232 (16), 2939–2950.
Raber, J.C., Elzinga, S., Kaplan, C., 2015. Understanding dabs: contamination concerns of cannabis concentrates and cannabinoid transfer during the act of dabbing. J. Toxicol. Sci. 40 (6), 797–803.
Radhakrishnan, R., Skosnik, P.D., Cortes-Briones, J., Sewell, R.A., Carbuto, M., Schnakenberg, A., D'Souza, D.C., 2015. GABA deficits enhance the psychotomimetic effects of Δ9-THC. Neuropsychopharmacology. Offic. Publ. Am. Coll. Neuropsychopharmacol. 40 (8), 2047–2056.
Ranganathan, M., Carbuto, M., Braley, G., Elander, J., Perry, E., Pittman, B., D'Souza, D.C., 2012. Naltrexone does not attenuate the effects of intravenous Δ9- tetrahydrocannabinol in healthy humans. Int. J. Neuropsychopharmacol. 15 (9), 1251–1264.
Ranganathan, M., D'Souza, D.C., D'Souza, D.C., 2006. The acute effects of cannabinoids on memory in humans: a review. Psychopharmacology 188 (4), 425–444.
Reginsson, G.W., Ingason, A., Euesden, J., Bjornsdottir, G., Olafsson, S., Sigurdsson, E., Stefansson, K., 2017. Polygenic risk scores for schizophrenia and bipolar disorder associate with addiction. Addict. Biol.
Renault, P.F., Schuster, C.R., Freedman, D.X., Sikic, B., de Mello, D.N., 1974. Repeat administration of marihuana smoke to humans. Archives General Psychiatry 31 (1), 95–102.
Rentzsch, J., Penzhorn, A., Kernbichler, K., Plöckl, D., Gómez-Carrillo de Castro, A., Gallinat, J., Jockers-Scherübl, M.C., 2007. Differential impact of heavy cannabis use on sensory gating in schizophrenic patients and otherwise healthy controls. Exp. Neurol. 205 (1), 241–249.
Ripke, S., the Schizophrenia Working Group of the Psychiatric Genetics Consortium, 2014. Biological insights from 108 schizophrenia-associated genetic loci. Nature 511, 421–427.
Rigucci, S., Marques, T., Di Forti, M., et al., 2016. Effect of high-potency cannabis on corpus callosum microstructure. Psychol. Med. 46 (4), 841–854.
Rognli, E.B., Berge, J., Håkansson, A., Bramness, J.G., 2015. Long-term risk factors for substance-induced and primary psychosis after release from prison. A longitudinal study of substance users. Schizophr. Res. 168 (1–2), 185–190.
Roiser, J.P., Howes, O.D., Chaddock, C.A., Joyce, E.M., McGuire, P., 2012. Neural and behavioral correlates of aberrant salience in individuals at risk for psychosis. Schizophr. Bull. 39 (6), 1328–1336.
Roser, P., Juckel, G., Rentzsch, J., Nadulski, T., Gallinat, J., Stadelmann, A.M., 2008. Effects of acute oral Delta9-tetrahydrocannabinol and standardized cannabis extract on the auditory P300 event-related potential in healthy volunteers. Euro. Neuropsychopharmacol. J. Eur. Coll. Neuropsychopharmacol. 18 (8), 569–577.
Rössler, W., Hengartner, M.P., Angst, J., Ajdacic-Gross, V., 2012. Linking substance use with symptoms of subclinical psychosis in a community cohort over 30 years. Addiction 107 (6), 1174–1184.
Rovai, L., Maremmani, A.G.I., Pacini, M., Pani, P.P., Rugani, F., Lamanna, F., Maremmani, I., 2013. Negative dimension in psychiatry. Amotivational syndrome as a paradigm of negative symptoms in substance abuse. Riv. Di Psichiatr. 48 (1), 1–9.
Rozenfeld, R., 2011. Type I cannabinoid receptor trafficking: all roads lead to lysosome. Traffic 12 (1), 12–18.
Rubia, K., Russell, T., Bullmore, E.T., Soni, W., Brammer, M.J., Simmons, A., Sharma, T., 2001. An fMRI study of reduced left prefrontal activation in schizophrenia during normal inhibitory function. Schizophr. Res. 52 (1–2), 47–55.
Ruiz-Veguilla, M., Callado, L.F., Ferrin, M., 2012. Neurological soft signs in patients with psychosis and cannabis abuse: a systematic review and meta-analysis of paradox. Curr. Pharm. Des. 18 (32), 5156–5164.
Schacht, J.P., Hutchison, K.E., Filbey, F.M., 2012. Associations between cannabinoid receptor-1 (CNR1) variation and hippocampus and amygdala volumes in heavy cannabis users. Neuropsychopharmacol. Offic. Publ. Am. Coll. Neuropsychopharmacol. 37 (11), 2368–2376.
Schoeler, T., Kambeitz, J., Behlke, I., Murray, R., Bhattacharyya, S., 2016a. The effects of cannabis on memory function in users with and without a psychotic disorder: findings from a combined meta-analysis. Psychol. Med. 46 (1), 177–188.
Schoeler, T., Monk, A., Sami, M.B., Klamerus, E., Foglia, E., Brown, R., Bhattacharyya, S., 2016b. Continued versus discontinued cannabis use in patients with psychosis: a systematic review and meta-analysis. Lancet Psychiatry 3 (3), 215–225.
Schubart, C.D., Sommer, I.E.C., van Gastel, W. a, Goetgebuer, R.L., Kahn, R.S., Boks, M.P.M., 2011. Cannabis with high cannabidiol content is associated with fewer psychotic experiences. Schizophr. Res. 130 (1–3), 216–221.
Sevy, S., Smith, G.S., Ma, Y., Dhawan, V., Chaly, T., Kingsley, P.B., Eidelberg, D., 2008. Cerebral glucose metabolism and D2/D3 receptor availability in young adults with cannabis dependence measured with positron emission tomography. Psychopharmacology 197 (4), 549–556.
Sherif, M., Radhakrishnan, R., D'Souza, D.C., Ranganathan, M., 2016. Human laboratory studies on cannabinoids and psychosis. Biol. Psychiatry 79 (7), 526–538.
Shollenbarger, S.G., Price, J., Wieser, J., Lisdahl, K., 2015. Poorer frontolimbic white matter integrity is associated with chronic cannabis use, FAAH genotype, and increased depressive and apathy symptoms in adolescents and young adults. NeuroImage Clin. 8, 117–125.
Sneider, J.T., Mashhoon, Y., Silveri, M.M., 2013. A review of magnetic resonance spectroscopy studies in marijuana using adolescents and adults. J. Addict. Res. Ther. 4.
Solowij, N., Michie, P.T., 2007. Cannabis and cognitive dysfunction: parallels with endophenotypes of schizophrenia? J. Psychiatry & Neurosci. JPN 32 (1), 30–52.
Spaderna, M., Addy, P.H., D'Souza, D.C., 2013. Spicing things up: synthetic cannabinoids. Psychopharmacology 228 (4), 525–540.
Spencer, K.M., Niznikiewicz, M.A., Shenton, M.E., McCarley, R.W., 2008. Sensory-evoked gamma oscillations in chronic schizophrenia. Biol. Psychiatry 63 (8), 744–747.
Stadelmann, A.M., Juckel, G., Arning, L., Gallinat, J., Epplen, J.T., Roser, P., 2011. Association between a cannabinoid receptor gene (CNR1) polymorphism and cannabinoid-induced alterations of the auditory event-related P300 potential. Neurosci. Lett. 496 (1), 60–64.
Stella, N., Schweitzer, P., Piomelli, D., 1997. A second endogenous cannabinoid that modulates long-term potentiation. Nature 388 (6644), 773–778.
Stokes, P. R. a, Egerton, A., Watson, B., Reid, A., Breen, G., Lingford-Hughes, A., Mehta, M. a., 2010. Significant decreases in frontal and temporal [11C]-raclopride binding after THC challenge. NeuroImage 52 (4), 1521–1527.
Stokes, P. R. a, Mehta, M. a, Curran, H.V., Breen, G., Grasby, P.M., 2009. Can recreational doses of THC produce significant dopamine release in the human striatum? NeuroImage 48 (1), 186–190.
Straub, R.E., Lipska, B.K., Egan, M.F., Goldberg, T.E., Callicott, J.H., Mayhew, M.B., Weinberger, D.R., 2007. Allelic variation in GAD1 (GAD67) is associated with schizophrenia and influences cortical function and gene expression. Mol. Psychiatry 12 (9), 854–869.
Swift, W., Wong, A., Li, K.M., Arnold, J.C., McGregor, I.S., 2013. Analysis of cannabis seizures in NSW, Australia: cannabis potency and cannabinoid profile. PLoS One 8 (7), e70052.
Tait, R.J., Caldicott, D., Mountain, D., Hill, S.L., Lenton, S., 2015. A systematic review of adverse events arising from the use of synthetic cannabinoids and their associated treatment. Clin. Toxicol. Phila. Pa.) 1–13.
Tapert, S.F., Schweinsburg, A.D., Drummond, S.P.A., Paulus, M.P., Brown, S.A., Yang, T.T., Frank, L.R., 2007. Functional MRI of inhibitory processing in abstinent adolescent marijuana users. Psychopharmacology 194 (2), 173–183.
Tart, C., 1970. Marijuana intoxication : common experiences. Nature 226 (5247), 701–704.
Thompson, J.L., Urban, N., Slifstein, M., Xu, X., Kegeles, L.S., Girgis, R.R., Abi-Dargham, A., 2013. Striatal dopamine release in schizophrenia comorbid with substance dependence. Mol. Psychiatry 18 (8), 909–915.
Tien, A.Y., Anthony, J.C., 1990. Epidemiological analysis of alcohol and drug use as risk factors for psychotic experiences. J. Nerv. Ment. Dis. 178 (8), 473–480.
Tunbridge, E.M., Dunn, G., Murray, R.M., Evans, N., Lister, R., Stumpenhorst, K., Freeman, D., 2015. Genetic moderation of the effects of cannabis: catechol-O-methyltransferase (COMT) affects the impact of 9-tetrahydrocannabinol (THC) on working memory performance but not on the occurrence of psychotic experiences. J. Psychopharmacol.
Tzilos, G.K., Cintron, C.B., Wood, J.B.R., Simpson, N.S., Young, A.D., Pope Jr., H.G., Yurgelun-Todd, D.A., 2005. Lack of hippocampal volume change in long- term heavy cannabis users. Am. J. Addict. 14 (1), 64–72.
Urban, N.B.L., Slifstein, M., Thompson, J.L., Xu, X., Girgis, R.R., Raheja, S., Abi-Dargham, A., 2012. Dopamine release in chronic cannabis users: a [11c] raclopride positron emission tomography study. Biol. Psychiatry 71 (8), 677–683.
Urigüen, L., García-Fuster, M.J., Callado, L.F., Morentin, B., La Harpe, R., Casadó, V., Meana, J.J., 2009. Immunodensity and mRNA expression of A2A adenosine, D2 dopamine, and CB1 cannabinoid receptors in postmortem frontal cortex of subjects with schizophrenia: effect of antipsychotic treatment. Psychopharmacology 206 (2), 313–324.
van de Giessen, E., Weinstein, J.J., Cassidy, C.M., Haney, M., Dong, Z., Ghazzaoui, R., Abi-Dargham, A., 2017. Deficits in striatal dopamine release in cannabis dependence. Mol. Psychiatry 22 (1), 68–75. Cannabis Use and Psychosis: A Longitudinal Population-based Study. American Journal of Epidemiology, 156(4), 319–327.
van Winkel, R., van Beveren, N.J.M., Simons, C., 2011. AKT1 moderation of cannabis-induced cognitive alterations in psychotic disorder. Neuropsychopharmacol.: Offici. Publ. Am. Coll. Neuropsychopharmacol. 36 (12), 2529–2537.
Vaucher, J., Keating, B.J., Lasserre, A.M., Gan, W., Lyall, D.M., Ward, J., Holmes, M.V., 2017. Cannabis use and risk of schizophrenia: a Mendelian randomization study. Molecular Psychiatry. http://dx.doi.org/10.1038/mp.2016.252. Jan 24. [Epub ahead of print].
van Os, J., Bak, M., Hanssen, M., Bijl, R.V., Graaf, R. de, Verdoux, H., 2002. Cannabis use and psychosis: a longitudinal population-based study. Am. J. Epidemiol. 156 (4), 319–327.
Verweij, K.J.H., Abdellaoui, A., Nivard, M.G., Sainz Cort, A., Ligthart, L., Draisma, H.H.M., Vink, J.M., 2017. Short communication: genetic association between schizophrenia and cannabis use. Drug Alcohol Depend. 171.
Volk, D.W., Austin, M.C., Pierri, J.N., Sampson, A.R., Lewis, D.A., 2000. Decreased glutamic acid decarboxylase67 messenger RNA expression in a subset of

prefrontal cortical gamma-aminobutyric acid neurons in subjects with schizophrenia. Archives General Psychiatry 57 (3), 237–245.
Volk, D.W., Eggan, S.M., Horti, A.G., Wong, D.F., Lewis, D.A., 2014. Reciprocal alterations in cortical cannabinoid receptor 1 binding relative to protein immunoreactivity and transcript levels in schizophrenia. Schizophr. Res. 159 (1), 124–129.
Volk, D.W., Eggan, S.M., Lewis, D.A., 2010. Alterations in metabotropic glutamate receptor 1α and regulator of G protein signaling 4 in the prefrontal cortex in schizophrenia. Am. J. Psychiatry 167 (12), 1489–1498.
Volk, D.W., Lewis, D.A., 2016. The role of endocannabinoid signaling in cortical inhibitory neuron dysfunction in schizophrenia. Biol. Psychiatry 79 (7), 595–603.
Volk, D.W., Siegel, B.I., Verrico, C.D., Lewis, D.A., 2013. Endocannabinoid metabolism in the prefrontal cortex in schizophrenia. Schizophr. Res. 147 (1), 53–57.
Volkow, N.D., Swanson, J.M., Evins, A.E., DeLisi, L.E., Meier, M.H., Gonzalez, R., Baler, R., 2016. Effects of cannabis use on human behavior, including cognition, motivation, and psychosis: a review. JAMA Psychiatry 73 (3), 292.
Volkow, N.D., Wang, G.-J., Telang, F., Fowler, J.S., Alexoff, D., Logan, J., Tomasi, D., 2014. Decreased dopamine brain reactivity in marijuana abusers is associated with negative emotionality and addiction severity. Proc. Natl. Acad. Sci. 1–8.
Voruganti, L.N., Slomka, P., Zabel, P., Mattar, A., Awad, A.G., 2001. Cannabis induced dopamine release: an in-vivo SPECT study. Psychiatry Res. 107 (3), 173–177.
Wang, X., Dow-Edwards, D., Keller, E., Hurd, Y.L., 2003. Preferential limbic expression of the cannabinoid receptor mRNA in the human fetal brain. Neuroscience 118 (3), 681–694.
Weiland, B.J., Thayer, R.E., Depue, B.E., Sabbineni, A., Bryan, A.D., Hutchison, K.E., 2015. Daily marijuana use is not associated with brain morphometric measures in adolescents or adults. J. Neurosci. 35 (4), 1505–1512.
Weiser, M., Knobler, H.Y., Noy, S., Kaplan, Z., 2002. Clinical characteristics of adolescents later hospitalized for schizophrenia. Am. J. Med. Genet. 114 (8), 949–955.
Weiss, A.P., Heckers, S., 2001. Neuroimaging of declarative memory in schizophrenia. Scand. J. Psychol. 42 (3), 239–250.
Wijayendran, S.B., O'Neill, A., Bhattacharyya, S., 2016. The effects of cannabis use on salience attribution: a systematic review. Acta Neuropsychiatr. 1–15.
Wiles, N.J., Zammit, S., Bebbington, P., Singleton, N., Meltzer, H., Lewis, G., 2006, June 1. Self-reported psychotic symptoms in the general population: results from the longitudinal study of the British National psychiatric morbidity survey. Br. J. Psychiatry 188 (6), 519–526.
Wilson, R.I., Nicoll, R.A., 2002. Endocannabinoid signaling in the brain. Science 296 (5568), 678–682.
Wilson, W., Mathew, R., Turkington, T., Hawk, T., Coleman, E., Provenzale, J., 2000. Brain morphological changes and early marijuana use. J. Addict. Dis. 19 (1), 1–22.
Winstock, A., Lynskey, M., Borschmann, R., Waldron, J., 2015. Risk of emergency medical treatment following consumption of cannabis or synthetic cannabinoids in a large global sample. J. Psychopharmacol. (Oxf. Engl. 29 (6), 698–703.
Winterer, G., Coppola, R., Goldberg, T.E., Egan, M.F., Jones, D.W., Sanchez, C.E., Weinberger, D.R., 2004. Prefrontal broadband noise, working memory, and genetic risk for schizophrenia. Am. J. Psychiatry 161 (3), 490–500.
Winterer, G., Weinberger, D.R., 2003. Cortical signal-to-noise ratio: insight into the pathophysiology and genetics of schizophrenia. Clin. Neurosci. Res. 3 (1), 55–66.
Winton-Brown, T.T., Allen, P., Bhattacharyya, S., Bhattacharrya, S., Borgwardt, S.J., Fusar-Poli, P., McGuire, P.K., 2011. Modulation of auditory and visual processing by delta-9-tetrahydrocannabinol and cannabidiol: an FMRI study. Neuropsychopharmacology. Offic. Publ. Am. Coll. Neuropsychopharmacol. 36 (7), 1340–1348.
Yang, G.J., Murray, J.D., Repovs, G., Cole, M.W., Savic, A., Glasser, M.F., Anticevic, A., 2014. Altered global brain signal in schizophrenia. Proc. Natl. Acad. Sci. 111 (20), 7438–7443.
Yip, S.W., DeVito, E.E., Kober, H., Worhunsky, P.D., Carroll, K.M., Potenza, M.N., 2014. Pretreatment measures of brain structure and reward-processing brain function in cannabis dependence: an exploratory study of relationships with abstinence during behavioral treatment1. Drug Alcohol Depend. 140, 33–41.
Yoshida, T., Fukaya, M., Uchigashima, M., Miura, E., Kamiya, H., Kano, M., Watanabe, M., 2006. Localization of diacylglycerol lipase- around postsynaptic spine suggests close proximity between production site of an endocannabinoid, 2-arachidonoyl- glycerol, and presynaptic cannabinoid CB1 receptor. J. Neurosci. 26 (18), 4740–4751.
Yücel, M., Solowij, N., Respondek, C., Whittle, S., Fornito, A., Pantelis, C., Lubman, D.I., 2008. Regional brain abnormalities associated with long-term heavy cannabis use. Archives General Psychiatry 65 (6), 694.
Yücel, M., Zalesky, A., Takagi, M.J., Bora, E., Fornito, A., Ditchfield, M., Lubman, D.I., 2010. White-matter abnormalities in adolescents with long-term inhalant and cannabis use: a diffusion magnetic resonance imaging study. J. Psychiatry Neurosci. 35 (6), 409–412.
Zalesky, A., Solowij, N., Yücel, M., Lubman, D.I., Takagi, M., Harding, I.H., Seal, M., 2012. Effect of long-term cannabis use on axonal fibre connectivity. Brain 135 (7), 2245–2255.
Zammit, S., Allebeck, P., Andreasson, S., Lundberg, I., Lewis, G., Gur, R. E. R. C., McGuire, P. K. (2002). Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study, 325(7374), 1199–1199.
Zammit, S., Owen, M.J., Evans, J., Heron, J., Lewis, G., 2011. Cannabis, COMT and psychotic experiences. Br. J. Psychiatry 199 (5), 380–385.
Zavitsanou, K., Garrick, T., Huang, X.F., 2004. Selective antagonist [3H]SR141716A binding to cannabinoid CB1 receptors is increased in the anterior cingulate cortex in schizophrenia. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 28 (2), 355–376.
Zuurman, L., Roy, C., Schoemaker, R.C., Hazekamp, A., den Hartigh, J., Bender, J.C.M.E., et al., 2008. Effect of intrapulmonary tetrahydrocannabinol administration in humans. J. Psychopharmacol. 22 (7), 707–716.