Does Smoking Cannabis Increase the Risk of Developing Schizophrenia?

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Abstract:

The association between cannabis and schizophrenia is both contentious and multifactorial. Schizophrenia is a psychotic disorder with complex epidemiology and aetiology, which often change over time and vary geographically. Cannabis has been used in many cultural settings for millennia, with constantly shifting trends in usage, potency and criminalisation over that time. The underpinning of any association between cannabis and schizophrenia is inextricably linked with how cannabinoids affect the brain. Exogenous cannabinoids, including those found in cannabis, disrupt the normal function of a naturally occurring cannabinoid system in the brain, with numerous consequences. An abundance of epidemiological, clinical and experimental evidence supports an association between the effects of cannabis on the brain and psychoses including schizophrenia. However, numerous methodological limitations affect these studies, and equally there is evidence which does not support an associative link. It therefore seems prudent to conceive of cannabis as a component cause, neither necessary nor sufficient but which should be taken seriously, particularly in susceptible individuals. Avenues for future research may change this consensus, indeed there is certainly still much to discover about the effects of cannabis and its constituents on the human brain.

Introduction:

There are many factors well-recognised as being potentially contributory in the aetiology of psychotic illnesses. One such well-established association is that between consumption of cannabis and the susceptibility to schizophrenic illness. This matter has been under intense scrutiny for many years, with myriad evidence demonstrating a positive association, whilst some studies fail to detect any association. Interest in this matter has filtered from scientific circles to become a matter of socio-political importance. The yo-yo fashion of changes in its legal classification reflects the fluctuations in current opinion. Its relative harm as a potentiating substance in serious mental illness is still not fully appreciated.

The following discussion will aim to address the above question, taking into account matters of established consensus as well as recent discoveries. By first introducing schizophrenia and cannabis as separate entities and discussing their elements, we may provide a platform on which to identify how the two may be intimately connected. Taking into account methodological issues and research limitations, what will then follow is an examination of the cumulative evidence to conclude whether, and to what extent, this association exists.

Schizophrenia:

The term 'Schizophrenia', coined by Swiss psychiatrist Eugene Bleuler in the early 20th century, is derived from the Greek words *skhizein* and *phrēn* meaning 'to split' and 'mind' respectively (Stringer et al., 2009). This likens schizophrenia to a condition characterised by a split personality, which was indeed the prevailing (mis)perception of the disease and its symptoms for many years. In fact, schizophrenia is broadly a psychotic illness but is more difficult to define specifically. Criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and the International Classification of Mental and Behavioural Disorders (ICD-10) are built on a constantly adapted consensus on symptomatic features and their duration to define schizophrenia (and other related psychotic disorders). However, even the details in these two manuals are somewhat disparate. Table 1 below summarizes the criteria used in each manual (American Psychiatric Association, 2000) (World Health Organization, 1992).

	ICD-10	DSM-IV
>1 of... (characteristic symptoms)	Thought echo, thought insertion/withdrawal/broadcast, passivity, delusional perception, third person auditory hallucinations, running commentary, persistent bizarre delusions	Bizarre delusions, third person auditory hallucinations, running commentary
OR >2 of... (characteristic symptoms)	Persistent hallucinations, thought disorder, catatonic behaviour, negative symptoms, significant behaviour change	Delusions, hallucinations, disorganized speech, grossly disorganized behaviour, negative symptoms
Duration	>1 month	>1 month of characteristic symptoms with >6 months of social/occupational dysfunction
Exclusion Criteria	Mood disorders, schizoaffective disorder, Overt brain disease, drug intoxication or withdrawal	Schizoaffective or mood disorders, direct consequences of substance use or general medical condition, pervasive developmental disorders

Table 1 – **Diagnostic criteria for Schizophrenia used in ICD-10 and DSM-IV**. ICD-10 requires either one of Schneider's first-rank symptoms, or persistent bizarre delusions, or two or more other characteristic symptoms, present for at least one month. This does not include any prodromal phase. DSM-IV requires at least two characteristic symptoms (or one thereof if one of the three cardinal symptoms is present). These must be present for at least one month, in addition to a six-month period of social/occupational dysfunction inclusive of any prodrome (American Psychiatric Association, 2000) (World Health Organization, 1992).

As described above, schizophrenia features a characteristic, though not prescriptive, set of symptoms broadly classed as positive, negative or cognitive (Bossong & Niesink, 2010). Overt schizophrenia is often preceded by an 'at-risk mental state' (ARM) previously known as the prodromal phase, though this terminology erroneously suggests that psychosis is inevitable (Stringer et al., 2009). However, in schizophrenic patients, the ARM is invariably followed by an acute psychotic phase, with primarily positive symptoms such as delusions (fixed irrational beliefs held despite evidence to the contrary),

hallucinations (sensory perceptions without stimuli) and lack of insight (Bossong & Niesink, 2010). Over time (typically years) the disorder enters a chronic phase, featuring predominantly negative symptoms (such as apathy, blunted affect and poverty of thought/speech) though positive psychotic symptoms may also persist (Stringer et al., 2009). This latter stage is often indefinite and immensely debilitating. Schizophrenia has a number of significant subtypes, identified according to the most prominent presenting symptoms (Weinberger & Harrison, 2011). These are:

- **Paranoid** – the most common type, characterised by prominent delusions and hallucinations
- **Catatonic** – dominated by psychomotor perturbation including stupor, posturing, rigidity and perseveration
- **Hebephrenic** (disorganized) – usually diagnosed in younger people (15-25 years) and featuring disorganized speech, chaotic mood inappropriate/aimless behaviour
- **Simple** (undifferentiated) – negative features only with no history of positive psychotic symptoms
- **Residual** – only negative symptoms are president following an episode of positive psychosis has subsided

Although these distinctions are made diagnostically, patterns of behaviour can overlap and there is little realistic difference in the biopsychosocial management (Weinberger & Harrison, 2011).

The epidemiology of schizophrenia has proven difficult to establish reliably. This is in part due to differences in diagnostic method and criteria for defined schizophrenic inception in different parts of the world (Messias et al., 2007). However, recent improvements in methodology and consistency have yielded more reliable data, which put paid to the past assumption that schizophrenia is an equalitarian disorder (Messias et al., 2007) (Murray et al., 2009). Incidence rates have been shown to range from 0.11-0.70/1000/year dependent on region, with the average at 0.20/1000/year (Messias et al., 2007). The point prevalence at any given time (dependent on age distribution) is approximately

five per thousand, often more than ten times the incidence, which reflects the chronic nature of the disorder (Messias et al., 2007). The force of morbidity peaks in early adulthood during the 15-24 decade, with males generally affected earlier and more severely (Messias et al., 2007) (Murray et al., 2009). Indeed lifetime risk of developing schizophrenia in males has been measured as being up to 40% higher than in females (Aleman et al., 2003) (McGrath et al., 2004).

The aetiology of schizophrenia is also difficult to establish, with a complex and multifactorial web of contributory elements. There is a well-recognized genetic contribution, with first-degree relatives of sufferers at 10% lifetime risk, and concordance in monozygotic twins as high as 50% (Gejman et al., 2011). Obstetric complications are also established predictors. Those occurring during pregnancy or delivery have been linked with malnutrition, prematurity and hypoxia as direct causal factors in susceptibility to schizophrenia (Isohanni et al., 2005). This also ties in with the season of birth association, which attempts to rationalise the higher rates in those born in winter vs. summer by implicating seasonal infections as a kind of obstetric risk-factor (Davies et al., 2003). The canonical pathogen was the influenza virus, though results from a recent meta-analysis by Selten et al (2009) did not support the maternal influenza hypothesis. Social factors also contribute significantly to one's risk of developing schizophrenia. Migration status is a strong predictor; indeed a recent high-quality meta-analysis by Bourque et al (2011) of 21 studies produced a mean-weighted incidence rate ratio of 2.3 for first-generation immigrants, particularly in those of Black African and Black Caribbean ethnicity. Incidence rates have also been found to be higher in urban compared to rural areas, perhaps due to drift or stresses specific to urban areas (McGrath et al., 2004). Among the most robust findings are those associating low premorbid intelligence (IQ) with an increased risk of developing schizophrenia (Weinberger & Harrison, 2011). Dickson et al (2012) conducted a meta-analysis which showed that, by the age of 16, individuals who subsequently develop schizophrenia display a significant deficit in IQ (d = 0.51).

One obvious omission in this aetiological catalogue is substance abuse. Many drugs including cocaine, LSD and amphetamine can induce psychosis, but one drug in particular is causally linked, and increasingly so, with outright schizophrenia; cannabis.

Cannabis:

Though recognised culturally under numerous synonyms, all preparations of the drug are obtained from *Cannabis sativa*, an herbal dicotyledon grown around the world for millennia (Hall & Pacula, 2003). Different parts of the plant can be used to produce substances of varying potency with respect to the principle active ingredients; cannabinoids. There have been over 100 chemically distinct cannabinoid isoforms discovered. However, the pharmacology of few of these is well understood, the most important being Δ^9-tetrahydrocannabinol (THC) (Castle et al., 2011). It is primarily this which produces the psychoactive effects, and can vary in concentration from 0.5-5% in dried leaves (marijuana) to 7-14% in sinsemilla (skunk), with a consequent range in degree of effect (Castle et al., 2011). This potential for high potency is exploited by growers and traders on the illegal drug market, to produce strains with greater THC concentrations per unit weight. Indeed there is comprehensive evidence to show that average THC content of marijuana, sinsemilla and ditch weed (fibre-type feral cannabis) seized by the authorities in countries such as the US has been on the rise for the last four decades (Figure 1) (Castle et al., 2011).

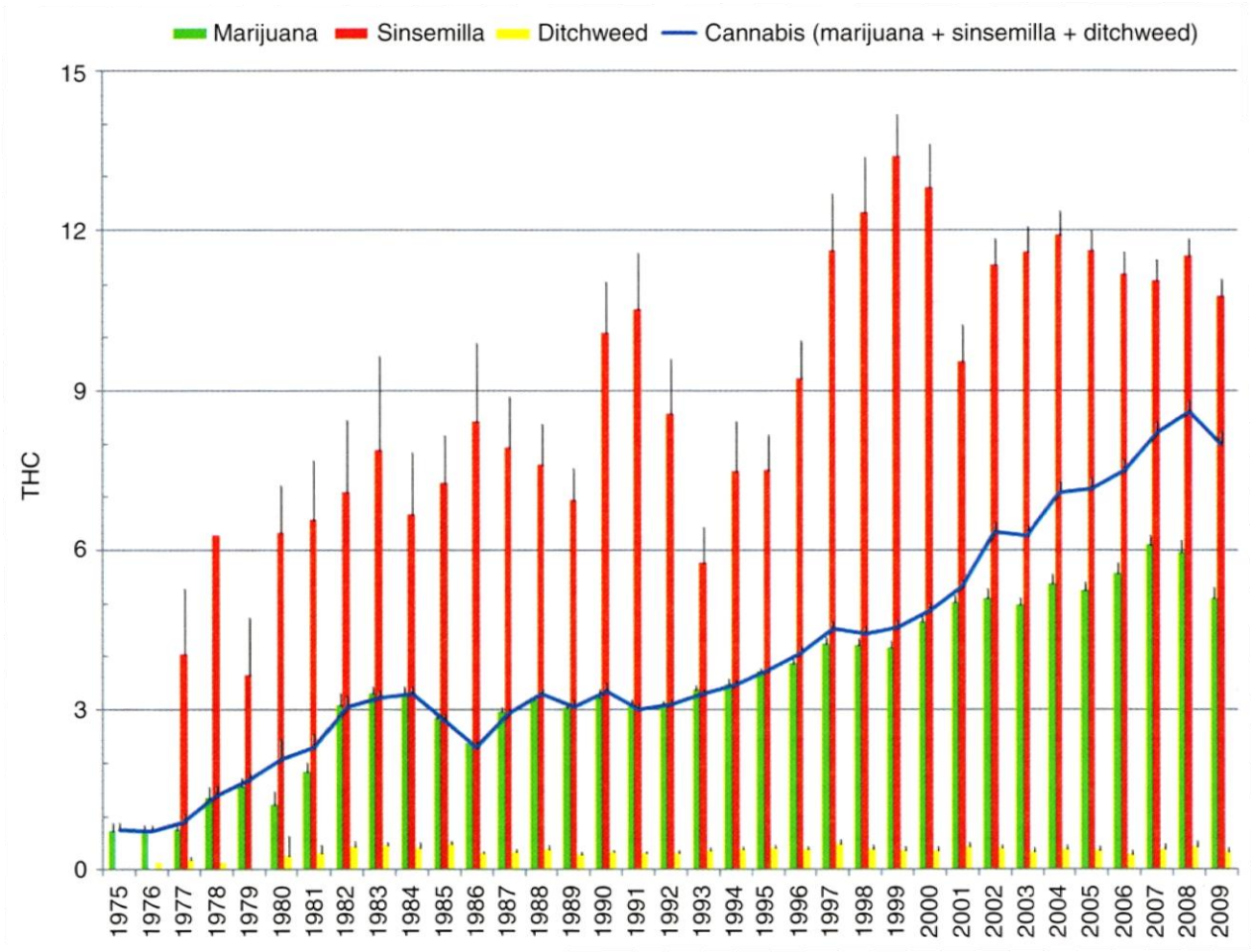

Figure 1 – **THC content of various preparations of *Cannabis sativa* spanning four decades**. Mean THC content (%) with 95% confidence intervals for marijuana, ditchweed and sinsemilla seized in the USA between 1975 and 2009 (graph taken from (Castle et al., 2011) built using data from (ElSohly et al., 1985) (ElSohly et al., 2000) (Mehmedic et al., 2010).

Cannabis use is widespread and variably condemned around the world, indeed its legal classification in the UK has fluctuated over the years. Its misuse has long been recognised as a public health issue. However, the class of drug according to the Misuse of Drugs Act 1971 (which determines penalties for possession and distribution) into which cannabis should be placed has been a contentious issue (ACMD, 2008). In 2004, on the recommendation of the Advisory Council on the Misuse of Drugs (ACMD), cannabis was reclassified from Class B (where it had been since 1971) to Class C (ACMD, 2002). This reflected the professional consensus that the relative harms of cannabis cannot be

proportionately and appropriately equated with other Class B drugs, such as amphetamines (ACMD, 2002). The council were then urged by the Home Office to review their advice in 2005 and 2007, in light of public concern about the potential mental health effects of cannabis use (ACMD, 2008). The ACMD again determined that the harmfulness of cannabis equates more closely with other Class C drugs and should remain as such, to ensure that anti-misuse measures are predominantly public health initiatives rather than criminal proceedings (ACMD, 2008). Nevertheless, cannabis was again reclassified to Class B in 2009, bringing with it harsh criminal penalties. This move, against the advice of the ACMD, was met with criticism. Neuropsychopharmacologist David Nutt, who was sacked from the ACMD following a controversial article he published discussing relative drug harms (2007), criticised the move and the reasoning behind it (Nutt, 2009). He conceded that the drug is not safe and is inextricably linked with psychotic illness (Nutt, 2009). However, he affirmed that it only harms a relative minority of users and that, again, criminalisation as a means of reducing usage is implausible (Nutt, 2009). He also cited the ACMD's estimate that to prevent one case of schizophrenia in men, we would have to stop 5000 young men from ever taking cannabis (ACMD, 2008). Nevertheless, for better or worse, the classification remains unchanged today.

In order to rationalise concerns into the risk posed to people's mental health by cannabis use, one must understand how the constituents of the drugs affect the brain. Important recent advances have been made in this area, illuminating potential mechanisms underlying the relationship between cannabis and mental health.

Cannabinoids and the brain:

As discussed, the psychoactive effects of cannabis are achieved through the action of cannabinoids. Research into the receptors with which THC interacts potentiated the discovery of a system of naturally occurring G-protein coupled (GPCR) cannabinoid receptors – highly conserved throughout evolution (Fernandez-Espejo et al., 2009). Both exogenous (e.g. THC and cannabidiol) and endogenous (e.g. anandamide and 2-arachidonoylglycerol) cannabinoid ligands bind these receptors with variable affinity (Devane et al., 1992) (Sugiura & Waku, 2000). The predominant subtype is CB1, found at high levels in the brain (particularly the cerebral cortex, basal ganglia, cerebellum and hippocampus), while the more sparsely distributed CB2 receptor is found mainly in cells of the immune system (Pertwee, 2006). In fact, CB1 is the most abundant GPCR, with densities up to fifty times greater than classical neurotransmitters, including the opioid receptor (Fernandez-Espejo et al., 2009) (Terry et al., 2009).

Results from autoradiographic and immunohistochemical studies have shown CB1 receptors to be localized to pre-synaptic nerve terminals and axons (Egertova et al., 1998) (Egertova & Elphick, 2000) (Herkenham et al., 1991). This suggests a role for cannabinoids in modulating release of neurotransmitters such as GABA, glutamate and dopamine from local axon terminals, which is indeed the case (Schlicker & Kathmann, 2001). More specifically, endogenous cannabinoids are involved in a collective rapid modulation of synaptic transmission via retrograde signalling, controlling depolarization-induced suppression of inhibition or excitation (DSI/E) (Gerdeman, 2008) (Schlicker & Kathmann, 2001). A good example is the ‘fine tuning’ of neurotransmission in the hippocampus during memory formation. Stimulation of an excitatory projection to a CA1 pyramidal neuron results in post-synaptic release of endocannabinoids, which act on pre-synaptic CB1 receptors of adjacent inhibitory GABAergic neurons (Gerdeman, 2008) (Schlicker & Kathmann, 2001). This depresses their inhibitory tone and facilitates long-term potentiation (LTP) at adjacent glutamatergic excitatory

synapses (this is DSI) (Gerdeman, 2008) (Schlicker & Kathmann, 2001). The released endocannabinoids are also autoregulatory, limiting their own synthesis via CB1 receptor activation (Schlicker & Kathmann, 2001). However, exogenous cannabinoids (THC) disrupt this normal mechanism, activating CB1 receptors indiscriminately and inhibiting LTP, leading to learning and memory impairments (Schlicker & Kathmann, 2001). This effect has been induced in animal studies, with exogenous cannabinoids producing deficits in short-term memory in spatial learning tasks such as the radial arm maze and delayed matching tests (Hampson & Deadwyler, 1999). Similar research is underway at the Institute of Psychiatry using mice to examine whether there are critical periods of life (e.g. adolescence) during which THC may be particularly disruptive to memory formation (Cannabis: The Evil Weed?, 2009) (Fernandes, 2012). This is particularly salient for humans, given that adolescence is already purported to be a high-risk period of susceptibility to the harmful effects of cannabis, which will be discussed later.

This disruption by THC to normal functioning of endocannabinoids is homologous in many areas of the brain, reflective of the wide distribution of CB1. Consequently, THC has an effect on neuronal systems involved in psychomotor control, appetite and body weight (Castle et al., 2011). However, arguably that which has garnered most interest is also that which is still relatively uncertain. How might exposure to cannabis impact on neuroanatomy and physiology such as to precipitate or potentiate psychotic illness, including schizophrenia? Indeed, does the association have a foundation in evidence? What follows is a discussion of the epidemiological groundwork and the experimental evidence which supplements it.

Cannabis and schizophrenia – epidemiological evidence:

Schizophrenia is a multifactorial and exceedingly complex disorder, with individual risk factors never exclusively sufficient to induce it (Rothman & Greenland, 2005). Thus schizophrenia can occur exclusive of cannabis use and vice versa. However, there is an abundance of evidence demonstrating a positive association between cannabis use and psychosis. Epidemiological surveys have shown that cannabis can induce core psychotic symptoms (delusions, hallucinations and thought disorder) in individuals without clinical psychosis (Verdoux et al., 2003). The transient nature of this phenomenon minimises detriment to functioning, but whether the effect goes beyond the immediate into the territory of permanent, debilitating psychotic states is of greater concern.

A significant body of evidence assessing the association comes in the form of population-level studies. Retrospective case-control and cross-sectional studies have been used to assess the propensity of those with established psychosis to use cannabis, compared to those with no psychotic disorder. McCreadie (2002) compared drug use in patients with schizophrenia against the general population in Scotland using the Schedules for Clinical Assessment in Neuropsychiatry, with controls from a spectrum of sociogeographical settings. Problematic drug use was reported in 7% of patients (cannabis in 4%) compared to 2% of controls (McCreadie, 2002). Similar results were drawn from a hospital-based study in The Netherlands comparing cannabis use between first-episode schizophrenics and a control group (Veling et al., 2008). Despite cannabis being legal and more socially permissible in that region, its use was nevertheless much more common in patients (59%) than controls (21%) (Veling et al., 2008). A more recent study conducted in London looked into the likelihood of frequent use of higher potency cannabis in first-episode psychosis patients, compared with control groups (Di Forti et al., 2009). Patients were 6.4 times more likely to have smoked cannabis for longer than 5 years, and among them 78% reported using high-potency cannabis (skunk) (Di Forti et al., 2009).

A number of similar studies have compared the prevalence of psychotic symptoms, as opposed to established psychotic illness, in users and non-users of cannabis. Studies conducted in Finland (Miettunen et al., 2008) and The Netherlands (Ferdinand et al., 2005) found a positive association, with the former noting a significant dose-response relationship and the latter identifying a bi-directional causality. An additional large-scale Australian study helps to bridge the gap between short-term psychosis and established schizophrenia (McGrath et al., 2010). The results indicate a positive association, which persisted even after omitting patients who had used cannabis in the month prior to assessment, indicating that symptoms were not attributable to recent intoxication (McGrath et al., 2010).

As will be discussed later, the power of these studies is limited. Longitudinal cohort studies can bolster the literature and alleviate some of the weaknesses inherent in the aforementioned designs. However, studies of this modality have been undertaken comparatively infrequently, given the considerable time, funding and sample sizes necessary to implement them effectively. In fact, a systematic review published in 2007 only identified seven such studies assessing psychotic outcomes in users and non-users of cannabis (Moore et al., 2007). Of these studies, only three used actual psychotic disorders as outcomes; namely schizophreniform disorder (Arseneault et al., 2002), psychotic symptoms fulfilling psychotic disorder criteria (van Os et al., 2002) and schizophrenia (Andréasson et al., 1987). The latter, using the Swedish conscript cohort, was the first large-scale longitudinal study examining the association between cannabis and any psychosis outcome (Arseneault et al., 2004). The cohort of 50,087 Swedish men were interviewed at conscription age (18) to determine baseline mental health and cannabis use, and followed up over a fifteen-year period for hospital admissions due to schizophrenia (Andréasson et al., 1987). The results of this study and the other six included in the review by Moore *et al.* (2007) are shown below in the form of an adjusted odds ratio (Figure 3 a & b).

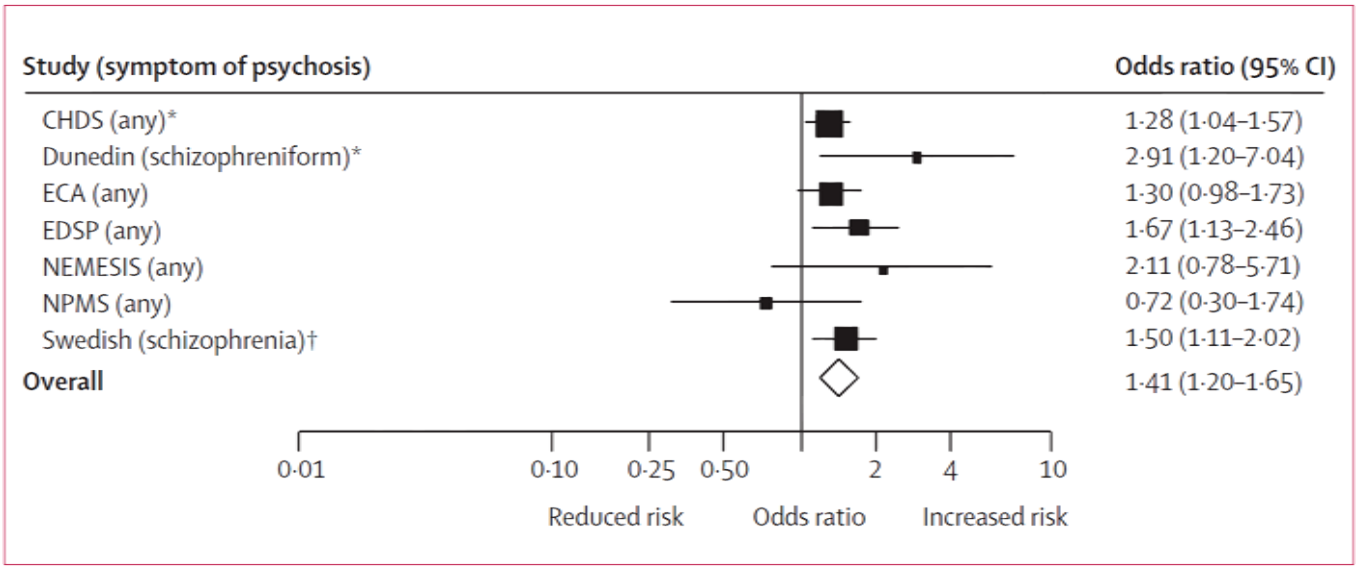

Figure 3 (a) & (b) **– Adjusted odds ratio (OR) for psychosis outcomes across seven cohort studies.** Forest plots indicating adjusted ORs at 95% confidence intervals (CI) for any psychosis outcome in individual studies, according to ever use* **(a)** and frequent use **(b)** of cannabis (Moore et al., 2007).
*Cannabis measure in **(a)** was ever use except for the NPMS, in which ever use was over the past year only.

CHDS, Christchurch Health & Development Study; ECA, Epidemiological Catchment Area; EDSP, Early Developmental Stages of Psychopathology; NEMESIS, Netherlands Mental Health Survey & Incidence Study; NPMS, National Psychiatric Morbidity Survey.

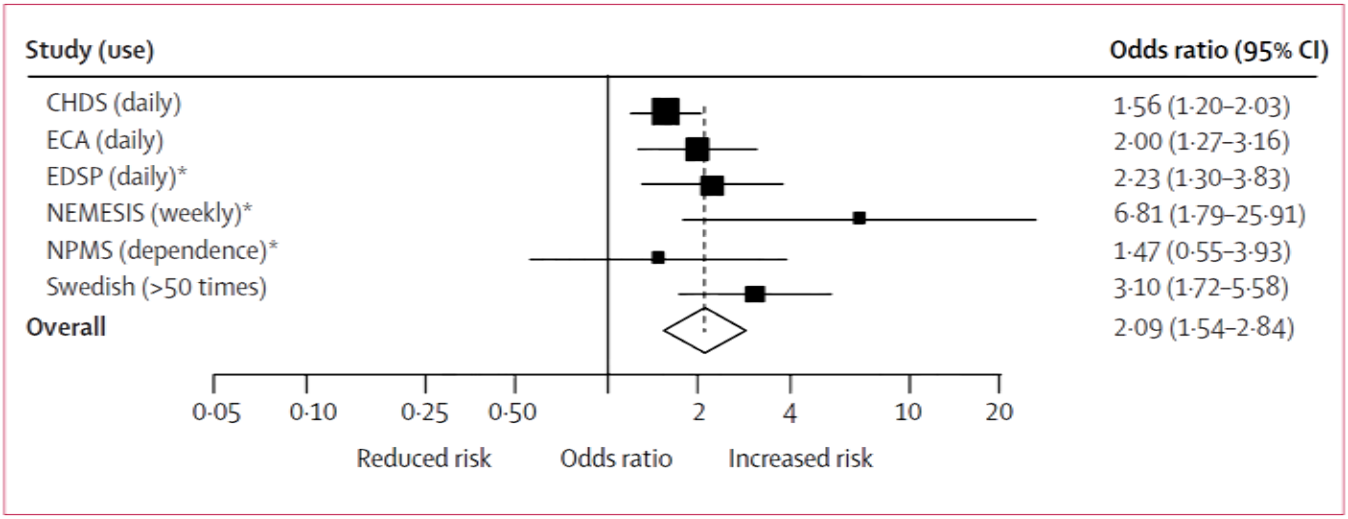

Figure 3 (b) (Moore et al., 2007)

Results of all the above studies provide evidence of an increased risk of psychosis in individuals who had ever used cannabis, persisting in six of the seven when confounders were controlled for (adjusted OR of 1.41) (Moore et al., 2007). As per Figure 3 (B), results from all studies additionally indicated a dose-response effect, with an adjusted OR of 2.09 for psychotic outcomes in the most frequent users (Moore et al., 2007). This also persisted in sensitivity analyses for most frequent cannabis users, in which results from the NEMESIS study were omitted due to their effect on heterogeneity, with a pooled OR of 1.92 (Moore et al., 2007) (van Os et al., 2002).

Two other prospective studies, published since the aforementioned review, are supportive of preceding evidence indicating a positive association. The Zurich Study followed a group of 591 participants aged 20/21 years over 20-year period, conducting interviews at various milestones to identify clusters of psychotic symptoms over that time (Rössler et al., 2007). Results indicated that cannabis use at baseline was associated with a persistent high-load of 'schizophrenia nuclear symptoms' (also known as Schneider's First-Rank Symptoms), with an additional dose-response relationship noted (ORs 4.3 in frequent users vs. 2.3 in occasional users) (Rössler et al., 2007). A more recent study by McGrath *et al.* (2010) used a sibling pair analysis to examine the association among 3,801 individuals born into the Mater-University Study of Pregnancy. At a 21-year follow-up, duration of cannabis use was found to be strongly associated with diagnosis of non-affective psychosis, with a pooled OR of 1.76 for any use and 2.2 for ≥6 years of use (McGrath et al., 2010).

The latter of those two studies, though not investigating its influence directly, was focused on what is an important variable when considering the risk of psychosis with cannabis use; age. Of course the exact influence of isolated risk factors and their interactions with others is extremely difficult to establish. Indeed the value of doing so with respect to notions of aetiology or prevention has been questioned (Zammit et al., 2010). However, the greater risk conferred by adolescent onset of cannabis use in developing psychosis has a firm grounding in evidence, and is widely accepted.

Previously mentioned as part of the review by Moore et al. (2007), The Dunedin birth cohort study followed a group of 1,037 individuals from birth to twenty-six years of age, assessing cannabis use and psychiatric symptoms at intervals along the way (Arseneault et al., 2002). Reports of cannabis use were obtained at ages fifteen and eighteen, with information on psychotic symptoms obtained separately at ages eleven (self-report) and twenty-six (psychiatric interview using DSM-IV criteria for symptoms of schizophreniform disorder) (Arseneault et al., 2002). Those using cannabis before the age of fifteen were 3.4 times more likely than controls to meet diagnostic criteria for schizophreniform disorder at age twenty-six years (Arseneault et al., 2002). A birth cohort cross-sectional analysis conducted in Greece also concluded that the risk of psychosis later in life was highest in subjects whose first use of cannabis was earliest (Stefanis et al., 2004).

In contrast to this body of evidence, there have also been numerous instances of published results which are inconsistent with a causal relationship. For example, the National Psychiatric Morbidity Survey (NPMS) was the only study included in the review by Moore et al. (2007) which found a negative association. After adjusting for reverse causality and intoxication effects, the OR for any psychosis outcome in those who had ever used cannabis dropped to 0.8 (Wiles et al., 2006). Another argument made against the causal association is that, while strength and usage of cannabis has been increasing, rates of incidence of schizophrenia have not seemed to change in parallel. A study by Frisher *et al.* (2009) examined the General Practice Research Database (GPRD) to establish trends of annual prevalence and incidence of schizophrenia in the UK over a 9-year period (Frisher et al., 2009). Rates of schizophrenia and other psychoses were found to be either stable or declining, with the authors considering that this is more likely to be genuine than artefactual (due to, for example, under-reporting of psychotic symptoms to GPs) (Frisher et al., 2009). They concluded therefore that, although cannabis use may be increasing, data regarding rates of schizophrenia do not support a causal link between the two. A similar conclusion was reached in a study by Degenhardt *et al.* 2003 assessing the relationship between cannabis use and psychosis. Eight large-scale cohort studies

conducted in Australia between 1940 and 1979 were included in the study (Degenhardt et al., 2003). Despite a rise in the prevalence of cannabis use and decrease in age of initiation, and the consistent observation that cannabis use is more common in patients with schizophrenia, there was no correlating rise in incidence of schizophrenia in that given time period (Degenhardt et al., 2003).

It does seem though that the body of epidemiological evidence is strong enough to tip the scales in the positive direction. In a comment article written shortly after the publication of the review by Moore et al. (2007), Nordentoft & Hjorthøj (2007) offer the opinion that there currently exists sufficient evidence to warn young people of the dangers of cannabis use as regards their risk of psychosis in later life. There are of course unsurpassable limits to the conclusive power of these studies, creating a growing mandate for more direct investigation into exactly how cannabis may mediate its effects.

Cannabis and schizophrenia – clinical and experimental evidence:

Additive to the epidemiological evidence linking cannabis with psychotic disorders is a host of clinical and experimental data.

As previously discussed, the primary psychoactive constituent of cannabis (THC) operates through a naturally occurring system of cannabinoid receptors in the brain. A recent randomized, double-blind, placebo-controlled study by Morrison et al. (2011) looked into THC psychopathology and its relation to electroencephalography (EEG) changes and cognitive performance. Results showed that administration of intravenous THC in healthy volunteers is associated with the evocation of positive and negative psychotic symptoms as measured by the positive and negative syndrome scale (PANSS) (Figure 4 A & B), and that this also correlated with slowed working memory performance and reduced theta wave coherence (Figure 5) (Morrison et al., 2011).

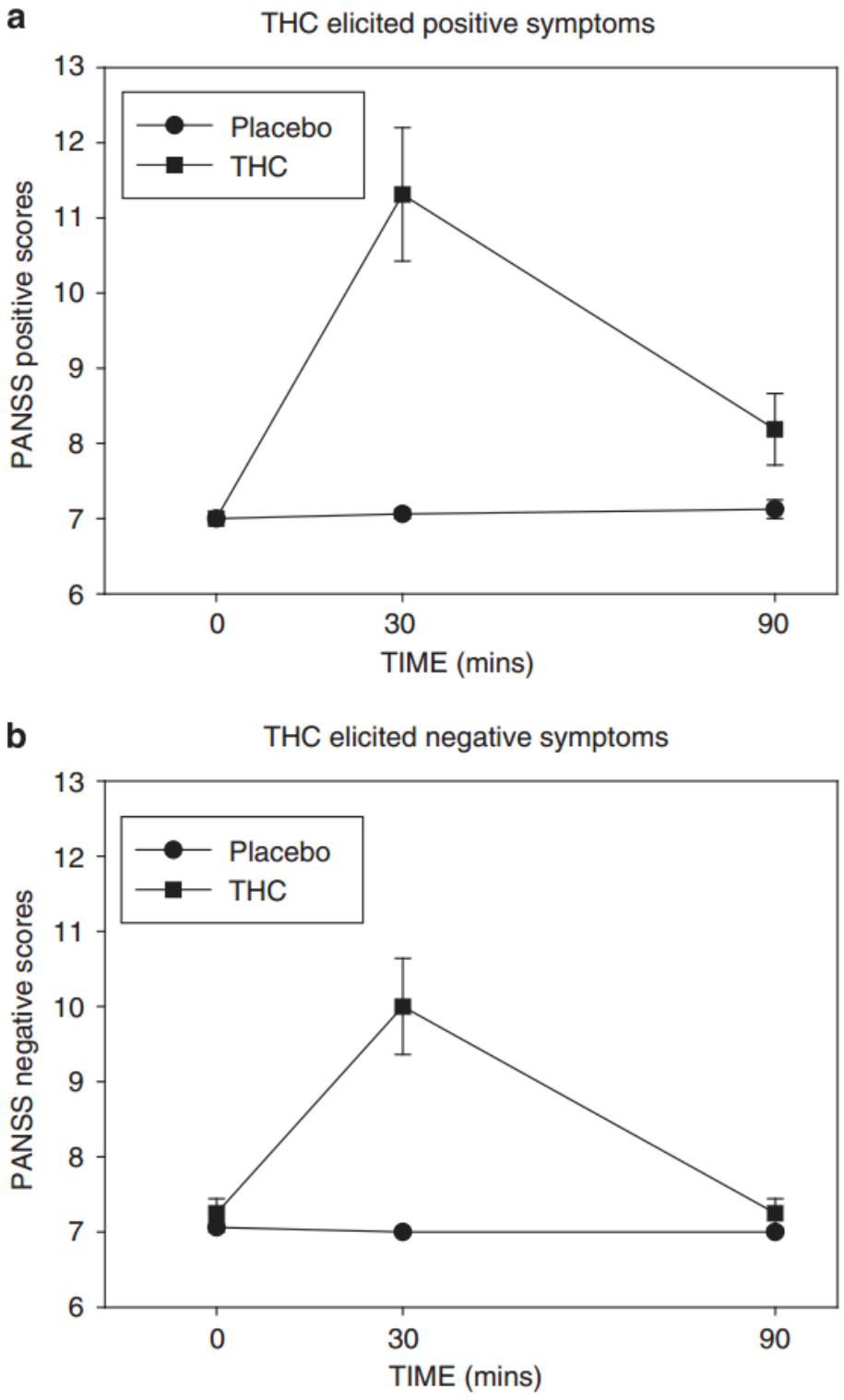

Figure 4 (a) & (b) **– THC elicited positive and negative psychotic symptoms**. Positive (**a**) and negative (**b**) symptoms as measured by the PANSS scale increased from baseline measurements following administration of intravenous THC or placebo. (Morrison et al., 2011)

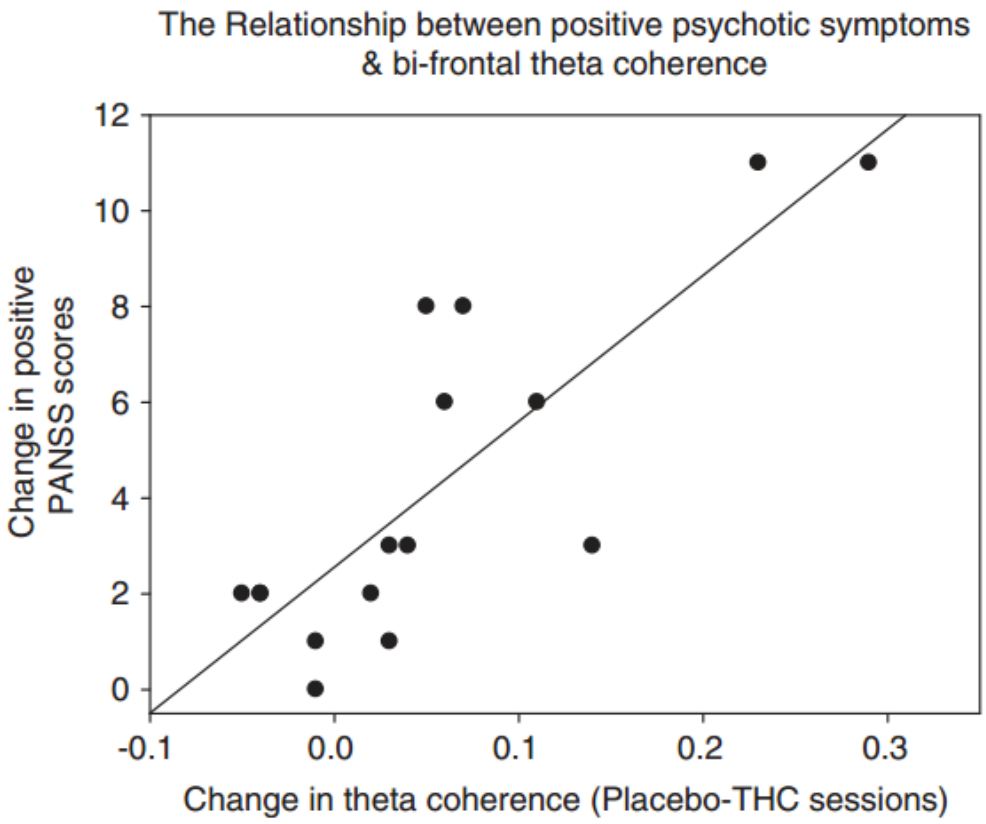

Figure 5 **– Reductions in theta wave coherence correlate with positive psychotic symptoms under THC**. Changes in theta wave coherence between left and right hemispheres, measured by EEG, correlate with positive PANSS score changes ($p<0.001$) (Morrison et al., 2011). Statistical significance also survived the removal of two potential outliers ($p<0.006$) (Morrison et al., 2011)

Interestingly, similar results with respect to THC and psychosis were garnered in a study of comparable construction. D'Souza *et al.* (2005) conducted a randomized, double-blind, placebo controlled study in which clinically stable schizophrenic patients taking antipsychotic medication long-term were given either THC or placebo. THC transiently exacerbated positive and negative symptom manifestations (as measures by the PANSS), which were similar to those typically experienced by patients throughout the past course of their illness; despite being clinically stable (D'Souza et al., 2005). Schizophrenic patients appeared to be more sensitive to THC, with 80% displaying a supra-threshold response (score >3 on the PANSS) to the lowest does of THC (2.5mg), compared to 35% in controls (D'Souza et al., 2005). It is quite possible, though speculative, that differences may have been starker had patients not been clinically stable and on treatment.

Results from these studies suggest that THC can produce psychotic symptoms in healthy patients and exacerbate those in schizophrenic patients. The study by Morrison *et al.* (2011) highlights the distinct possibility of this occurring by disruption of neural networks. However, the exact neurobiological basis of the link between endocannabinoid disruption and psychosis is not yet fully established (Kuepper et al., 2010).

Animal studies, as introduced above, have contributed to current understanding of how exogenous cannabinoids can disrupt normal neural mechanisms, and how this may link with schizophrenia (Hampson & Deadwyler, 1999). Psychosis per se is difficult to study experimentally using these models, since it is essentially a human concept. This makes sense when appreciating that, according to in-situ hybridization and immunohistochemical studies, expression of CB1 is much higher in cognitive brain areas in humans (cerebral cortex) rather than movement areas in rats (caudate-putamen) (McPartland et al., 2007). However there are particular psychotic-like alterations in animals which have clear and acceptable human correlates (Fernandez-Espejo et al., 2009). For example pre-pulse inhibition (PPI), a normal sensorimotor gating phenomenon typically disrupted in patients with schizophrenia, is considered a predictor of psychosis-like properties of drugs in animal models (Geyer et al., 2001). PPI is disrupted by synthetic CB1 receptor agonists (e.g. WIN 55-212,2), leading to a deranged startle response in rats (Schneider & Koch, 2002). This has also been shown to be reversible using CB1 antagonists (e.g. AM251) in rats, which essentially act as antipsychotics (Ballmaier et al., 2007). As a CB1 agonist, THC in cannabis could be exploiting this very mechanism to disrupt PPI in humans, contributing to the disorganized behaviour seen in patients with schizophrenia (Fernandez-Espejo et al., 2009).

As previously mentioned, the endocannabinoid system plays an important role in regulating other neurotransmitters. One important and relevant candidate when considering schizophrenia is dopamine (DA) (D'Souza et al., 2009) (Di Forti et al., 2007). Indeed the well-known ‘dopamine

hypothesis' states that schizophrenia occurs as a result of dopamine dysregulation in the brain, with positive symptoms attributable to overactivity in mesolimbic tracts and negative symptoms to underactivity in mesocortical tracts (Di Forti et al., 2007) (Stringer et al., 2009). Observational evidence for this includes the facts that all antipsychotics are dopamine antagonists, antipsychotic agents work more effectively against positive than negative symptoms and dopaminergic agents (e.g. cocaine and amphetamine) can induce psychosis (Stringer et al., 2009) (D'Souza et al., 2009). Aberrant dopamine signalling has been shown experimentally to be induced directly by CB1 activation in the striatum and mesolimbic tracts of rats (French, 1997) (French et al., 1997) (Gardner, 2005). In keeping with this preclinical work, Bossong *et al.* (2009) have shown using a DA receptor tracer and positron emission topography (PET) that a clinically relevant dose of THC triggers dopamine release in the striatum of healthy human brains. Furthermore, administration of the DA receptor antagonist haloperidol does not reverse the psychotomimetic effects THC in humans, indicating that DA receptors are much less important in this phenomenon that those of the cannabinoid system (D'Souza et al., 2008). This is compelling evidence of the role that THC in cannabis likely plays in triggering aberrant dopamine signalling in various areas of the brain, and thus in contributing to psychotic symptoms seen in schizophrenia.

Linking with this, research in the last decade has identified a number of genetic alterations associated with increased vulnerability to schizophrenia following cannabis use. Most notably is that conducted on the gene encoding an enzyme which breaks down dopamine in the synaptic cleft; catechol-*O*-methyl transferase (COMT) (Caspi et al., 2005) (D'Souza et al., 2009) (Henquet et al., 2005). This supplements the epidemiological indication that age of use is important, by adding in a well-substantiated susceptibility factor. Caspi et al. (2005) genotyped patients within the Dunedin birth cohort (discussed previously) for a functional polymorphism of the COMT gene; Valine158Met. The authors found that those patients with the Val-Val isoform of the gene were significantly more prone

to psychosis (including schizophreniform disorder) later in life if they had used cannabis during adolescence, compared to those with the Met-Met isoform (Figure 6) (Caspi et al., 2005).

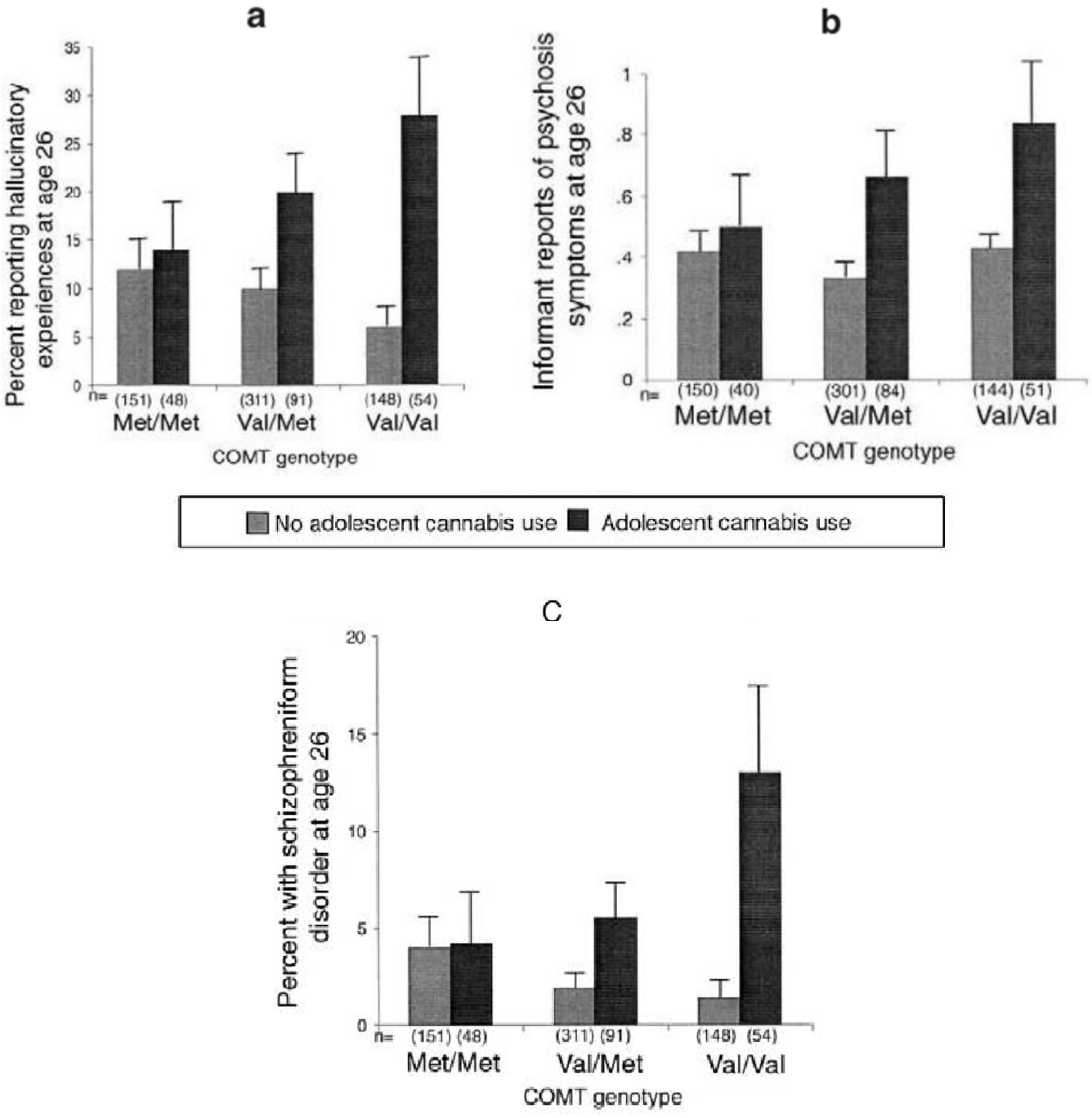

Figure 6 **– Adolescent cannabis use and the effect on propensity to developing psychotic outcomes according to COMT genotype**. (**a**) Patients reporting at least one hallucinatory experience by age 26 (%). (**b**) Means on reports of psychotic symptoms by age 26 (+ standard errors). (**c**) Percentage of participants meeting criteria for a diagnosis of schizophreniform disorder by age 26 (Caspi et al., 2005).

This is a strong association and constitutes a valid explanation (at least in part) as to how one can be predisposed to psychosis with cannabis use. However, this data has not yet been replicated in other independent samples and, though compelling, is not fully supported by current literature. Nonetheless, this study has paved the way for the identification other susceptibility genes, including the CB1 receptor gene CNR1 (Chavarría-Siles et al., 2008) and neuregulin 1 (which has a role in NMDA receptor activation, with haplotypes implicated in schizophrenia) (Munafo et al., 2008).

One interesting area of observed interaction is that between cannabis abuse and neuroanatomy. A systematic review of structural MRI studies by Lorenzetti et al. (2010) suggests that THC exposure can affect brain morphology, particularly regional changes (such as the hippocampus and parahippocampus) in heavy cannabis users (Yücel et al., 2008). This has also recently been extended to established cortical thickness loss in CB1 receptor-rich areas during the first years of schizophrenia (Bangalore et al., 2008) (Rais et al., 2010). This phenomenon appears to be particularly important during, again, adolescence, not least because the endocannabinoid system plays an important role in brain development in postnatal and (up to) adolescent life (Bossong & Niesink, 2010) (Castle et al., 2011). THC has been found to have adverse effects on experience-dependent maturation of neural circuits in young people which, dependent on dose and temporality, could predispose them to psychosis later in life (Bossong & Niesink, 2010). The exact mechanism of these changes is still not entirely clear, neither is an established consensus on their sequelae, though it is widely reported that schizophrenic patients display such changes in brain morphology post-mortem (Weinberger & Harrison, 2011). Of emerging interest is the effect of cannabis on the cerebellum. Cerebellar neurons are thought to form closed-loop circuits with the cerebrum and basal ganglia, coordinating a range of functions from working memory to affect (Strick et al., 2009). Patients with cerebellar lesions have also been characterized as having cognitive-affective syndromes similar to schizophrenia (Schmahmann & Sherman, 1998). Indeed, schizophrenic patients are often found to display abnormal cerebellar anatomy post-mortem (Castle et al., 2011). Cannabinoid receptors play an important role

in cerebellar neuronal plasticity, in fact the cerebellum displays the second highest density rates for CB1 receptors (after the basal ganglia) (Qiu & Knöpfel, 2009). Furthermore, cannabis users have displayed cerebellar hypoactivity (Block et al, 2000) and perturbed cognitive/psychomotor responses (Hunault et al, 2009). This appears to implicate cannabis in schizophrenia via cerebellar mechanisms, though there are no published data explicitly examining this link. The natural assumption is that this area has explorative potential.

Studies covering the neurophysiological, neuroanatomical and biochemical aspects of schizophrenia psychopathology have improved understanding of how cannabis and its constituents may be involved. However, the collated evidence above is by no means an exhaustive examination, and all studies are susceptible to methodological limitations and error. This is particularly the case with epidemiological evidence on this subject. This shall be taken into account hereafter, by way of ensuring that any conclusions made are balanced and unblinkered.

Methodological issues and study limitations:

On the face of it, the weight of evidence seems clearly in favour of a positive association between cannabis and schizophrenia. However, association is not the same as causation, indeed multicausality is a reiterated principle in general aetiology (Rothman & Greenland, 2005). Controversy therefore persists, since the question of whether cannabis can cause schizophrenia has not been unequivocally answered. This is due in no small part to various methodological issues which are not always recognised, or more importantly controlled for as far as possible. This is the case most notably in epidemiological studies which, due to the nature of their design, are susceptible to flaws and limitations. These could contribute to what may be, in this case, an over-estimation of a true causal relationship between cannabis and schizophrenia (Castle et al., 2011). On the other hand, there are reasons whereby the relationship may have been under-estimated, and it is important to consider both sides of this coin.

One obvious stumbling block comes in the form of measures of outcomes. Schizophrenia is relatively rare, so to facilitate larger scale population studies, overt schizophrenia is often substituted for a continuum of symptoms (Castle et al., 2011). This can be inclusive of schizophrenia, but not dependent on it. These are two very different pictures, since psychotic symptoms by no means lead inexorably to definitive clinical schizophrenia. Differing definitions of schizophrenia and different symptomatic criteria across studies renders results more difficult to interlink and conclusions based on pooled evidence less reliable. A review of cohort studies by McLaren *et al.* (2010) identified one of its major constituent studies as suffering from this limitation. In the Christchurch Health and Development Study (another New Zealand birth cohort from the 1970s, also featured in the review by Moore *et al.*), the SCL-90 symptom checklist was used to collate symptoms into ‘psychoticism’ and ‘paranoid ideation’ scales (Fergusson et al., 2005). This tool, aside from having low sensitivity and specificity, is better suited as a global measure of psychological distress rather than psychotic

symptoms specific to certain disorders (McLaren et al., 2010). McLaren et al. also criticised the lack of clarity in this study, in terms of what they define as cardinal symptoms or minor symptoms, as there was no indication as to which symptoms were more significant than others (2010).

A significant factor to consider, which can impact on a huge variety of studies, is confounding. In this instance, confounding is the most likely factor to cause over-estimation of the true causal relationship between cannabis and psychosis (Castle et al., 2011). Often individuals who use cannabis differ from those who don't in many ways, some of which may be contributory in the development of psychosis. For example, the use of other psycho-stimulant substances such as amphetamines, adverse rearing conditions and the presence of certain social personality traits all have potentially detrimental effects on the integrity of conclusions (Arseneault et al., 2004). A good example of this impact can be found in Dunedin birth cohort study (Arseneault et al., 2002). Despite the 10.3% vs 3% rate of schizophreniform disorder in pre-15 cannabis users compared to controls, when controlling for psychotic symptoms at 11-years (a potential confounder in later development of the disorder), the higher risk was no longer statistically significant (McLaren et al., 2010). It must be said that many studies do implement measures to adjust for confounding. All seven longitudinal studies included in the review by Moore et al. (2007) did just that, although original estimates of association were attenuated by an average of 50% as a result (Moore et al., 2007). The sibling pair analyses undertaken by McGrath et al. (2010) in the Mater-University Study of Pregnancy help to minimize the effects of unmeasured residual confounding, including shared genetic and environmental characteristics. Although this method has no effect on non-shared confounding, it is a laudable measure in controlling for many confounding factors and should perhaps be implemented in similar future studies.

Another key potentially detrimental factor is that of reverse causality. This 'chicken and egg' phenomenon refers to the chance that any measured association between cannabis and

schizophrenia may occur as a result of individuals initiating or increasing cannabis use after illness onset rather than before (ACMD, 2008). In this instance, cannabis is sought and used as form of self-medication to remedy psychotic symptoms, given its psychotropic properties. This has been documented in a qualitative study aimed at assessing whether patients with schizophrenia who use cannabis believe that it may have contributed to their condition (Buadze et al., 2010). None of the ten patients interviewed identified a causal link, indeed four of them considered cannabis to be a therapeutic aid owing to its positive effects (relief of anxiety and tension) (Buadze et al., 2010). Although longitudinal study constructs can limit the effect of reverse causality, the possibility of undetected psychotic symptoms or an ARM being present is inescapable (Castle et al., 2011). The paper produced in the clinical study by Caspi *et al.* (2005) cited this limitation as a particular weakness in their data. In a review of five of the aforementioned cohort studies by Arseneault et al. (2004), the authors report that the majority of studies were unable to establish whether or not prodromal (ARM) manifestations of schizophrenia preceded cannabis use. This leaves open the possibility that cannabis use may be a consequence of early schizophrenia rather than the trigger for it. The significance of this particular factor is, ironically, best exemplified by the effect produced by attempting to control for it. Adjustments made to ORs in the review by Moore *et al.* (2007) reduced their significance by between 15% and 80%, which is striking. The best results following adjustments made on account of reverse causality (amongst other confounding factors) were obtained by Zammit et al. (2002) in a follow-up study of the Swedish conscript cohort. Consistent with previous findings, the heaviest cannabis users (more than fifty times) were 6.7 times more likely to be diagnosed with schizophrenia twenty-seven years later compared to non-users (Zammit et al., 2002). This was attenuated (by 50%) once another thirteen potential confounders had been controlled for, but nevertheless a statistically significant association persisted (Zammit et al., 2002). Other studies, however, have not managed such water-tight results.

Selection bias is a big problem in observational studies. It is very difficult, if not impossible, to determine with certainty that psychotic symptoms are not attributable to recent intoxication with cannabis, particularly in frequent and heavy users. Equally, whether psychotic patients can be relied upon to give an honest and accurate account of their recent cannabis use is debatable (Arseneault et al., 2004). Coupled together, these limitations again skew the reliability of observed associations. As discussed, an attempt was made by McGrath *et al.* (2010) to limit selection bias by omitting patients who has used cannabis up to one month prior to interview. However, this measure seems rather arbitrary and, again, does not render self-reports of cannabis use more reliable.

Equally so, there are methods used in longitudinal studies which may have led to an under-estimation of the true causal association. Misclassification bias is inherent in how cannabis use is graded given that, in the absence of quantitative measures of THC content for all cannabis smoked, the degree to which a person has been exposed to psychoactive substances is uncertain. Biological availability and smoking practices also differ broadly which, when taken in the context of random misclassification across a cohort, often leads to underestimates of association (Castle et al., 2011). Attrition is also a potential problem, whereby subjects lost to follow-up (often in these instances due to concurrent drug use or worsening mental health) can skew results in favour of under-estimation (Allott et al., 2006).

Some more general criticisms can be levied at features of many of the epidemiological studies discussed thus far. In McCreadie's case-control study (2002), differential methods of identifying patients/controls were used in different areas (with reduced expertise in some areas). Also, not all patients were interviewed so some controls may have been cannabis users, while users may have under-played the extent of their use (McCreadie, 2002). The case-control study by Veling *et al.* (2008) defines cannabis exposure as use >5 times, but the effects of cannabis can be extremely variable between casual and frequent users. For example, four times may be enough in a susceptible

individual to experience clinical psychosis, though this individual would be discounted on the basis of the methodological distinction. There was also a lack of reliable information on age of first use and duration of use, and again a potential under estimation of drug use besides cannabis. Finally, an interesting aspect to the study conducted by Di forti *et al.* (2009) was the very public and advertisement-heavy recruitment campaign. Whether this means of gathering controls constitutes a random process is uncertain, but it may have appealed more acutely to a particular demographic of cannabis users; high-functioning and socially-adjusted.

Experimental studies are often less vulnerable to methodological issues given that they examine direct cause and effect, but there are examples. A weakness of the study on THC in humans by Morrison et al. (2011) is that only one dose of THC was used. The sample size was also small for teasing out interactions, but typical for studies of this type, including another THC study by D'Souza et al. (2005). Furthermore the results published by Caspi et al. (2005), as well as awaiting replication, are vulnerable to the same criticism levied at the study's parent cohort (Arseneault et al., 2002). Studies of the influence of exogenous cannabinoids on phenomena such as PPI in animal models also require a considerable leap of faith in order to extrapolate in the absence of dedicated human studies.

Conclusion:

The link between cannabis and schizophrenia has been one of evolution, but also contention. A strong body of evidence supports a causative link, but this must be viewed in the context of the limitations of these composite studies and the evidence identifying no apparent association at all. It is most likely that, while neither sufficient nor necessary, cannabis is a 'component cause' in the aetiology of schizophrenia (D'Souza, 2009).

Inconsistencies of definitions of schizophrenia across studies of different modalities hamper any attempt to draw unified conclusions. Most research has been constructed around psychosis-related phenomena as outcome measures, as opposed to schizophrenia itself. This is due in part to its relative rarity and the challenge of inducing it experimentally, in animals or humans. There will always be cannabis users who live functional lives whilst enduring psychotic symptoms, never presenting to health services and become part of the data. Important to note also is that most people who ever use cannabis will not develop any psychotic disorder, let alone schizophrenia (Arseneault et al., 2004). Equally so, not all patients with schizophrenia have been exposed to cannabis at some point in their lives.

Another issue with making firm conclusions is our residual lack of understanding of cannabinoids. Cannabis contains many different cannabinoids, most of which are poorly understood. We may be simply yet to discover the crucial influence of cannabinoids other than THC. There is some evidence identifying cannabidiol (CBD, another cannabinoid found in cannabis) as a protective agent against psychosis, but further investigation is warranted (Bhattacharyya et al., 2010). Beyond this lies a huge scope of potential association between other cannabinoids and psychosis.

Though preferable, future randomised-controlled trials on long-term cannabis exposure are not feasible or ethical, equally trials on cannabis use interventions are unlikely to be sufficiently

informative when considering rare outcomes like schizophrenia. Further longitudinal studies should be conducted to assess broader endophenotypes of psychosis strongly causally associated with schizophrenia. Experimental work should focus on pinning down and corroborating susceptibility loci, with the aim of enriching current understanding of whom may be at highest risk.

Despite the lack of evidential unity, it seems prudent to encourage abstinence from cannabis use, at least in seemingly at risk groups including young people, those with measured genetic predispositions and patients with established psychotic illness. How cannabis should be treated judicially and culturally is a matter for debate, but it will be fascinating to see how this field evolves in the future and what impact this will have on science and society.

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