Gene-Environment Interactions Underlying the Effect of Cannabis in First Episode Psychosis

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Abstract: Cannabis use may be considered as an additional risk factor in a diathesis-stress model of schizophrenia where the risk of developing the illness would be higher in genetic vulnerable people. In this regard, much of the research on cannabis and psychosis is currently focusing on gene-environment interactions. The present review will focus on the interaction between genes and cannabis exposure in the development of psychotic symptoms and schizophrenia and the biological mechanisms of cannabis. Cannabis use has been shown to act together with other environmental factors such as childhood trauma or urbanicity producing synergistic dopamine sensitization effects. Studies on gene-environment interaction have mainly included genetic variants involved in the regulation of the dopaminergic system. The most promising genetic variants in this field are COMT, CNR1, BDNF, AKT1 and NRG1. Additionally, the interaction with other environmental factors and possible gene-gene interactions are considered in the etiological model.

Keywords: Schizophrenia, cannabinoids, gene-environment interaction, genetics, CB1, causality, COMT.

INTRODUCTION

Cannabis is probably the most commonly used illicit addictive substance among patients with schizophrenia, with a lifetime prevalence of cannabis use disorders higher than 25% [1]. The use of cannabis has been reported to be higher in patients suffering their first episode showing rates of cannabis use of nearly half of the patients [2]. This use of cannabis has been consistently associated with relapse and non adherence in patients with schizophrenia, but associations with clinical severity are more disparate [3]. Additionally, a causal relation between cannabis and psychosis has been suggested.

For some healthy individuals, cannabis use may be accompanied by psychotic experiences and neurophysiologic alterations that are similar to those seen in schizophrenic patients [4-6] Psychotic symptoms are usually self-limited, but in some cases, the psychotic manifestations associated with cannabis use are eventually followed by schizophrenia, a chronic and invalidating illness [7].

In 1987, *The Lancet* published an epidemiological study by Andreasson *et al*. examining the risk of hospitalization for schizophrenia in a cohort of Swedish cannabis and non-cannabis users over a 15-year period. Psychiatric admissions were 6.0 times more common in regular cannabis smokers and 2.3 times more frequent in occasional smokers than in subjects who had never smoked cannabis [8].

In 2002, Zammit *et al*. reanalysed the same sample of Swedish patients after adjusting the results by the dose of cannabis used and found that in the group of patients with the highest cannabis use (>50 times), the odds ratio of developing schizophrenia was 3.1 [9]. In a recent published study from this group, the risk of developing schizophrenia was again 3.7 among frequent cannabis users compared with non-users after 35 years of follow up [10]. Other studies with prospective designs have also shown an increased risk of developing psychosis after using cannabis [4, 7]. Ultimately, several meta-analyses have consistently showed that the use of cannabis is associated with a twofold risk of developing psychotic symptoms or a psychotic illness [11, 12], after adjustment for factors such as age, sex, social class, ethnicity, urbanicity, and use of other drugs.

In contrast, it has been argued by some authors that only a minority of cannabis users develop psychosis. The observed dose response effect [4, 9] may partly explain this fact. In addition, some studies have suggested that exposure to cannabis in a vulnerable at a young age (early adolescence) may be related to a much higher risk of developing psychosis than cannabis use in later years [13]. Finally, cannabis use may be considered as an additional risk factor in a diathesis-stress model of schizophrenia where the risk of developing the illness would be higher in genetically vulnerable people. In this regard, much of the research on cannabis and psychosis is currently focusing on gene-environmental interactions and their involvement in the pathogenesis of psychosis [14, 15].

Growing evidence suggests that the combination of certain genetic factors with environmental exposures such as cannabis use may significantly increase the risk of developing schizophrenia. In light of theses findings, the present review will focus on the putative mechanisms of action of specific genetic variations and environmental factors during the onset of a first episode of psychosis.

NEUROPHYSIOLOGY OF CANNABIS

The Endocannabinoid System

The human endocannabinoid system consists of endocannabinoid receptors and the endogenous endocannabinoids. There are two types of human endocannabinoid receptors: CB1 and CB2. The CB1 receptors were first described in the brain in 1988 [16]. CB1 receptors are found in the limbic system (hippocampus and amygdala), the basal ganglia, the cerebellum and the prefrontal area at GABAergic and glutamatergic terminals [17].

CB1 receptors are G-protein coupled receptors and adenylcyclase inhibitors that stimulate the activity of protein kinases A [18] and which in turn inhibit certain calcium channels while activating potassium channels. This combined effect could explain the inhibitory action of endocannabinoids on the liberation of neurotransmitters such as dopamine in the ventral tegmental area-mesolimbic pathway [19].

CB2 cannabinoid receptors have a similar structure to CB1 receptors [20], although their proportion in the central nervous system is much lesser than for CB1 receptors [21].

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CB1 and CB2 receptors have different types of ligands both endocannabinoid (such as anandamide and 2-arachidonoilglycerol) and non endocannabinoid [16, 22]. Unlike some other neurotransmitters that can be synthesized and stored for later use, endocannabinoids are generated and liberated on demand and their synthesis is modulated by intracellular calcium concentrations [23]. It is thought that endocannabinoids mediate short and long term depression of synaptic strength via retrograde transsynaptic signalling [24]. In fact, CB1 receptor agonists act as retrograde synaptic mediators of the phenomenon of depolarization-induced suppression of inhibition (DSI) and excitation (DSE). Thereby, they reduce neurotransmission in GABAergic neurons of the striate nucleus and glutamatergic neurons in the dorsolateral striate nucleus [24, 25]. In this sense, the activation of CB1 receptors protects the nervous system against the overactivation or the overinhibition produced by GABA and glutamate neurotransmitters.

Some authors have explored the relation between the cannabinoid and dopaminergic systems to better explain the link between cannabis and psychosis [26]. It has been found that an acute exposure to exogenous cannabinoid substances activates the dopamine D2 receptors of the striate nucleus [27, 28], increasing striatal dopamine levels. Even though other authors have also described clear inhibiting effects of cannabinoids on dopaminergic neurons [29], it seems that cannabinoids produce an increase in dopamine levels in the nucleus accumbens and the ventral tegmental area [30]. In humans, increases in dopamine levels in the mesolimbic cortex, striate nucleus and dorsal precommisural putamen after cannabis use have been reported in patients with schizophrenia [31] and healthy subjects [32, 33], using SPECT and PET neuroimaging techniques. Inversely, a significant reduction of ligand binding was seen at the levels of the frontal and temporal lobes [34]. Finally, animal model studies have suggested that a prolonged exposure to cannabis could sensitize CB1 receptors [35] and eventually reduce prefrontal levels of dopamine in rats [36]. Taken together, these data suggest that acute exposure to exogenous cannabinoids activate D2 receptors and dopaminergic transmission in striatum and mesolimbic areas whereas prolonged exposure to cannabinoids results in a reduction of the dopamine in the prefrontal cortex.

Exogenous and Endogenous Cannabinoids

Delta-9-tetrahidrocannabinol (THC), the main psychoactive substance in cannabis, acts as an agonist on CB1 cannabinoid receptors [37] and inhibits the liberation of neurotransmitters from the nerve terminals expressing CB1 receptors, consequently preventing DSI and DSE phenomenon [38]. THC and other exogenous cannabinoids also increase dopaminergic activity of neurons from the ventral tegmental area, an important pleasure-mediating centre [39] and in mesolimbic reward centres, at the nucleus accumbens [30].

The endocannabinoid 2-arachidonoyl-glycerol or 2-AG, as well as anandamide to a lesser extent, have been shown to act as modulators of glutamate release via an inhibitory effect on presynaptic CB1 receptors. 2-AG can reduce the release of glutamate especially in regions of the central nervous system involved in the pathophysiology of schizophrenia, such as the hippocampus [40], the prefrontal cortex [41], the nucleus accumbens [42] and the amygdala[43]. This glutamatergic hypoactivity in the prefrontal cortex could be related to the prefrontal dopaminergic hypofunction of patients with schizophrenia, mediated by NMDA/D1 receptor complexes. In addition, glutamate release in the mesolimbic system of both patients with schizophrenia and cannabis users have been shown to be reduced compared to non cannabis users [41]. Postmortem studies have shown a global increase in the number of CB1 receptors of patients with schizophrenia and a reduction of CB1 receptors and CB1 messenger RNA in the prefrontal area of these patients [44]. This accounts for a reduction in GABA release by presynaptic prefrontal neurons [45] and could help explain the seemingly paradoxical "therapeutic effect" attributed to cannabis by certain patients, especially in those where negative symptoms are predominant.

At the striatal level, the release of glutamate stimulates the production of 2-AG through postsynaptic mGLUR5 receptors, which in turn suppresses glutamate release through a negative feedback mechanism [46]. 2-AG is hence thought to play a physiological role distinct from that of anandamide in psychotic disorders, anandamide having a stronger effect on GABA and dopamine release than on glutamate release.

Patients with schizophrenia present higher than normal serum and cerebro-spinal fluid concentrations of anandamide [26]. This seems to be due to the fact that stimulation of dopamine D2 receptors produces the release of endocannabinoids [34], via striatal medium GABAergic neurons, which retroactively counteract the effects of dopamine. Typical antipsychotics reduce this excess of anandamide by specifically antagonizing D2 receptors, which is suggested to explain the negative correlation between psychotic symptoms and anandamide levels highlighted by some authors. [26]. A detailed description of the endocannabinoid system is presented in other papers published in the present issue.

Physiological Effects of Endocannabinoids

The activation of CB1 receptors in humans reproduces all of the main classical effects observed with cannabis use (euphoria, anxiety [47], decreased pain sensation, increased appetite, and dry mouth). The activation of CB2 doesn't produce these same effects, as these receptors are mostly present at the peripheral level. Cannabinoids inhibit the release of GABA in the corpus striatum [48] and of GABA and glutamate in the other nuclei [43]. A possible function of the endocannabinoid system is the inhibition of tonic release of glutamate in the substancia nigra and regularization of levels of basal motor activity [49]. Exogenous cannabinoids can suppress GABA release in the substancia nigra that decreases inhibitory signals towards the thalamic-cortical pathways and causes a subsequent inhibition of movement. The near absence of cannabinoid receptors in the brain stem explains the non-lethal character of acute cannabis intoxication.

Endocannabinoid excess or prolonged cannabis use produce an excess of dopamine in the mesolimbic lobe, but a reduction of dopamine level at the prefrontal level, which mirrors the neurochemical states seen in schizophrenia. In the brain of patients with schizophrenia, it was shown that there is an approximately 64% increase in CB1 receptor binding in the anterior cingulate cortex [50], a part of the brain involved in cognitive and emotional processes.

The cognitive effects of cannabis use in healthy subjects, patients with schizophrenia and their siblings are well described [6, 12]. The deficits in working memory, attention and information retrieval caused by long term cannabis use are similar to those seen in patients with schizophrenia, [51]. Memory deficits associated to acute expositions to cannabis may be explained by the inhibition of GABA and glutamate release in the hippocampal circuit because of the reduction of CB1 receptor expression.

Cognitive impairments caused by cannabis are usually transient and dose-dependant [52]. There is little evidence that the cognitive effects due to cannabis use persist after a period of abstinence in healthy subjects [53]. Interestingly, some studies have shown that cannabis use prior to a first psychotic episode might be predictive of a better cognitive function [54] and a recent meta-analysis have suggested that use of cannabis in patients with schizophrenia is related to superior cognitive performance compared to non users [55]. Nevertheless, it is well known that cannabis use increases relapse rates and decreases the duration of symptom-free periods in patients with psychosis [56]. Reasons for this effect include a significant reduction in compliance to treatments and alterations in the response to medication. Accordingly, patients with schizophrenia

and comorbid cannabis use appear to have more positive symptoms [57]. Premorbid and experimental cannabis exposures have also been related to a greater positive symptomatology [58, 59]. In contrast, a number of studies have reported reductions in negative symptoms of patients with schizophrenia and comorbid cannabis use, showing that the effects of cannabis on psychotic symptoms cannot be considered as all-white or all-black [60].

NEUROIMAGING

In healthy samples, some studies have shown that cannabis use may be associated with significant reductions in hippocampus and amygdale volumes, in gray matter density in right parahippocampal gyrus and in white matter density in the left parahippocampal gyrus [61]. Additionally, the use of cannabis in young healthy subjects has been recently associated with a decreased gyrification pattern of the brain, showing bilateral decreased concavity of the sulci and thinner sulci in the right frontal lobe [62]. These results may suggest that cannabis use in adolescence and early-adulthood might involve a premature alteration in cortical gyrification similar to what is normally observed at a later age, probably through disruption of normal neurodevelopment. Functional neuroimaging has shown that resting global and prefrontal blood flow are lower in cannabis users than in controls [63] with inconsistent results in activation studies. Surprisingly, these changes did not seem to have a significant impact on performances in neuropsychological testing [64]. Functional neuroimaging studies in healthy volunteers have further suggested different cannabinoids (i.e. THC and CBD) exert opposite/distinct modulation of the neural networks underlying cognitive [65, 66] or emotional [67] processes. There is additional evidence indicating cannabinoids can significantly affect effective connectivity between brain areas implicated in the above processes [68].

The imaging alterations produced by cannabis use in patients presenting a first psychotic episode are more controversial. However, some recent studies have shown significant changes, such as the enlargement of lateral ventricles [69]. Some of the brain regions where activity was reduced in patients with a first psychotic episode and comorbid cannabis use were the limbic and paralimbic cortices [70-72]. Recently, a case-control study that used Magnetic Resonance Imaging (MRI), has reported the different impacts of cannabis use on the frontal and parahippocampal regions of the brains of patients with schizophrenia, cannabis consuming healthy siblings and healthy cannabis-users. The thinning of these regions in patients and siblings, but not in controls, supports the existence of gene-environment interactions in psychosis [73]. Detailed discussion of neuroimaging findings in cannabis users and psychotic subjects are presented in other papers published in the present issue.

CANNABIS USE AND PSYCHOSIS LIABILITY

Scientific evidence suggests that the expression of schizophrenia is brought by a combination of environmental factors and genetic susceptibility [14], in such a way that in a complete absence of environmental factors, the illness would not be expressed. This should be reflected by associations between the risk of psychosis in cannabis users and psychosis liability, expressed by family background or intermediate phenotypes.

Apart from the above-mentioned neurocognitive deficits and effects seen on neuroimaging, other psychosis endophenotypes have been studied in relation to the use of cannabis. Interestingly, variations in the increase in neurological soft signs (NSS or minor neurologic signs) have been observed in relation to cannabis use in schizophrenia, suggesting that the incidence of NSS is lower in individuals with psychosis and comorbid cannabis use [74, 75]. This result may be attributed to a higher release of dopamine in certain areas of the brain in cannabis users.

An interesting phenotype is the age of onset of the psychotic illness, as an earlier onset may indicate a possible association with underlying genetic liability to schizophrenia [76, 77] and age of onset has a high heritability in patients with schizophrenia [78]. The association between cannabis use and an earlier age of onset of the illness has been consistently replicated in retrospective studies, first episode psychosis patients [79-82] and at risk mental state samples [83], although it was not present in all the studies [84]. These results are in accordance with the notion that cannabis use in adolescence may play a role in neurodevelopment because of changes in the endocannabinoid system and dopamine sensitization [37].

An additional finding on the effects of cannabis use and psychosis vulnerability is a greater psychotogenetic effect of cannabis use in patients with schizophrenia who have a family history of psychosis, suggesting that genetic inheritability together with exposure to exogenous cannabinoids can both contribute to the pathogenesis of schizophrenia [85]. Additionally, an earlier use of cannabis was shown to increase the effect of this combination of factors, suggesting an association with cerebral maturation in younger patients depending on their genetic heritage. Accordingly, healthy siblings of patients with psychotic disorders have shown more schizotypical symptomatology after consuming cannabis, than healthy controls [86], suggesting that inclusion of genetic moderation may be necessary to elucidate specific neurobiological mechanisms.

In addition, it has been suggested that individuals with first degree relatives suffering from schizophrenia have a higher risk of contracting psychiatric disorders if they become cannabis users than individuals without a family history of psychotic disorders [87].

Contrarily to these results, it has been previously suggested that cannabis use as a risk factor in the development of schizophrenia could be independent from genetic predispositions [88]. However, more recent studies have shown that vulnerability to schizophrenia could not be necessary for cannabis users to develop psychotic symptoms, but that the combination of vulnerability and cannabis use greatly potentiated the risks [12].

ENVIRONMENTAL FACTORS UNDERLYING THE EFFECT OF CANNABIS IN FIRST EPISODE PSYCHOSIS

The predominant role of genetic factors in the etiology of schizophrenia has been formerly defined by classical twins' studies, which have shown substantial heritability for liability to schizophrenia [89, 90]. However, referring to schizophrenia, the estimated concordance rates are 41-65% in monozygotic twins [91], which highlights the role of environmental factors in disease etiology; as a result, gene-environment or environment-environment interactions may underlie this association [92]. Additionally, there is evidence that familial association of psychotic disorders is greater in risk environments such as urban environment or minority groups [14].

To date there is evidence for at least five (proxy) environmental factors that may contribute to genetic factors in the development of psychosis: cannabis, urbanicity, minority status or discrimination, early adolescent or childhood trauma, and prenatal environment [93]. Some of these environmental factors have additionally been shown to involve cumulative effects interacting with cannabis use on genetic psychotic risk, mainly urbanicity and childhood exposure trauma [94]. Environmental risk factors involved in illness etiology could be separated into environmental factors that predispose to disease, mainly childhood or prenatal exposures like vitamin deficiency, obstetric complications, viral infections or childhood trauma and disease precipitating factors. In this group, we can include toxic exposure, immigration, and urbanicity. Environmental factors may act synergistically on the same final common pathway, with a more than additive interaction [95]

Childhood trauma has been reported to more prevalent in patients with psychosis compared to controls, although the causal association has not been consistently demonstrated [96]. Interestingly, a study by Houston *et al* showed a significant interaction

between early exposure to cannabis and childhood sexual trauma. In a more recent report, this group explored the multiplicative effect of these variables on a large community sample and found that sexual trauma was associated with an increase in the risk of developing a diagnosis of psychosis but only in those individuals who had used cannabis before the age of 16 years [97]. Further studies support the hypothesis about childhood maltreatment and cannabis interaction increasing psychotic risk, suggesting that the psychosis-inducing effects of cannabis were stronger in individuals exposed to earlier sexual or physical mistreatment [95] and that the presence of both childhood trauma and early cannabis use may increased the risk for psychotic symptoms beyond the risk associated to either risk factor alone [98]. Exposure to trauma may occasionally cause abnormalities in neurotransmitter system and structural brain changes [99] that may predispose to the psychotogenetic effect of cannabis use. Psychotic reactivity to stress may result from a sensitization process through which previous exposure to stress sensitizes people to stresses of daily life [100]. These findings may suggest that the additive effects may result from a cross-sensitization process between repeated exposure to stress and THC. Consistently, studies in rodents have shown that stressful conditions induce higher increases in dopamine uptake induced by THC [101]. Several studies have replicated this additive interaction [95, 98, 102], although negative results have also been reported.

Notwithstanding, replication studies on the interaction between cannabis and childhood trauma have also provided negative results [103]; these differences could be due to sampling variation or different time of follow-up.

Growing in an urban environment has been consistently associated with psychosis [93, 104]. The effect of urban environment has been proposed to be mediated by an interaction between individual and social fragmentation [105]. Additionally, it has been suggested that urban exposure may impact on risk for psychosis by causing an abnormal persistence of a developmentally common expression of psychotic experiences [106]. A recent study has reported a significant interaction between cannabis and urbanicity [107] in a general population. The effect of cannabis use on psychotic symptoms was stronger in subjects who grew in an urban environment compared with those from rural surroundings. This interaction can be explained by synergic mechanisms, as both factors may increase dopamine sensitization [93, 107].

Interestingly, it has been shown that whereas negative symptoms in general population may be related to a profile of developmental impairment, positive symptoms experiences are associated to environmental risk factors such as cannabis exposure, urbanicity, self-reported trauma, and lower educational level [108] and only negative symptoms, when combined with these environmental exposures, results in positive psychotic symptoms increasing the risk of impairment and clinical relevance. In this regard, cannabis use, childhood trauma and urbanicity may act additively, and the level of environmental risk combines synergistically with non-clinical developmental expression of psychosis [94].

Taken together, these findings suggest that environmental risks for psychosis act additively, and that the level of environmental risk combines synergistically with non-clinical developmental expression of psychosis to cause abnormal persistence of psychotic symptoms. This highlights the role of gene-environment multilevel interactions in the pathogenesis of psychosis.

GENETIC FACTORS UNDERLYING THE EFFECT OF CANNABIS IN FIRST EPISODE PSYCHOSIS

The discussed gene variants have been summarized in Table **1**.

-COMT Genetic Variants

As it has been previously stated, the exposure to CB1 agonists such as THC may influence the proposed dopaminergic pathways to psychosis, in both the subcortical and the cortical pathways. In this regard, genetic variants influencing dopamine systems have been proposed to interact with cannabis use in the development of psychosis.

The COMT gene encodes the enzyme Catechol-O-Methyltransferase, directly involved in the catabolism of dopamine [109]. The function of the COMT enzyme is particularly important in the prefrontal cortex [110, 111], but it has also been shown to regulate dopaminergic transmission in the midbrain by an indirect effect mediated by prefrontal feedback.

The COMT gene contains a common functional polymorphism (Val158Met, rs4680) that involves a Met to Val substitution at codon 158 and results in 2 allelic variants, the Valine (Val or H, high activity) allele and the Methionine (Met or L, Low activity) allele. The COMT Val158Met polymorphism had been initially postulated as an accepted candidate gene for schizophrenia, however, recent meta-analyses have questioned this association [112]. With regard to intermediate phenotypes, COMT Val158Met polymorphism has been associated with cognitive performance [110], structural abnormalities of the brain [69], neurophysiologic markers [113] and several clinical traits such as aggressiveness [114], and psychotic symptoms [115].

Additionally, other polymorphisms within the COMT gene have been shown to have an impact on the COMT enzyme function, suggesting that the association between COMT and schizophrenia may be more complex than was previously thought [111]. In this regard, a three marker haplotype (including rs165688, rs737865 and rs165599, related to mRNA expression) has been associated to schizophrenia risk [116] and prefrontal cortex inefficiency [117].

The first study reporting a Gene-Environment Interaction was the Dunedain Study, performed by Caspi *et al* [118]. In this study, the COMT Val158Met polymorphism was found to moderate the risk of developing schizophreniform disorder at 26 years in subjects who were cannabis users during adolescence. Adolescent cannabis use was associated with an increased risk in adulthood among Val/Val individuals (OR: 10.9) and, to a lesser extent, among Val/Met individuals (OR: 2.5), but not in Met/Met individuals. Accordingly, cannabis use was associated with psychosis symptoms and hallucinatory experiences in the Val/Val and Val/Met individuals, but not among Met/Met subjects. The results were not altered after controlling for the use of cannabis or other drugs in adulthood and the polymorphism was not related to cannabis use or to psychosis by itself, discarding a gene environment correlation.

Soon afterwards, Henquet *et al* [119] performed an experimental study of Delta-9-TetraHydroCannabinol (THC) exposure in patients with psychosis and healthy controls. Carriers of the Val allele were more sensitive to Delta-9-THC induced psychotic experiences, and memory and attention impairments. Interestingly, the effects on psychotic experiences were conditional on prior evidence of psychosis liability, so the authors proposed that the association between cannabis and psychosis may represent higher order gene-environment (i.e.: Val158Met x Cannabis interaction) and gene-gene interactions (i.e.: Val158Met x Liability). A second study from this group [120] evaluated the effects of interactions between COMT Val158Met genotype and exposure to cannabis with a structured diary technique in patients with a psychotic disorder and healthy subjects. Again, carriers of the Val158 allele but not the Met158 homozygote subjects showed an increase in hallucinations after cannabis exposure. This effect was also conditioned on prior evidence of psychometric psychosis liability. The authors suggest that the Val allele, associated with lower levels of prefrontal dopamine may exhibit less tonic inhibition of mesolimbic phasic dopamine, a system related to regulation of salience assignment. However, neither cannabis nor the COMT Val158Met genotype alone may be sufficient to influence this regulation in order to bring a clinical impact. Even this interaction would only arise in the pres-

Table 1. Summary of Genes Underlying Cannabis Effects in First Episode of Psychosis

Gene	Affected poly-morfism	Activity	Outcomes (interaction effects with cannabis use)
COMT gene	rs4680	Met to Val substitution at codon 158. Two allelic variants: Val or H, high activity and Met or L, low activity. Associated to cognitive performance brain structural volumes and clinical symptoms in psychosis	Higher psychosis risk in Val/Val and Val/Met individuals. [118] Negative results in higher psychosis risk [121, 122] Carriers of Val are more sensitive to delta-9-THC, conditional on prior psychosis liability [119, 120] Earlier age of onset of psychosis [82, 126] Longer duration of untreated Psychosis [82] Negative results in affective symptoms [124] Exposure to THC in adolescent COMT knockout mice produce a higher expression of psychosis phenotype [123]
	rs165688 rs737865 rs165599	Involved in dopamine catabolism and mRNA expression	Negative results in higher psychosis risk [122]
	rs6269 rs4818 rs4633 rs4680		Patients with a Met158 homozygote genotype at rs4680 doubled the probability of cannabis use [127]
CNR1 gene	rs1049353	Regulate striatal dopamine. Modulate effects of exogenous cannabis	Negative association with risk of psychosis [121] G allele schizophrenia patients carriers are more sensitive to the effect of cannabis in temporal lobe WM volumes [129]
AKT1 gene	rs2494732 rs3730358, rs1130233	Protein kinase involved in cellular functions. Haplotype associated with worse perform-ance on the N-back task	Cannabis use interact with AKTI rs2494732 genotype to affect CPT (Continuous Performance Test) reaction time and CPT accuracy [133]
BDNF gene	rs6265	Val66Met. Encoded brain derived neurotro-phic factor a protein which encourage the growth and differentiation of neurons. D9-THC was shown to up-regulate BDNF mRNA in the hippocampus of mice Met66 allele has been associated with the age of onset of psychosis	In female patients, cannabis use was associated with earlier age of onset of psychosis in BDNF Met66-carriers [142]
NRG1gene (experimental)	Nrg1HET mice. Nrg1WD mice	Encodes neuregulin 1, which act in Epider-mic Grow Factor Receptors (EGFR). Candidate gene for schizophrenia, related to neurodevelopmental processes.	Nrg1 HET mice are more sensitive to the behavioral effects of the main psychoactive constituent of cannabis, Delta(9)-tetrahydrocannabinol (THC) after stress interaction [146,147]

ence of previous liability and therefore a pre-existing hyperdopa-minergic or sensitized dopaminergic system.

Zammit *et al.* [121] tried to replicate these results in a case-only design and failed to find a differential effect of cannabis use in psychosis risk according to variations in the Val158Met polymor-phism in COMT and other single nucleotide polymorphisms. How-ever, the quality of data on cannabis use was limited in this study. A new study from this group [122] examined the risk of developing psychotic symptoms in a longitudinal follow up of an epidemiol-ogical cohort (followed from ages 7.5 to 16 years). The study showed further evidence of the association between cannabis use and subsequent onset of psychotic symptoms (OR: 2.5) but failed to find evidence of interaction under a multiplicative model between cannabis and COMT genotype in Val158Met polymorphism (rs4680) or other known COMT polymorphism genotypes (rs737865, rs2097603, rs6269, rs4818, rs165599 or the haplotype conformed by rs6269, rs4818 and rs4680). A proposed explanation by the authors was that psychotic symptoms were evaluated at age 16, compared to age 26 in the Dunedain study. This may suggest that the differential effect of cannabis becomes evident only after a more chronic use of the substance. Accordingly, a study in COMT knockout mice [123] showed that Exposure to THC during adoles-cence induced a larger increase in exploratory activity, greater im-pairment in spatial working memory, and a stronger anti-anxiety effect in COMT Knockout than in Wild Type mice, with no effect on novel object recognition and social behaviour. No such effects were evident for any behaviour after adult THC administration. These findings indicate processes through which adolescent THC

exposure could result in deleterious effects on several aspects of normal, adult functioning that are disrupted in schizophrenia, and that could be modulated by the COMT genotype.

Kantrowitch *et al.* [124] also reported negative results for the association between COMT Val158Met genotype, cannabis use and affective symptoms in patients with a diagnosis of schizophrenia, schizoaffective disorder or Psychosis Not Otherwise Specified (PNOS) independently of the ethnic origin.

Given the possible interaction between Cannabis use and COMT Val158Met Polymorphism, our research group performed a study in patients with a first episode of non affective psychosis with the aim of evaluating the effects of an interaction between the Val158Met genotype and premorbid cannabis use [82]. In our study, the premorbid use of cannabis was again associated with an earlier age of onset in the first episode and the cannabis use modulated the effect of the genotype. Patients with a Met158 homozygote genotype showed a later age of onset compared to other genotypes but the use of cannabis seemed to suppress the delaying effect of Met158 allele. Additionally, the results showed an interaction between the genotype and cannabis in the duration of untreated psychosis (DUP). Patients with a Val158 Homozygote genotype showed longer DUPs in the absence of premorbid cannabis use, but this effect was moderated in the case of cannabis users. The association between the Val158 allele and longer DUPs may be explained by a relation with negative symptoms, previously reported in our sample of patients with a first psychotic episode [125]. The reduction of DUP in Val158 homozygote patients who used cannabis could be explained by an increase of psychotic symptomatology (particularly in the SAPS hallucinations item) that would lead the patients or their families to an earlier use of medical resources.

A recent study on a sample of patients with recent onset psychosis also showed an interaction effect between the COMT Val158Met polymorphism and both lifetime cannabis use and age at first cannabis use as predictors of age of onset of psychiatric disorder, in the same way as previous studies had shown [126]. Additionally, although the effect of cannabis use on age of onset was similar in schizophrenia and other psychiatric illness the effect of the genotype and the interaction appeared to be specific to schizophrenia spectrum disorders. This would indicate that these patients are more sensitive to the effect of cannabis on the regulation of dopaminergic systems due to their genetic background.

Finally, a recent study found an association between four common polymorphisms of the COMT gene (rs6269, rs4633, rs4818 and rs4680 and three common haplotypes defined by these) and lifetime cannabis use in patients with schizophrenia [127]. In this study, the low activity COMT variants were associated with cannabis use and the patients with a Met158 homozygote genotype at rs4680 doubled the probability of cannabis use compared to Val158 homozygous. These results are in contrast with previous studies that showed no association between cannabis use and COMT genotype.

-Other Genetic Variants

It is unlikely that variations in a single gene account for the differential sensitivity to THC in individuals at risk for psychosis. As some of the previous studies have shown that psychosis liability may condition the interaction between cannabis and COMT, this suggests that gene-gene interactions may underlie the association between cannabis and psychosis [92]. Candidate genes for this interaction should be related to the endocannabinoid system, and other systems associated with it, such as the dopaminergic system.

In the first study from Zammit *et al.* [121], the rs1049353 polymorphism from the cannabinoid receptor 1 gene, CNR1, was studied. Although no associations or interactions were reported between CNR1, schizophrenia and cannabis use, this is a gene of interest as it has been suggested to regulate striatal dopamine as well as modulate the effects of exogenous cannabis [128]. In a recent study, Ho *et al.* [129] evaluated the interaction between 12 CNR1 tag polymorphisms and cannabis use on brain volume and cognitive function among patients with schizophrenia. CNR1 rs12720071 G allele carriers, rs7766029 C Homozygotes and rs9450898 C homozygotes were associated with smaller white matter (WM) brain volumes. Additionally, rs12720071 G allele carriers appeared to be especially vulnerable to the effect of cannabis in parietal lobe WM volumes and on impairing problem solving skills. The potential role of these three polymorphisms is unknown to date, as they are located on introns or within the untranslated region of exon 4 of the gene. The observed abnormalities associated with this polymorphism may be related to a Linkage Disequilibrium with known functional variants or to yet unknown direct or regulatory effects in the gene.

A second gene related to schizophrenia and cannabis use is AKT1, a protein kinase involved in cellular functions including stress, cell-cycle regulation and apoptosis [130]. Additionally, it is involved in molecules downstream of D2 dopamine [131] and several studies suggest a genetic association with schizophrenia [132]. Cannabinoids may activate the AKT1/GSK3 pathway, activating CB1 and CB2 receptors *in vitro* and phosphorylating AKT1 [131]. An AKT haplotype consisting of rs3730358, rs1130233, and rs2494732 G-A-C alleles was associated with worse performance on the N-back task in healthy subjects [132]. Accordingly, an interaction has been observed between cannabis use and AKT1 rs2494732 genotype in CPT (continuous performance test) reaction time and accuracy, showing that cannabis user patients and the C/C genotype were slower and less accurate in the test, whereas users with a T/T genotype had similar performance than cannabis non-users [133]. As performance in CPT in related to prefrontal dopamine functioning, these results are in agreement with the notion that AKT1 modulates dopamine prefrontal functioning and may suggest that the cannabis effects in psychosis may be mediated by dopamine prefrontal-striatal interactions. The interaction was also present in patients without use in the last 12 months, but absent in unaffected siblings and healthy control. Additionally no effects were observed in verbal memory.

Another gene studied in schizophrenia in relation with cannabis and psychosis is the Brain-derived neurotrophic factor (BDNF) gene, a neurotrophine implied in the development of mesolimbic dopaminergic neurons [134] and in the modulation of dopamine, glutamate, serotonin and GABA [135]. BDNF and cannabis signalling both involve the AKT1-GSK3 pathway downstream of their receptors--TrkB receptors--, which are transactivated by endocannabinoids [136]. Cannabinoids may alter BDNF expression via the extracellular signal-regulated kinase (ERK) signalling pathway, as the injection of D9-THC was shown to up-regulate BDNF mRNA in the hippocampus of mice [137]. In agreement with these findings, BDNF serum levels have been shown to be increased in healthy subjects [138] and drug naive patients with a first episode of psychosis after use of cannabis [139], but decreased in chronic users, suggesting an implication of CB1 down regulation and the possibility of gene–environment interactions between cannabis and the BDNF Val66Met genotype. A Val to Met substitution at codon 66 (rs6265) of the brain-derived neurotrophic factor (BDNF) gene, results in less efficient intracellular trafficking and decreased activity-dependent BDNF secretion [140]. The Met66 allele has been reported to be associated with the age of onset [141] in patients with schizophrenia and a BDNF-sex-cannabis interaction has been shown [142]. Cannabis use predicted an earlier age of onset in male patients independently of genotype, whereas in female patients, cannabis use was only associated with age of onset in BDNF Met-carriers. These results would be in agreement with earlier studies in which BDNF excretion was shown to be an adaptative response to psychotogenic effects of THC, although it was only demonstrated in female subjects [137-139].

Finally, two experimental studies have been published suggesting Neuregulin 1 gene (NRG1) as a candidate gene to be involved in the gene-cannabis interaction in schizophrenia. NRG1, a candidate gene for schizophrenia [143], is a ligand for the ErbB receptor Tyrosin Kinases, related to neurodevelopmental processes in schizophrenia, including myelination, axon guidance, neuronal migration and glial differentiation [144]. Mutant mice heterozygous for the trasnmembrane domain of NRG1 (Nrg1 HET mice) have demonstrated to exhibit a schizophrenia related behavioural phenotype and a deficit in NMDA receptor expression [145]. In a first study, HET mice were more sensitive to the locomotor suppressant and anxiogenic effects of THC than wild type-like (WT) mice and had facilitated sensoriomotor gating measured by prepulse inhibition [146]. In a second study, using c-Fos inmunohistochemistry to examine the effects of THC on neuronal activity, exposure to THC brought a greater increase in c-Fos expression in Nrg1 HET mice compared to WT mice in the central nucleus of the amygdala, in the bed nucleus of the stria terminalis and in the paraventricular nucleus of the hypothalamus [147]. Interestingly, THC selectively increased c-Fos expression in the lateral septum of Nrg1 HET mice but not in WT mice. This effect was shown to interact with stress, which was necessary in order to observe these effects. All these results indicate that NRG1 genotypes may alter the sensitivity to neurobehavioural effects of THC under conditions of stress and suggest new possible gene-interaction studies in clinical samples of patients with psychosis and comorbid cannabis use.

-SUBJECTS AT ENHANCED CLINICAL RISK (HR) FOR PSYCHOSIS

Over the recent years, a growing research interest has focused on the so-called 'putatively prodromal stage of schizophrenia'. A number of terms have been proposed to describe this pre-psychotic phase (which thereafter we call clinical high risk state, HR), including "ultra high risk (UHR)", "at risk mental state (ARMS) [148], or simply "high risk". Two broad sets of criteria have been used to diagnose the CHR state: the "ultra high risk (UHR)" and the "basic symptoms (BS)" criteria [149]. These criteria are considered valid in help seeking individuals usually aged 8-40. The UHR criteria have been the most widely applied in the literature to date and inclusion requires the presence of one or more of: 1. attenuated psychotic symptoms (APS), 2. brief limited intermittent psychotic symptoms (BLIPS), 3. trait vulnerability plus a marked decline in psychosocial functioning (Genetic Risk and Deterioration Syndrome: GRD), or 4. unspecified prodromal symptoms (UPS). BS are subjective experiences of disturbances of thought processing, language and attention. These experiences are distinct from classical psychotic symptoms in that they are independent of abnormal thought content and reality testing; also insight into the symptoms' psychopathological nature is intact [150]. The HR state is associated with an enhanced but not inevitable risk of developing a psychotic episode over the following years. In a recent meta-analysis of about 2500 HR subjects, it was shown that there was a mean transition risk, independent of the psychometric instruments used, of 18% after six months of follow-up, 22% after one year, 29% after two years and 36% after three years [151]. The HR state is characterized by depressed mood, anxiety, irritability and sub-threshold or attenuated psychotic symptoms [152-154]. Cognitive impairment is subtle but significant as compared to matched healthy controls and is associated with alterations in the structure [155, 156], function [157], or brain chemistry [158-160].

The impact of cannabis use in this dynamic phase is still unclear but may play a crucial role affecting the longitudinal risk towards psychosis transition. Of the four studies that examined effects of cannabis use on transition to a first episode of psychosis from a HR state [83, 161, 162], only one study reported a significant association [163]. This study adopted a short follow-up time and enrolled HR subjects with a previous cannabis use disorder in remission or not in remission. These methodological caveats undermine the significance of the results. The other negative studies employed longer follow-up and different definitions of cannabis abuse. Overall, these studies provide only very limited support for the theory that cannabis use is associated with transition to a first psychotic episode.

However, these results should be interpreted cautiously, in the light of the heterogeneity underlying the HR group. The HR sample is heterogeneous in terms of inclusion criteria (UHR vs. BS; Early vs. late HR criteria), presentation, clinical needs and outcome; it comprises individuals with true prodromal symptoms, false positives as well as subjects presenting with HR symptoms which will fully remit to remerge later during the follow-up period (outpost syndrome). Even within the so called "false positives", some of them will continue to present impairment in functioning or other psychiatric problems at follow-up. Because of these problems it would be premature to conclude that cannabis abuse has no effect on psychosis transition in the HR individuals and future studies in the field are needed.

CONCLUSIONS

Although cannabis use was consistently reported to be associated with psychosis, only a small proportion of cannabis users in the general population will develop a psychotic illness. Some of the factors implied in the onset of psychosis will be the age at which cannabis use was initiated and the amount of cannabis used in the vulnerability period. Also the genetic background of the individual (the psychosis liability) and other environmental factors that can modulate the sensitivity to cannabis and THC must be considered. The understanding of the underlying mechanisms in this interaction may help to increase the current knowledge on the pathogenesis of the illness and to design new therapeutic targets. Given the mechanisms of action of THC and its relation to endocannabinoid and dopaminergic systems, the studies on gene-environment interaction in cannabis use and psychosis have included to date genetic factors involved in the regulation of these systems. Interactions with COMT polymorphisms in the development of psychotic symptoms, a first episode of psychosis or in the modulation of age of onset of the illness appears to be promising given the relation in the regulation of prefrontal dopamine and the preliminary results. However, despite a considerable number of studies reported to date, a lack of reproducibility between studies has not allowed to replicate or refuse results. A single genetic factor is unlikely to explain the complex interactions between cannabis and psychosis and therefore, other genetic and non-genetic variants should be considered to be included in the Gene environmental interaction model for cannabis and psychosis. Some of the most promising genetic variants in this field are CNR1, BDNF, AKT1 and NRG1. Yet, most of the findings related to these genetic variants have not been replicated or have not been studied in clinical samples yet. Additionally, other environmental factors involved in the interaction with the dopaminergic system or the vulnerability continuum such as stress should be included in the model. Further experimental and clinical studies are warranted to better understand the underlying mechanisms explaining why cannabis may increase the risk of psychosis. Given the relation to the onset of the illness, studies on first episodes of psychosis and at risk mental states should play a predominant role in future research in order to avoid confounding bias associated to chronicity and previous treatment.

ABBREVIATIONS

2-AG	=	2-arachidonoyl-glycerol
AKT1	=	v-akt murine thymoma viral oncogene homolog 1
APS	=	Attenuated Psychotic Symptoms
ARMS	=	At Risk Mental State
BDNF	=	Brain-Derived Neurotrophic Factor

BLIPS	=	Brief Limited Intermittent Psychotic Symptoms
BS	=	Basic Symptoms
CB1	=	Cannabinoid receptor type 1
CB2	=	Cannabinoid receptor type 2
CHR	=	clinical High Risk state
COMT	=	Catechol-*O*-Methyl Transferase
CNR1	=	Cannabinoid Receptor 1 (brain)
CPT	=	Continuous Performance Test
D2	=	Dopamine receptor 2
DSI	=	Depolarization-induced Suppression of Inhibition
DSE	=	Depolarization-induced Suppression of Excitation
DUP	=	Duration of Untreated Psychosis
ERK	=	Extracellular signal-Regulated Kinase
GABA	=	γ-AminoButyric Acid
GRD	=	Genetic Risk and Deterioration Syndrome
GSK3	=	Glycogen synthase kinase 3
HET	=	Heterozygous
HR	=	High Risk
MRI	=	Magnetic Resonance Imaging
NMDA	=	*N*-Methyl-D-aspartic acid or *N*-Methyl-D-aspartate
NRG1	=	Neuregulin 1
NSS	=	Neurological Soft Signs
PET	=	Positron Emission Tomography
PNOS	=	Psychosis Not Otherwise Specified
SPECT	=	Single Photon Emission Computed Tomography
THC	=	Tetrahydrocannabinol
TrkB receptors	=	TrkB tyrosine kinase or BDNF/NT-3 growth factors receptor or neurotrophic tyrosine kinase, receptor, type 2
UHR	=	Ultra High Risk
UPS	=	Unspecified Prodromal Symptoms
WM	=	White Matter
WT	=	Wild Type

CONFLICT OF INTEREST

There are no conflicts of interest.

ACKNOWLEDGEMENT

None declared.

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Received: Mach 30, 2012 **Accepted: April 19, 2012**