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Cannabis and Psychosis: A Systematic Review of Genetic Studies

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Abstract: Though the basic pathophysiology of psychosis is largely unknown, there is reliable evidence that genes contribute to its aetiology. Epidemiologic studies suggested that chronic use of cannabis is a risk factor for the development of psychosis. Recent researches have focused on the identification of genetic variants that moderate the effect of cannabis on psychosis occurrence.

We undertook a systematic review of primary studies that reported the direct measures of genetic risk in the association between cannabis use and psychosis considering cannabis use as an environmental factor under the gene-environment interaction model. The initial search from PubMed revealed 187 records, of which 113 were excluded on reading the abstract. Of 74 papers screened in full, 60 were reviews, 14 were included for data extraction.

We report a structured summary of populations studied, study design, evaluations of cannabis use, genetic variations, outcome measures and main results. The 14 primary studies included in the survey applied the candidate gene approach, *COMT* being the most investigated; also *CNR1*, *BDNF* and *SLC6A4* were examined; a novel candidate gene, *AKT1*, was identified through a multistage approach.

Few candidate genes were investigated, and reliable replications were provided only for *AKT1*. Studies were heterogeneous in terms of experimental design and outcome measures, thus hampering an effective synthesis. We conclude that additional primary studies are warranted. An effort in harmonisation of data, coupled with the recent advances in genetic technologies, should be encouraged.

Keywords: Psychosis, schizophrenia, cannabis, genetic association, gene-environment interaction, polymorphisms.

INTRODUCTION

Genetic Liability to Psychosis

Psychosis can be considered a multidimensional syndrome with a lifetime prevalence of 2-3% [1], in which the poor outcome fraction is schizophrenia (SCZ), diagnosed in around 0.5-1% of the population during their lifetimes [2]. Psychosis (hallucinations and delusions), motivational impairment (avolition or amotivation), affective dysregulation (depression, mania) and alterations in information processing (cognitive impairment) are considered symptom dimensions of the psychotic syndrome [3].

The pathophysiology of psychosis is largely unknown, though the role of synaptic dysfunction and altered neuronal connectivity that originate early in neurodevelopment has long been recognised. Formal genetics demonstrated high heritability of SCZ (up to 80%) and bipolar disorder, thus supporting the influence of genetic variations on common liability to psychosis [4, 5]. Many efforts were devoted to identify susceptibility genes with main effects, through association studies with candidate gene approach and genome-wide association studies (GWASs), but no genes with large effect were identified [6-8].

Recently, copy number variants (CNVs) emerged as risk factors for psychosis with relatively high odds ratios (ORs), ranging between 2 and greater than 30 in SCZ [9, 10]. Moreover, application of next-generation sequencing in SCZ supported the notion that multiple de novo genetic variants contribute to the genetic risk of psychosis [11, 12]. Data deriving from these studies is consistent with a heterogeneity model of genetic risk in psychosis: the phenotype can be caused both by a large number of common variant with small effects or by rare variants with large effects in different individual.

Besides genetic factors, there is increasingly evidence that a significant role in the psychosis proneness is played by environmental factors, such as urbanicity, minority group position, developmental trauma, as well as cannabis use [2, 3, 13-15]. A mechanism of sensitization was postulated, that is repeated exposure to environmental risk factors may cause

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subclinical psychotic experiences to persist and become more severe, resulting in onset of psychotic illness in a minority of susceptible individuals [3, 16, 17]. Based on these lines of knowledge, psychosis can be interpreted as a complex trait, in which multiple environmental and genetic determinants interact to funnel through a single common pathway essential for the developmental of specific neural connectivity [17].

Cannabis and Psychosis

There have been claims for many years that cannabis use can induce a psychotic illness, termed cannabis-induced psychosis [18-20]. Subsequently, the disorder was considered an early sign of psychosis rather than a distinct clinical entity. It has also been noted that patients with diagnosed psychosis use more cannabis than the general population [21, 22]. The use of cannabis was associated with increased levels of psychotic symptoms and with higher relapse rates and poor treatment outcome of schizophrenia-like disorders [23, 24].

Epidemiologic studies showed that cannabis use increases the risk for the psychosis outcome: the association was confirmed in different types of studies and in different cohorts, and a biological gradient ("dose response") was found [23, 25-29] (see also for review: [24, 30]). This finding cannot be explained entirely by confounding factors, as the effect of cannabis remained significant after adjustment for age, sex, social class, ethnicity, urbanicity, and use of other drugs [24, 31, 32]. Meta-analyses of the prospective studies on the development of psychosis associated with prior cannabis use resulted in OR of 2.1 (95% CI: 1.7-2.5) [31] and 1.4 (95% CI 1.2-1.7) [32].

It should be noted that, although *Cannabis* is properly a genus name, in most literature different varieties and preparations for recreational use are grouped under the generic term cannabis [33], regardless of the content in Δ9-tetrahydrocannabinol (THC), the main psychoactive substance in cannabis, and its availability.

The critical period of exposition to cannabis seems to be adolescence (an important era in brain development during which stimuli from the external environment are implicated in anatomical and functional changes), the risk being dose-dependent with a time lag between exposure onset of symptoms [31, 34, 35]. THC acts on cannabinoid receptors type 1 (CB1), the primary binding site of endogenous cannabinoid system (eCB). The eCB is critically involved in process of brain maturation through its regulating role in the release of glutamate and GABA. THC during the adolescence seems to predominantly affect the maturation of specific neurocircuitries involving also the dopaminergic transmission, ultimately giving rise to psychotic symptoms [34, 36].

Gene-environment Interaction

Direct measures of the interplay between genetic and environmental factors were investigated using the approach called gene-environmental interaction (GxE). GxE can be defined as "a different effect of an environmental exposure on disease risk in person with different genotypes" or, equivalently, "a different effect of a genotype on disease risk in person with different environmental exposures" [37, 38]. In addition to the three conventional designs used in genetic association studies (family-based, retrospective case-control and prospective cohort), the case-only design was developed for GxE studies. The case-only paradigm is based on the assumption of independence between the two factors in the study base (in the present field cannabis use and a given genotype).

The majority of GxE studies in psychiatry used the candidate gene approach. A recent review examined data deriving from the first decade (2000-2009) of candidate GxE studies in psychiatry, suggesting a proliferation of type I errors, due to a strong publication bias toward positive findings, both for novel results and replication studies, and to underpowered studies [39]. After the advent of GWASs, efforts focused on finding approaches to study GxE using genome-wide data, so-called Gene-Environment Wide Interactions Studies (GWEIS) [40].

Aim of the Review

The objective of the present survey was to systematically appraise the current state of knowledge on genetic variants associated to psychosis liability whose effect is modified by exposure to cannabis, by examining primary studies which used the GxE interaction model.

We systematically searched current literature to check whether there was evidence reliably supporting a pattern of GxE interaction and whether specific genetic variants were consistently confirmed by replication studies. We also attempted to identify what study design and clinical endpoint emerge as the most effective to reveal signal of GxE interaction.

After a preliminary inspection of the relevant literature we anticipated that a formal meta-analysis was not feasible, given the heterogeneity of primary data. We therefore addressed lack of evidence and limitations of studies, and discussed how the application of new genetics technologies and harmonisation of data could facilitate the discovery of genetic determinants involved in the interplay with exposure to cannabis which in turn leads to the susceptibility to psychosis.

METHODS

A systematic literature search was performed to identify genetic studies that explored the association between cannabis and psychosis. Potential eligible articles were systematically searched in the PubMed on literature published between 1950 and the 3rd week of September 2011. The search strategy used was highly sensitive, and without language restrictions. The string used was (canna* OR Marijuana* OR marihuana* OR THC) AND (Genetic* OR Polymorphism*) AND (psychosis* OR schizophreni* OR schizoaffec* OR psychotic*).

We included original articles that reported the direct measures of genetic risk in the association between cannabis use and psychosis, and that considered cannabis use as an environmental factor influencing the occurrence of psychosis and not as a substance abuse disorder. Editorials and case reports were excluded. Articles on genetic epidemiology

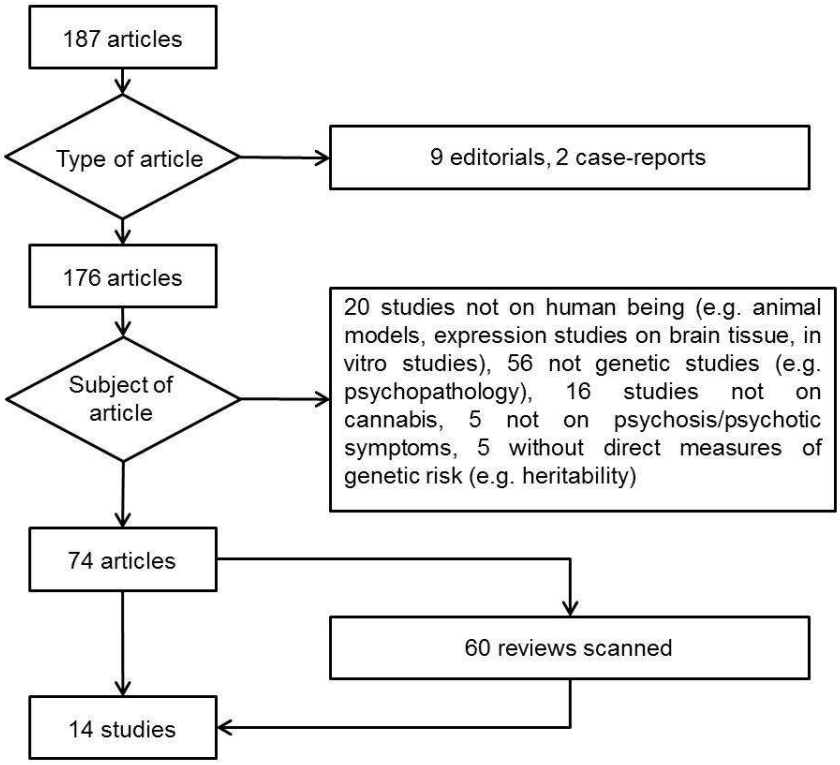

Fig. (1). Flow-chart of the systematic review process.

(e.g. evaluation of heritability) as well as studies not on humans (e.g. animal models, *in vitro* experiments) were excluded (Fig. **1**).

RESULTS

One-hundred and eighty-seven articles were identified in the screening phase. After the exclusion of not relevant articles, 60 reviews were examined and scanned for additional articles. Fourteen genetic studies on cannabis and psychosis matched the inclusion criteria at the completion of the systematic search (Fig. **1**). Details of the population, methodology, analysed genotypes, outcome measures and main findings are described below and summarised in Table **1**.

Design of the Studies

To investigate the relationship between cannabis and psychosis seven studies used the case-only paradigm, alone or in combination with other approaches [41-45]. Pelayo-Teran and co-workers described data obtained from an epidemiological 3-year longitudinal intervention program of first-episode psychosis (PAFIP) [43].

The only prospective cohort was collected through the Dunedin Multidisciplinary Health and Developmental Study. The analysis was based on 803 individuals, followed-up from birth to 26 year-old [46].

Two clinical trials were found, both with a double-bind, placebo-controlled cross-over design. One study scheduled two test sessions, separated by 1 week, in which blinded subjects received in randomised order either 300 or 0 mcg THC/kg body weight in tobacco cigarettes in the exposures or in the placebo condition, respectively [47]. In the other study, each subject was administered on three consecutive weeks four capsules a day with either THC (total dose of 10 mg) or cannabis extract (total dose of 10 mg THC and 5.4 mg cannabidiol) or placebo [48].

A multistage design was applied by van Winkel and co-workers [49] for identifying novel polymorphisms implicated in differential sensitivity to cannabis. Participants were recruited as a part of the Genetic Risk and Outcome in Psychosis (GROUP) study, a longitudinal study focusing on GxE interaction relevant to psychotic disorders. The first part of the study used the so-called "at-risk GxE interaction paradigm". Genetic moderation of recent cannabis use on positive schizotypy in unaffected siblings of patients with psychosis was examined for a range of a priori candidate SNPs. Subsequently, significant SNPs were re-examined using different epidemiological models of GxE interaction in a sample consisting of cases with psychosis [49]. A subsequent study based on GROUP participants further explored the hypothesis of interaction between the SNP identified in the afore-mentioned first multistage study using the case-control and case-sibling designs [50].

Psychiatric Evaluations and Outcomes

In all studies the clinical psychiatric diagnoses were according to the DSM-IV criteria. The phenotypes used as outcomes were both psychiatric diagnoses and specific endpoints evaluated with different interviews.

The prospective cohort study evaluated genetic moderation on both diagnosis (schizophreniform disorder, SCZD) and

Table 1. Molecular Genetic Studies that Explored the Association between Cannabis and Psychosis

Source [Ref]	Study Design	Population (N)	Gene(s) [See Table 2]	Hypothesis Tested	Diagnosis and Psychiatric Evaluation	Psychiatric Endpoints	Measures of Cannabis use	Cannabis Effects	Results
Caspi *et al*., 2005 [46]	Prospective cohort	803 individuals	*COMT*	The genotype moderates the association between cannabis use and the risk of developing psychosis	DSM-IV criteria for SCZD; self- and informant-reports of psychotic symptoms at 26 years	SCZD Psychotic symptoms	Adolescent-onset cannabis use (at age 13, 15 and 18)	Chronic exposure	The genotype interacted with adolescent-onset cannabis use to predict the emergence of adult psychosis.
Henquet *et al*., 2006 [47]	Clinical trial	30 patients, 21 relatives, 32 controls	*COMT*	The genotype moderates the acute effects of THC on psychotic symptoms and on cognition in individuals with different levels of psychosis liability	DSM-IV criteria for psychotic disorder; illness risk (RDC); psychotic symptoms (PANSS); psychosis liability (CAPE); cognition (VVLT, CPT, others)	Expression of psychosis and cognition	THC or tobacco smoke	Acute effects	THC impacted on cognition and psychoses outcomes. The genotype moderated sensitivity to THC on psychotic symptoms, less on cognitive measures.
Zammit *et al*., 2007 [41]	Case-only	797 patients	*CNR1* *COMT*	The genotype moderates the association between cannabis and psychosis	DSM-IV criteria for SCZ	SCZ	i) cannabis use (Y/N); ii) age of first use	Chronic exposure	No evidence of interactions.
Henquet *et al*., 2009 [54]	Case-control	32 patients, 29 control	*COMT*	i) Association between exposure to cannabis and psychotic symptoms; ii) the genotype moderates the association between cannabis exposure and psychotic symptoms	Clinical diagnosis of psychotic disorder; psychosis liability (CAPE); ESM (current mood, thoughts and severity of symptoms)	Psychotic symptoms	Cannabis use (ESM)	Acute effects	Cannabis significantly increased hallucinatory experiences only in individuals: i) carriers of the Val allele and ii) with high levels of psychometric psychosis liability.
Kantrowitz *et al*., 2009 [42]	Case-only	92 patients	*COMT*	The genotype is associated with adolescent cannabis use and affective symptoms in psychotic patients	SCZ, schizoaffective disorder or other psychosis (SCID); affective symptoms (SCID)	Affective symptoms	Adolescent use of cannabis (SCID)	Chronic exposure	No significant association between cannabis use and affective symptoms. No significant association between the genotype and either cannabis use or affective symptoms.
Pelayo-Teran *et al*., 2010 [43]	Case-only	169 patients	*COMT*	Effects of the COMT genotype, cannabis and their interaction with AOP and DUP in first-episode non-affective psychosis patients	DSM-IV criteria for brief psychotic disorder, SCZD, SCZ or schizoaffective disorder; evaluation of AOP and DUP	AOP and DUP	Cannabis use during the year previous to the first psychiatric contact	Chronic exposure	Evidence of interaction between the use of cannabis and the genotype in the modulation of age of onset and presentation of psychosis.
De Pradier *et al*., 2010 [55]	Case-only	137 patients	*SLC6A4*	i) association between psychotic symptoms in BD with 5-HTTLPR or childhood sexual abuse ii) interaction between 5-HTTLPR and childhood sexual trauma or cannabis on psychotic symptoms in BD	DSM-IV criteria for BD; DIGS (psychiatric disorders, age at onset of BD and cannabis abuse or dependence); Trauma Questionnaire History (childhood sexual abuse)	Psychotic symptoms	Cannabis abuse or dependence (DSM criteria) with onset before BD diagnosis	Chronic exposure	Cannabis and genotype were significantly related to psychotic symptoms in BD patients. No interaction between genotype and childhood sexual trauma or cannabis was found.

Table 1. contd….

Source [Ref]	Study Design	Population (N)	Gene(s) [See Table 2]	Hypothesis Tested	Diagnosis and Psychiatric Evaluation	Psychiatric Endpoints	Measures of Cannabis use	Cannabis Effects	Results
Estrada *et al*., 2011 [53]	Case-control	157 patients	*COMT*	i) association between age at first cannabis use and age at emergence of psychiatric disorders; ii) the association is modulated by the genotype	DSM-IV-TR criteria for SCZ, SCZD, psychosis, conduct, affective and personality disorders; evaluation of AOP	Age at emergence of psychiatric disorders	i) lifetime cannabis use ii) age at first cannabis use (DIGS)	Chronic exposure	No association between age at onset and lifetime use; in users, age at first use correlated with age of onset; no effect of the genotype on diagnosis and on exposure; effect of genotype on age at onset in users with SCZ-spectrum.
Stadelmann *et al*., 2011 [48]	Clinical trial	20 healthy subjects	*CNR1*	The genotype is associated with the P300 potential in healthy subjects and differentially modulates the effects of THC and cannabis extract on P300 generation		Auditory event-related P300 potential	Administration of THC capsules , cannabis extract or placebo	Acute effects	The genotype seems to be involved in the regulation of the P300 wave; effects of genotype on P300 amplitude were found under the THC condition but not under the cannabis extract condition.
Van Winkel *et al*., 2011 [49]	Multistage: 1-at-risk paradigm 2-GxE designs	740 siblings 801 patients 419 controls	phase 1: 46 genes; phase 2: *AKT, LRRTM1*	1- Genetic moderation of the effect of recent cannabis use ; 2- significant SNPs re-examined using different models of GxE interaction	DSM-IV criteria for SCZ and related disorders, psychosis; schizotypy (SIS-R) in controls and siblings	1- schizotypy 2- psychotic disorder	i) recent use (urine analysis) ii) CIDI section during heaviest use (before AOP)	1-acute effects 2- chronic exposure	1- 3 significant SNPs (2 in *AKT1* and 1 in *LRRTM1*). 2- Case-only: 1 SNP in *AKT1*. Case-sibling: support for association with *AKT1*; case-control: trend for association..
Van Winkel *et al*., 2011 [50]	Case-control and case-sibling	714 patients 790 siblings 414 controls	*AKT1*	Genotype moderates cognitive effects of cannabis use on psychosis	DSM-IV criteria for SCZ, psychosis, psychotic illness in substance abuse or somatic illness; evaluation of cognition (WLT, CPT, WAIS)	Cognition	i) CIDI section on substance abuse; ii) frequency in the past 12 months; iii) recent use (urine analysis)	Chronic exposure	Variation in sustained attention was associated with the genotype. Genotype x cannabis interactions specific to patients with psychotic disorder, not observed in siblings or controls.
Decoster *et al*., 2011 [44]	Case-only	587 patients	*BDNF*	Association between cannabis use, genotype and AOP using different models of GxE interaction.	Psychiatric diagnoses (experienced psychiatrists); evaluation of AOP	AOP	CIDI section on substance abuse or by case-note review (at least five times)	Chronic exposure	Cannabis associated with earlier AOP; significant genotype x cannabis x sex interaction.
Ho *et al*., 2011 [45]	Case-only	235 patients	*CNR1*	Interactions between *CNR1* genetic variants and heavy marijuana misuse on brain volumes and cognitive function	SCZ-spectrum disorders (CASH); morphometric brain data; neurocognitive assessment (WAIS-R)	Brain volume; cognitive function	Lifetime cannabis use (CASH)	Chronic exposure	Effect of 3 SNPs on brain volumes in SCZ; the genotype interacted with heavy use to influence WM volume deficits and cognitive dysfunction; different WM volumes between cannabis users and non-users.
Costas *et al*., 2011 [52]	Case-only	748 patients	*COMT*	The genotype (based on SNPs and haplotypes) moderates the association between cannabis and SCZ	DSM-IV criteria for SCZ	SCZ	Lifetime cannabis abuse according to DSM-IV criteria	Chronic exposure	Significant association between *COMT* variants (based on SNPs and haplotypes) and cannabis use in SCZ.

Abbreviations: AOP=age at onset of psychosis, BD=bipolar disorder, CAPE= Comunity Assessment of Psychic experiences CASH=Comprehensive Assessment of Symptoms and History, CIDI=Composite International Diagnostic Interview, CPT=continuous performance test, DIGS=Diagnostic Interview for Genetic Studies, DUP=duration of untreated psychosis, ESM=experience sampling method, SCID=Structured Clinical Interview for DSM-IV Disorders, PANSS= Positive and Negative Syndrome Scale, RDC= Research Diagnostic criteria, SCZD=Schizophreniform disorder, SIS-R=Structured Interview for Schizotype-Revised, SNP=single nucleotide polymorphism, VVLT=Visual Verbal Learning Test, WAIS=Wechsler Adult Intelligence Scale, WLT=Word Learning Task, WM=white matter.

psychosis measures [46]. At 26 years of age, 3,6% of the cohort (29 individuals) met DSM-IV criteria for the diagnosis. Quantitative psychosis measures were obtained respectively from the psychiatric interview of the participants and from a 60-item questionnaire mailed to informants. Continuous (a scale of psychotic symptoms) and categoric (evidence of hallucinatory experience symptoms; evidence of delusional belief symptoms) measures of outcome were extracted from reports [46].

The study based on the GROUP sample [49] evaluated diagnoses of SCZ and related disorders, other psychotic disorders and psychotic illness in the context of substance abuse or somatic illness. Assessment of controls included Family Interview for Genetic Studies (FIGS) to exclude first-degree relatives with a psychotic disorder. The Structured Interview for Schizotypy-Revised (SIS-R) was administered to controls and siblings and used in the at-risk paradigm to determine the outcome of interest (positive schizotypy).

The endpoint of the clinical study reported by Stadelmann *et al*. [48] was P300 wave, a cognitive event-related brain potential component, as measured 3 hours after drug administration. Deficient P300 wave generation reflects attentional resource allocation and active working memory, and is a robust finding in SCZ [51].

The other clinical trial [47] included as outcomes: diagnosis made according to Research Diagnostic criteria (RDC) in order to determine illness risk; psychotic symptoms in the last 2 weeks according to the Positive and Negative Syndrome Scale (PANSS); psychosis liability assessed using the 40-item Comunity Assessment of Psychic experiences (CAPE). The cognitive battery consisted of tests on verbal and nonverbal learning and memory (Visual Verbal Learning Test, VVLT, and Abstract Visual Pattern Learning, ABPL), sustained and selective attention (Continuous Performance Test, CPT, and Stroop Color-Word) and psychomotor speed (Digit Symbol Substitution Test, DSST).

Effects on cognition were considered in other two recent studies. Memory (Word Learning Task, WLT), sustained attention (CPT) and Intelligence Quotient (abbreviate version of the Wechsler Adult Intelligence Scale, WAIS) were the cognitive outcome measures in the study by van Winkel *et al.* [50]. Ho and co-workers [45] evaluated the effect of cannabis on cognition and brain volumes. This is the only study that considered imaging parameters. The cognitive assessments were derived from the WAIS–Revised Edition, that evaluated intelligence quotient, verbal memory, attention, problem solving, language, visuospatial abilities and motor skills.

Other studies considered effect of cannabis use on categorical diagnoses according to DSM-IV criteria: two considered the diagnosis of SCZ as psychiatric outcome [41, 52]; the second step of the multistage design study considered SCZ and related disorder [49].

Age at onset of psychiatric disorders was considered in three studies [43, 44, 53]. Pelayo-Teran and co-workers [43] considered also duration of untreated psychosis.

A case-control study used the experience sampling methods (ESM), a random time sampling self-assessment technique collecting reports twelve times a day on six consecutive days about cannabis use, current mood, thoughts and severity of symptoms [54]. Patients with a clinical diagnosis of psychotic disorder and controls were evaluated using CAPE to assess their psychometric psychosis liability.

One study evaluated the effects of cannabis on affective symptoms in patients with psychosis [42].

Cannabis use Measures

Both acute and lifetime use of cannabis were considered across studies. Moreover, different definitions of cannabis user were applied. Caspi and co-workers [46] reported that adolescent-onset cannabis study members were individuals that used cannabis at ages 13 or 15, or used cannabis at least once per month at age 18. Pelayo-Teran and co-workers [43] defined as cannabis users the individuals consuming 1 or more units per week in the previous year to the inclusion (a unit of cannabis was defined as a joint smoke).

Data on both cannabis use and age at first using were obtained from interview and case-note records in one study [41]. Other studies evaluated lifetime cannabis use with specific section of structured interviews, namely Structured Clinical Interview for DSM-IV (SCID) [42], Diagnostic Interview for Genetic Studies (DIGS) [53], Composite International Diagnostic Interview (CIDI) [44, 49, 50] and Comprehensive Assessment of Symptoms and History (CASH) [45]. One study considered heavy cannabis use evaluated as abuse or dependence [45] and one considered abuse [52] according to DSM-IV criteria.

Studies deriving from the GROUP cohort evaluated both lifetime and recent use of cannabis [49, 50]. Lifetime use was evaluated with CIDI cannabis pattern, through a categorical scale (none, 0; less than weekly, 1; weekly, 2; daily, 3). Recent use was established by urinanalysis (negative/positive). Henquet and co-workers [54] evaluated recent cannabis use considering the ESM reports. The clinical trials had a direct measure of administered cannabis [47, 48].

Genetic Analysis

The most common approach was the candidate gene association design. Genetic regions were selected based on their putative relationship with the neurobiological processes underlying the psychosis liability and the cannabinoid system. Eight out of 14 studies focused on the *COMT* gene [41-43, 46, 47, 52-54]. After the first positive finding by Caspi and co-workers [46], other studies detected a significant effect on psychosis of *COMT* and lifetime cannabis use. However, psychiatric outcomes and cannabis measures differed between studies. One clinical trial and a case-control study, which used a random sampling technique, considered acute effects of cannabis on psychosis, and found that *COMT* rs4680 modulated sensitivity to THC on psychotic symptoms [47, 54]. Three studies examined the gene *CNR1*. Zammit and co-workers [41] found no interaction between rs1049353 and cannabis use on psychosis. Ho and co-workers [45] investigated *CNR1* tagging SNPs and found three independent SNPs (rs12720071,

rs7766029, rs9450898) showing significant effects on brain volumes, whereas rs12720071 showed a significant interaction with marijuana misuse on problem solving skills. An interaction between the (AAT)n triplet repeat polymorphisms in the *CNR1* gene and acute effects of the THC on P300 generation in healthy human subjects was found by Stadelmann *et al.* [48].

The Val/Met polymorphism in the *BDNF* gene was tested in one study [44]. Considering the possibility of a sex-specific effect, cannabis use was found associated to earlier onset of psychosis in female Met-carriers.

The functional polymorphism rs4795541 located in the promoter region of the gene coding the serotonin transporter (*SLC6A4*) was tested in one study which considered bipolar patients [55]. Cannabis use and the presence of the *s* allele were found significantly associated to psychotic symptoms.

Only one study used a holistic approach to test a panel of 46 genes [49]. The study identified as associated the rs2494732 SNP in the *AKT1* gene, that had not been previously considered in genetic studies on relation between cannabis and psychosis. After this multistage exploratory approach, the same group re-examined rs2494732 and found that *AKT1* gene influences the effect of cannabis use on sustained attention [50].

Confoundings

Information about age, gender and ethnicity were reported by eight studies [43-46, 49, 50, 52, 55]. Urbanicity and social class were not included. Six out of the eleven studies that evaluated lifetime and recent use of cannabis measured the use of other drugs: Caspi and co-workers [46] adjusted for the use of amphetamines or hallucinogens; Ho and co-workers [45] included the alcohol/non-cannabis illicit substance abuse/dependence as covariate; De Pradier and co-workers [55] evaluated the patients for other drug abuse and dependence according to DSM-IV; in the GROUP study amphetamine and cocaine use were considered [49, 50]; Estrada and co-workers [53] evaluated the use of other psychoactive drugs.

DISCUSSION

Epidemiologic studies had suggested that adolescent cannabis use is likely a factor that unmasks susceptibility to psychosis. Based on this line of evidence, the GxE interaction model could be effective in searching genetic variants involved in the relationship between cannabis and psychosis. After the first study published in 2005 [46] there was a remarkable increase in the number of studies along the years (see Table **1**).

This review encompassed 14 genetic primary studies that examined the relationship between cannabis and psychosis. All studies applied the candidate gene approach, though the respective strategies for gene selection were different. Four genes were investigated: *COMT*, *CNR1*, *BDNF*, *SLC6A4* and *AKT1*.

The rs4680 polymorphism of the *COMT* gene was examined in 8 studies. Different models of interaction between cannabis and psychosis were considered: two studies by Henquet and co-workers [47, 54] modeled the acute effect of cannabis in subjects with psychosis-proneness; other studies tested the effect of chronic use of cannabis on different psychiatric endpoints, namely diagnosis of psychosis disorders [41, 46, 52], age at onset of disorders [43, 53], affective symptoms [42]. The polymorphism was examined under different genetic models, namely recessive, dominant or codominant (see Table **2**). Considering the studies on chronic use of cannabis, one found that the under the recessive model the Val allele increases the risk of developing adult psychosis in adolescent cannabis users [46], one found an effect of Met as risk allele using allelic association model [52] and one failed to reveal a significant association using additive model [41]. In summary, provided that the association between *COMT* variants and psychosis is supported by previous evidence, additional clues in favour of an increased liability to psychosis in cannabis users were provided. However, current data did not allow to draw a conclusion about the effect of the rs4680 polymorphism and ultimately the interaction of *COMT* with cannabis use has still to be proven.

Thirteen polymorphisms in *CNR1* gene were examined in three studies, providing three positive signals in two studies based on different design (see Table **2**) [41, 45, 48].

Single positive findings on *BDNF* and *SLC6A4* [44, 55] were not replicated.

The experimental path proposed by van Winkel and co-workers is an example of a knowledge-based procedure for candidate gene selection. This is the only study that used a holistich approach through an elegant multi-stage design to test new candidate genes [49]. In the first step, the authors used the current knowledge about how the cannabis increased the psychosis risk to build a scan for putative candidate genes. Polymorphisms were chosen among those identified in previous studies on psychosis liability and supported by the evidence of biological function. In the following step, they examined the effect of lifetime use of cannabis on diagnoses of psychotic disorders through different GxE designs to replicate the first stage findings. Notably, the study identified a SNP, rs2494732 in the *AKT1* gene, that was not considered in previous studies using the candidate GxE design [49]. The effect of interaction between rs2494732 and cannabis was confirmed on sustained attention in a subsequent replication study by the same group [50]. Remarkably, a recent article appeared after the completion of our systematic search has confirmed that cannabis users who carry the C/C genotype at the rs2494732 locus have an increased likelihood of a psychotic disorder [56], thus supporting the evidence that *AKT1* influences the risk of psychosis interacting with cannabis.

The primary studies remarkably differed in outcome measures. The diagnoses ranged from schizophrenia to the wider phenotypic group of the psychoses. Different measures of psychosis occurrence and severity were in found in primary studies, such as effect of cognition [45, 47, 50], symptoms [46, 47, 54, 55], age at onset [43, 44, 53], affective symptoms [42], duration of untreated illness [43]. Two studies postulated the effect of interaction on endophenotypes,

Table 2. Relevant Features of Genetic Variants Examined and Main Findings

Gene Name(s) and Chro-mosomal Location	Function	Genetic Studies on Psychiatric Disorders	Ref.	N	Ancestry	Variant	Nucleotide Change	Ammino-acid Change	MAF	MAF	Ref. MAF[1]	Outcome	Model	Statistics	
									Cases	Contr.				OR (CI)	P
COMT Catechol-O-Methyltransferase 22q11.2	The enzyme is involved in one of the major degradation pathways of the catecholamine transmitters, including dopamine, epinephrine, and norepinephrine [64]. The functional variant rs4680 corresponds to three different phenotypes: high, intermediate and low levels of activity [65]. Two different haplotypes block were reported: one defined by rs4680 and two non-coding SNPs at either ends of the gene (rs727865 and rs165599), the other one defined by rs4680, rs4633, rs4818 and rs6265 [66, 67].	The COMT gene is a strong candidate for schizophrenia susceptibility, because it is involved in dopamine metabolism and it is located on 22q11, a region previously implicated in SCZ [46, 64]. Genetic association studies that evaluated the role of the gene on SCZ liability found mixed results [68, 69].	Caspi *et al.*, 2005 [46]	803 individuals 21 individuals with SCZD	Cau	rs4680	c.472G>A	Val158Met	nr	0.50	0.48	SCZD	Recessive	10.9 (2.2-54.1)	n/a
			Henquet *et al.*, 2006 [47]	30 patients, 21 relatives, 32 controls	Unknown (Europe)	rs4680	c.472G>A	Val158Met	0.49	n/a	0.48	Positive symptoms	Recessive	n/a	0.003
			Henquet *et al.*, 2009 [54]	31 patients, 25 controls	Unknown (Europe)	rs4680	c.472G>A	Val158Met	0.29	n/a	0.48	ESM hallucinations	Recessive	n/a	<0.001
			Kantrowitz *et al.*, 2009 [42]	92 patients	54 AA 38 Cau	rs4680	c.472G>A	Val158Met	AA: 0.32 Cau: 0.50	n/a	0.48 (0.27 in AA)	Affective symptoms	Recessive and dominant	n/a	ns
			Pelayo-Teran *et al.*, 2010 [43]	169 patients	Unknown (Spain)	rs4680	c.472G>A	Val158Met	0.44	n/a	0.48	AOP	Multi-variate analysis of covariance	n/a	0.007
			Estrada *et al.*, 2011 [53]	157 patients (80 SCZ-spectrum, 77 others)	Cau	rs4680	c.472G>A	Val158Met	0.50	n/a	0.48	AOP in SCZ-spectrum disorder	Codo-minant	n/a	0.04
			Zammit *et al.*, 2007 [41]	338 patients	Cau	rs4680[2]	c.472G>A	Val158Met	nr	n/a	0.48	SCZ (early cannabis use)	Additive	0.76 (0.41-1.40)	0.38
				338 patients	Cau	rs737865[2]	c.-92+701A>G		nr	n/a	0.33	SCZ (early cannabis use)	Additive	1.09 (0.56-2.00)	ns
				338 patients	Cau	rs165599[2]	c.*522G>A		nr	n/a	nr	SCZ (early cannabis use)	Additive	1.09 (0.57-2.08)	ns
				493 patients	Cau	Haplotype						SCZ	Haplotype analysis	n/a	0.69
			Costas *et al.*, 2011 [52]	748 patients	Unknown (Spain)	rs4680[2]	c.472G>A	Val158Met	0.42	n/a	0.48	SCZ	Allelic association	1.45 (1.12-1.85)	<0.001
				748 patients	Unknown (Spain)	rs737865[2]	c.-92+701A>G		0.34	n/a	0.33	SCZ	Allelic association	0.80 (0.61-1.06)	0.116

Table 2. contd….

Gene Name(s) and Chro-mosomal Location	Function	Genetic Studies on Psychiatric Disorders	Ref.	N	Ancestry	Variant	Nucleotide Change	Ammino-acid Change	MAF	MAF	Ref. MAF[1]	Outcome	Model	Statistics	
									Cases	Contr.				OR (CI)	P
				748 patients	Unknown (Spain)	rs6269[2]	c.1-98A>G		0.47	n/a	nr	SCZ	Allelic association	0.68 (0.53-0.89)	<0.001
				748 patients	Unknown (Spain)	rs4633[2]	c.186C>T	His62His	0.42	n/a	0.48	SCZ	Allelic association	1.54 (1.20-2.00)	<0.001
				748 patients	Unknown (Spain)	rs4818[2]	c.408C>G	Leu136Leu	0.47	n/a	nr	SCZ	Allelic association	0.70 (0.54-0.91)	<0.001
				748 patients	Unknown (Spain)	Haplotype						SCZ	Haplotype analysis	n/a	<0.001
CNR1 Cannabinoid Receptor 1 6q15	It encodes one of two cannabinoid receptors, that are members of the guanine-nucleotide-binding protein coupled receptor family [70]. Cannabinoid receptors are mainly localised to axons and nerve terminals and are widely expressed in the cerebral cortex, including PFC and medial temporal lobe [45, 70].	Discordant findings were reported by genetic association studies that evaluated the effect of *CNR1* variants, in particular rs1049353 and rs10591494, on the SCZ liability [71-73].	Zammit *et al.*, 2007 [41]	706 patients	Cau	rs1049353	c.1359G>A	Thr453Thr	0.29	0.29	0.23	SCZ	Allelic association	0.83 (0.65-1.05)	ns
			Stadelmann *et al.*, 2011 [48]	20 individuals	Cau	rs10591494 (ATT repeat; threshold 10)	g.88836897delAinsAATAATAAT		nr	nr	nr	P300 amplitude	Dominant	n/a	0.010
			Ho *et al.*, 2011 [45]	235 patients	Cau	rs1049353[2]	c.1359G>A	Thr453Thr	0.29	n/a	0.23	Brain WM volume	Allelic association	n/a	ns
				235 patients	Cau	rs806365[2]	g.88845949T>C		0.44	n/a	0.51	Brain WM volume	Allelic association	n/a	ns
				235 patients	Cau	rs7766029[2]	g.88847435T>C		0.49	n/a	0.50	Brain WM volume	Allelic association	n/a	0.05
				235 patients	Cau	rs806366[2]	g.88847589C>T		0.50	n/a	0.48	Brain WM volume	Allelic association	n/a	ns
				235 patients	Cau	rs806368[2]	g.88850100T>C		0.20	n/a	0.25	Brain WM volume	Allelic association	n/a	ns
				235 patients	Cau	rs12720071[2]	g.88851181T>C		0.08	n/a	0.10	Brain WM volume	Allelic association	n/a	0.05
				235 patients	Cau	rs806374[2]	g.88857320T>C		0.35	n/a	0.36	Brain WM volume	Allelic association	n/a	ns
				235 patients	Cau	rs806375[2]	g.88858521A>T		0.41	n/a	0.39	Brain WM volume	Allelic association	n/a	ns
				235 patients	Cau	rs806376[2]	g.88858648T>C		0.45	n/a	0.46	Brain WM volume	Allelic association	n/a	ns
				235 patients	Cau	rs6454672[2]	g.88861570T>C		0.13	n/a	0.88	Brain WM volume	Allelic association	n/a	ns
				235 patients	Cau	rs9450898[2]	g.88864063C>T		0.15	n/a	0.18	Brain WM volume	Allelic association	n/a	0.04
				235 patients	Cau	rs806380[2]	g.88864653A>G		0.30	n/a	0.32	Brain WM volume	Allelic association	n/a	ns
				235 patients	Cau	Haplotype						Brain WM volume	Haplotype analysis	n/a	ns

Table 2. contd….

Gene Name(s) and Chro-mosomal Location	Function	Genetic Studies on Psychiatric Disorders	Ref.	N	Ancestry	Variant	Nucleotide Change	Ammino-acid Change	MAF Cases	MAF Contr.	Ref. MAF[1]	Outcome	Model	Statistics OR (CI)	Statistics P
BDNF Brain-Derived Neurotrophic Factor 11p14.1	It encodes a member of the nerve growth factor family, induced by cortical neurons and necessary for survival of striatal neurons in the brain [74, 75]. Exposure to THC seems to alter serum BDNF levels in humans [76]. rs6265 is correlated with different activity-dependent BDNF secretion [77].	*BDNF* was suggested as candidate gene for SCZ [78-81]. Studies evaluating association between SCZ and rs6265 found mixed results [82-84].	Decoster *et al*., 2011 [44]	587 patients	Cau	rs6265	c.196G>A	Val66Met	0.22	n/a	0.20	Age at onset of psychotic disorder	Dominant	n/a	0.026
SLC6A4 Solute Carrier Family 6 Member 4, Neurotransmitter Transporter Serotonin SERT 5-HTT 17q11.2	It encodes an integral membrane protein that transports serotonin from synaptic spaces into presynaptic neurons, terminating the action of serotonin and recycling it in a sodium-dependent manner [85].	Studies examined the influence of rs4795541 on affective disorders and emotional traits, with mixed results [86, 87]	De Pradier *et al*., 2010 [55]	137 patients	Unknown (Europe)	rs4795541	ins44bp		0.49	n/a	0.57 [86, 88]	Psychosis symptoms	Additive	2.98 (1.46-6.03)	0.003
AKT1 V-AKT Murine Thymoma Viral Oncogene Homolog 1 14q32.33	It encodes a serine-threonine protein kinase, activated through phosphatidylinositol 3-kinase [89]. It is involved in multiple cellular functions and is a critical mediator of growth factor-induced neuronal survival [90, 91]. Cannabinoids are able to activate the AKT1/PI3K pathway by acting on their receptors *in vitro* [92].	AKT-GSK3B signalling pathway has a role in SCZ and *AKT1* was identified as a candidate gene [93]. Studies evaluating the association between *AKT1* and SCZ gave discordant results [94-98].	van Winkel *et al*., 2011 [49]	801 patients	Unknown (Europe)	rs2494732	c.1172+23 A>G		0.42	n/a	nr	SCZ and related disorder, psychosis	Recessive	1.90 (nr)	0.007
			van Winkel *et al*., 2011 [50]	601 patients	Unknown (Europe)	rs2494732	c.1172+23 A>G		0.42	n/a	nr	Sustained attention	Recessive	n/a	0.003

The table reports the 5 genes examined, a brief note on gene function, genotype and allele frequencies, if provided, resulting significance levels, odds ratios (ORs), 95% confidence intervals (CIs) and sample size for each marker examined. When multiple test were performed, we reported significant results on the main outcome. For the GWASs, only the result from the case-only approach for the significant SNP is reported.

[1]Reference minor allele frequency in Caucasians, according to HapMapDataRel28PhaseII+III, August 10, on NCBI B36 assembly, dbSNPb126.

[2]Considered also in the haplotype analysis.

Abbreviations: OR=odds ratio, CI=confidence interval, AA=Afro-American, n/a= not applicable, ns=not significant, nr= not reported (see also Table **1**).

i.e. auditory event-related P300 potential [48] and brain volume [45].

We recorded inconsistent measures of cannabis use, as both acute and chronic effect of cannabis were evaluated across studies, and different definitions of cannabis user were applied. Of note, age at first using could be a key parameter, as exposure during adolescence is supposed to be particularly relevant [34, 35].

Seven studies (see Table **1**) used the case-only design, a model based on the assumption that the genetic and environmental factors are independently distributed in the population. This paradigm allows to test for interaction (specifically, departure from a log-additive odds model) simply by testing whether the two factors are associated among cases. The case-only design has the attraction of not requiring collection of data from controls and being more powerful than standard case-control analysis based on logistic regression [57]. On the other hand, it allows testing only for interactions but not for main effects - this is a limitation while we are still attempting to establish the role for genetic effects in psychosis. Moreover, if the genotype examined and the measure of cannabis exposure are not independent in the population under study, this strategy can produce spurious results and type I error rate can be inflated. Despite these intrinsic limitations, the case-only approach can be used to increase the power of replication studies, in conjunction with hypothesis-generating studies, such as GWASs. Replication studies should have a similar range of exposures as the initial study, since different distributions may hamper to replicate the original interaction [58].

The assumption of independence between genotype and exposure is questionable in the present field, as liability to certain form of psychosis and use of psychotropic drugs may be linked. Genetic markers found as associated to psychosis may be also associated, in fact, with cannabis initiation, abuse, or dependence. Family and twin studies have shown that cannabis dependence (CaD) has an important genetic component, with heritability estimated to range from 45% to 78% [59]. Genome-wide linkage studies and candidate gene association studies identified a list of possible loci for cannabis use disorders, such as *MGLL*, *GABRA2*, *NGR1*, *CNR1*, *CRN2* and *FAAH* [60, 61]. A GWAS for CaD was conducted but no genetic marker achieved significance [62].

The typical concerns already discussed in GxE research [39] can be raised by most studies included in the present systematic search.

Sample size is a crucial issue in genetic association studies and GxE investigations require larger sample size than genetic studies for the main effect [63]. Only five of the examined studies had cohorts bigger than 500 subjects [41, 44, 49, 50, 52]. As a consequence, most studies were likely underpowered to detect positive signals - this implies that true GxE effects may have been missed. Moreover, each study often examined multiple hypotheses, thus increasing the false positive rate.

However, as clinical psychiatrists well know, single research groups can hardly collect a number of patients sufficient for well-powered studies. In some cases, existing cohorts could be retrospectively supplemented with additional data, whether genetic or clinical or environmental, to enable the study of gene-environmental interplay. In the field of psychiatric genetics, international consortia have proved to be a proper framework to establish very large data sets of patients data. Recent achievements of GWAS have taken advantage of such a strategy [8].

In case of large multicentre studies, though, a *caveat* must be quoted. As sample size inflates, power decreases in the presence of phenotypic and genotypic heterogeneity. Multicentre initiatives, hence, have to establish and share rigorous protocols for the assessment of the clinical phenotype and the exposure to cannabis. Furthermore, as also GxE association studies are prone to type I errors due to stratification, ancestry of patients and controls should be verified, possibly implementing a genetic control along the study protocol. Among the studies included in the present survey, none described a procedure to confirm self-reported ancestry.

Acting on the signal could be an additional strategy to increase statistical power of relatively small cohorts. The expected effect size might be increased, for example, including only well-characterised extreme phenotypes, such as patients with severe psychotic symptoms [39]. The use of continuous variables for outcome measures, such as quantitative evaluations of psychotic illness dimensions, could be recommended, as opposed to binary variables (i.e. disease present/absent).

Moreover, considering each single study, a limited number of known confoundings was reported. Urbanicity, social class and education level are known to influence the liability to psychotic illness [3], but were not included in the multivariate models of GxE interaction examined. An accurate characterisation in terms of socio-demographic information and exposure to other environmental factors involved in psychosis risk, including the use of other illicit substances, should be encouraged.

These remarks further highlight the need for accurate phenotyping of study cohorts, by the mean of valid and reproducible tools.

Finally, it is noteworthy that all studies included in the present survey relied on the common-disease-common-variant hypothesis. Recent findings seem to indicate that multiple *de novo* genetic variants that affect many different genes contribute to the genetic risk of psychosis, supporting the multiple rare variant hypothesis [11, 12]. The next phase of genetic studies also in the field of interaction between cannabis and psychosis is expected to entail a combination of genome-wide analyses (for common SNPs and CNVs) and resequencing studies (for rare variants).

CONCLUSIONS

Despite the large amount of studies which explored genetic susceptibility to psychosis, the body of literature on the interaction with cannabis use is quite limited, and a few candidate genes were investigated. In agreement with the general conclusion drawn on GxE studies in psychiatry [39], it could be argued that small samples, coupled with the

relatively low prior probability of association under the interaction model, increase the likelihood that positive findings of interaction between candidate genes and cannabis exposure represent spurious findings. Moreover, studies published to date are markedly heterogeneous in terms of experimental design and outcome measures, thus hampering an effective synthesis of results.

Additional primary studies are warranted to provide evidence of interaction between genetic variants and exposure to cannabis in patients suffering with psychosis.

To date, *AKT1* seems to be the most promising candidate gene. No robust replication was provided for the other candidate genes.

The investigation on genetic factors increasing the risk to psychosis through the interaction with environmental factors demands large cohorts and an effort in harmonisation of data gathered by mean of multicentre initiatives. Moreover, effective study designs should consider a comprehensive integration of the knowledge about genes, cannabis effects, psychosis risk and neuronal connectivity development.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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