REVIEW ARTICLE

Cannabis and psychosis: Neurobiology

Amresh Shrivastava[1,2], Megan Johnston[3], Kristen Terpstra[4], Yves Bureau[5]

[1]Department of Psychiatry, Elgin Early Intervention Program for Psychosis, [4]Department of Psychology, [5]Lawson Health Research Institute, University of Western Ontario, London, Ontario, [3]Department of Psychology, University of Toronto, St. George, Toronto, Canada, [2]Mental Health Resource Foundation, Mumbai, Maharashtra, India

ABSTRACT

Cannabis is a known risk factor for schizophrenia, although the exact neurobiological process through which the effects on psychosis occur is not well-understood. In this review, we attempt to develop and discuss a possible pathway for the development of psychosis. We examine the neurobiological changes due to cannabis to see if these changes are similar to those seen in schizophrenic patients the findings show similarities; however, these mere similarities cannot establish a 'cause-effect' relationship as a number of people with similar changes do not develop schizophrenia. Therefore, the 'transition-to-psychosis' due to cannabis, despite being a strong risk factor, remains uncertain based upon neurobiological changes. It appears that other multiple factors might be involved in these processes which are beyond neurobiological factors. Major advances have been made in understanding the underpinning of marijuana dependence, and the role of the cannabinoid system, which is a major area for targeting medications to treat marijuana withdrawal and dependence, as well as other addictions is of now, it is clear that some of the similarities in the neurobiology of cannabis and schizophrenia may indicate a mechanism for the development of psychosis, but its trajectories are undetermined.

Key words: Cannabinoid system, cannabis, psychosis, schizophrenia, transition to psychosis

TRANSITION TO PSYCHOSIS AND CANNABIS

Cannabis is involved in approximately 50% of psychosis, schizophrenia, and schizophreniform psychosis cases.[1-5] Cannabis is a known risk factor for schizophrenia, although the exact neurobiological process through which the effects on psychosis occur is not well understood. Cannabis is also of particular interest in both the first-episode psychosis (FEP)[6,7] and the ultra high risk (UHR) populations. This is mainly due to their increased susceptibility to cannabis abuse.[8,9] Amongst FEP patients, cannabis equally affects those who go on to develop schizophrenia and those who do not.[10] In spite of significant advancements, the sequence of biological events and a valid model of neurobiological mechanisms are lacking.[4,11,12] In this review, we attempt to develop and discuss a possible pathway for the development of psychosis.

Address for correspondence: Dr. Amresh Shrivastava, Department of Psychiatry, Western University, London, Ontario, Regional Mental Health Care, 467 Sunset Drive, St Thomas, N5H 3V9, Canada.
E-mail: dr.amresh@gmail.com

How to cite this article: Shrivastava A, Johnston M, Terpstra K, Bureau Y. Cannabis and psychosis: Neurobiology. Indian J Psychiatry 2014;56:8-16.

TETRAHYDROCANNABINOL

The biochemical mechanism by which cannabis exerts its effects on physiology and behavior remained a mystery until the components of cannabis were extracted, and Delta-9-tetrahydrocannabinol (THC) was found to be the main psychoactive constituent of cannabis.[13] The isolation of THC resulted in the characterization of a G protein-coupled receptor to which THC exerted specific and saturable binding,[14] indicating the presence of an endogenous receptor to which cannabinoids could exert their effects. "Cannabidols", have 64 active isomers, each having differing effects on health and behavior.[15] THC is the only active metabolite which has few important neurochemical properties and stimulates cannabinoid receptors type-1 (CB1) in the brain that differentially affect

Access this article online	
Website: www.indianjpsychiatry.org	Quick Response Code
DOI: 10.4103/0019-5545.124708	

patients with schizophrenia. It is a lipophilic compound, which disappears from extracellular spaces by dissolving in lipid-rich membranes, not by excretion from the body. THC is slowly released, leading to long-lasting effects originating from brain areas containing a large proportion of spare receptors (reserve receptors). This compound also induces withdrawal and tolerance as well as potentiates alcohol and heroin dependence. *In utero* exposure to THC hampers appropriate interneuron positioning during corticogenesis. With respect to psychosis, THC has been associated with independently causing positive symptoms and neurocognitive changes.[16] THC exposure induces changes in the prefrontal cortex (PFC) characterized by less synaptic density and/or efficiency.[17] Cannabis varies greatly in the amount of the major psychoactive constituent-THC, thus the psychoactive effects vary according to the nature of cannabis and its pattern of use which results in a dose-response relationship. In addition, it has been suggested that endogenous cannabidols may protect against some of the propsychotic effects of THC.[18,19]

THE LINK BETWEEN CANNABIS AND PSYCHOSIS

The past few years have led to the development of a plausible model in which schizophrenia is viewed as the consequence of a number of component causes, such as genes or early environmental hazards that subtly alter subsequent neurodevelopment. A recent study shows that the incidence of psychosis in cannabis exposed and non exposed population is 31 and 20%, respectively.[20] Cannabis exposure may be a "component cause" which interacts with other factors that may be a possible cause of schizophrenia or other psychotic disorders, but is neither necessary nor sufficient to do so alone.[21] Nevertheless, in the absence of the known causes of schizophrenia, the role of component causes remains important. The current focus of investigation is to find out pathways of neurobiological changes due to cannabis, which might be involved in the development of psychosis.[22,23] The hope is that, if these changes are reversible, possible risk of severity may be minimized and treatment outcome in psychotic disorders may be improved.

A causal relationship has been proposed but the pathophysiological mechanism remains to be explored. The main possibility is the effect on the neurodevelopmental process, such as synaptic plasticity, which is likely impaired in schizophrenia. Despite considerable variation in how cannabis exposure and psychosis were elicited or defined, there is a notable consistency in the findings of different studies.[22,24] Many of these studies suggest that cannabis is a risk factor whereby it increases the chances of developing schizophrenia by approximately three-fold, a finding supported by a dose-response relationship.[25] Various possibilities have been discussed for the association between cannabis and schizophrenia which include: (a) Common sociodemographic factors and shared genetic factors; (b) the hypothesis of 'self-medication' for symptoms of psychiatric diseases such as the negative symptoms of schizophrenia, anxiety, depression, or dysphoria;[26] (c) the vulnerability hypothesis, and; (d) acute intoxication leading to 'psychotic-like' experiences. The most consistent data suggests that cannabis causes exacerbation of psychosis and worsens it[27-29] which raises the possibility of a vulnerable group. It has been found that acute effects of cannabis were modified by the subject's level of vulnerability for psychosis.[30] A study by Mechoulam and Gaoni in 1965,[31] used intravenous THC in antipsychotic-treated patients with schizophrenia and controls found that THC exacerbated positive symptoms in patients as well as induced positive symptoms in controls; however, there was an exacerbated effect in patients. Similarly, the subjects with high vulnerability experienced more bizarre symptoms, primarily hostility, unusual perception, and strange impression. Recent attempts have also utilized vulnerability theory to explain this association,[32] placing it within the framework of current ideas regarding the neurobiology of psychosis.[33] This has strengthened the view that some individuals with schizophrenia might be biologically vulnerable to the rewarding effects of drugs of abuse.[16] Interestingly, a recent brain imaging study has found evidence that both males and females who start using cannabis before the age of 17 years have a lower percentage of cortical grey matter and an increased percentage of white matter compared to those who start later, which is unrelated to duration of cannabis use.[34] It may be that adolescence to early adulthood is a period of time during which the developing brain is more vulnerable to the adverse effects of cannabis; however, a recent study that used mathematical modeling to explore the possible effects of cannabis use and schizophrenia did not find support for a direct causal hypothesis.[35,36] The explanation for cannabis as a risk factor is shifting from clinical and epidemiological evidence towards a neurobiological one.

NEUROBIOLOGY OF CANNABIS

Brain development during pregnancy

It is reported that approximately 4% of women in the United States abuse substances, with marijuana being by far the most common substance used during pregnancy (75%).[37] The prevalence of prenatal cannabis exposure is between 2 and 5% in European countries and about 13% in high-risk populations.[38] One-third of the major psychoactive component of cannabis (THC)[39] undergoes crossplacental transfer upon cannabis smoking, which raises important concerns about the potential impact of maternal cannabis use on the developing fetus.[40] Marijuana impairs growth in midgestation fetuses, while adolescent exposure to cannabinoids might tamper with the normal development of neuronal processes possibly involving cergic and dopaminergic dysfunction.[41,42] Thus, prenatal cannabis exposure has an impact on the maturation of

neurotransmitter systems, which play key roles in mood, motivation, and reward.[43] Epidemiological and longitudinal studies have shown that newborns and infants born to cannabis users have increased tremors, exaggerated startle response, and poor habituation to novel stimuli.[44] In addition to this, recent evidence suggests that the mesocorticolimbic neuronal circuits remain vulnerable to this dysfunction later in life and thus could be sensitive to developmental events and environmental stressors that themselves can influence the onset and course of neuropsychiatric disorders.

Cannabis in adolescence

Adolescence is a critical phase for brain development, characterized by neuronal maturation and rearrangement processes, such as myelination, synaptic pruning and dendritic plasticity. The endocannabinoid system plays an important role in fundamental brain developmental processes such as neuronal cell proliferation, migration and differentiation, therefore, changes in endocannabinoid activity during this specific developmental phase induced by THC might lead to subtle but lasting neurobiological changes that can affect brain functions and behavior. A number of studies have investigated whether exposure to cannabis during adolescence is a risk factor for psychosis such as schizophrenia. Arkany *et al*.,[45] reported that those subjects who used cannabis by the age of 15 and 18 years had more schizophrenic symptoms than controls (never used cannabis or had used cannabis 'once or twice') at age 26. In addition, subjects at the earlier age group (15 years) conferred a greater risk of schizophrenia at a later age.[46]

Early onset of cannabis use has been found to be related to impairments in cognitive processes reliant on the dorsolateral prefrontal cortex (DLPFC) circuitry.[47] Cannabis exposure during early ontogeny is not benign and potential compensatory mechanisms that might be expected to occur during neurodevelopment appear insufficient to eliminate vulnerability to neuropsychiatric disorders in certain individuals. The endocannabinoid system also plays a crucial role in the ontogeny of the central nervous system and its activation during brain development which can induce subtle and long-lasting neurofunctional alterations in the offspring, despite being previously considered as relatively harmless.[48] As mentioned previously, maternal cannabis abuse is another contributing factor to psychosis. Both human longitudinal cohort studies and animal models strongly emphasize the long-term influence of prenatal cannabinoid exposure on behavior and mental health.[49] CB1 receptor levels tend to increase throughout adolescent development, although there may be regional and time-specific changes that associate with this ontogeny. Similar to the cannabinoid receptor, the endocannabinoid ligands are also involved.[50]

Endocannabinoid system and cannabis receptors

The endocannabinoid system is comprised of the CB1 and CB2 (and possibly other CB1 receptors) which are expressed in both the central nervous system and periphery. Cannabinoid receptors in the brain take part in the modulation of learning and are particularly important for working and short-term memory endocannabinoid signaling has been found to be present during the gestational period[51-54] and several studies have revealed the importance of this system for neural developmental processes.[2,48,55] THC induces long-term memory deficits and is mediated by CB1 expressed on gamma-aminobutyric acid (GABA) ergic neurons.[56] A growing body of literature has demonstrated that this system may also play a highly specialized and functionally distinct role during development that extends beyond the regulation of transmitter release. The role of the central nervous system (CNS) cannabinoid system is a major area for targeting medications to treat marijuana withdrawal and dependence as well as other addictions.

At the subcellular level, CB1 has been localized to presynaptic terminals, and is found at significantly higher levels on GABAergic rather than glutamatergic neurons in various brain regions.[12,57] Endocannabinoids are believed to be released by postsynaptic cells and function as retrograde signals and traverse back across the synapse, where they activate presynaptically located CB1 receptors and limit synaptic transmitter release. As such, this system represents a critical player in the maintenance and determination of synaptic plasticity.[58] CB1 also exhibits neuroprotective antioxidant activity. The endocannabinoid system modulates neurotransmission at inhibitory and excitatory synapses in brain regions relevant to the regulation of pain, emotion, motivation, and cognition. N-methyl-D-aspartate (NMDA)- and α-amino-3-hydroxy-5-methyl-4-isoxyzolepropionic acid (AMPA)-type glutamate receptor enhancers improve THC-induced impairment of spatial memory.[59] CB receptors are also known to play a role in the etiopathogenesis of schizophrenia.[60] During frequent cannabis use, a series of poorly understood neuroplastic changes occur, which lead to the development of dependence.

Neurochemistry

There are two neurochemical aspects which are significantly evident from research in human and experimental subjects: How THC causes dysfunction or modulates neurotransmission, as well as the role it plays in inhibiting neuroplasticity and neuroprotection, particularly in the developing brain the endocannabinoid system modulates neurotransmission at inhibitory and excitatory synapses in brain and exerts its pharmacological effects by activation of G protein-coupled type-1 (CB1) and type-2 (CB2) cannabinoid receptors. The biosynthetic pathways for the synthesis and release of endocannabinoids are still unclear. Unlike neurotransmitter molecules that are typically held in vesicles before synaptic release, endocannabinoids are synthesized on demand within the plasma membrane. Once released, they travel in a retrograde direction and

transiently suppress presynaptic neurotransmitter release through activation of cannabinoid receptors.

When people abuse cannabis, a series of poorly understood neuroplastic changes take place. Light users of cannabis have lower basal brain-derived neurotrophic factor (BDNF) and neuregulin levels. THC produced psychotomimetic effects, perceptual alterations, and "high" spatial memory impairments. The effects of cannabinoids on BDNF suggest a possible mechanism underlying the consequences of exposure to cannabis. This may be of particular importance for the developing brain and also in disorders believed to involve altered neurodevelopment such as schizophrenia.[61]

Dopamine

The biological mechanism whereby cannabis increases the risk for psychosis remains poorly understood. Animal research suggests that THC increases dopamine levels in several regions of the brain, including striatal and prefrontal areas.[62] Since dopamine is hypothesized to represent a crucial common final pathway between brain biology and actual experience of psychosis, a focus on dopamine may be initially productive in the examination of effects of cannabis.[63] Despite advancements, the endocannabinoid system is still far from being understood and its interactions with other neurotransmitter systems including the dopamine system are complex.[64] Many studies now show a robust and consistent association between cannabis consumption and the development of psychosis. Furthermore, our better understanding of cannabis biology allows for the proposal of a plausible hypothetical model, based notably on the possible interactions between cannabis and dopaminergic neurotransmission.[65] Animal studies using an active cannabidol (THC) have demonstrated enhanced dopaminergic neurotransmission in brain regions in humans, THC induces psychotic-like states and memory impairments in healthy volunteers.[66] THC and cannabinoid agonists enhance striatal and mesocorticolimbic dopamine levels and affect the maturation of the dopamine system, which directly regulates motor function, cognition, motivation, and emotional processes.[67] Thus, increased dopamine neurotransmission due to THC may be a possible explanation for development of psychosis.

Genetics

There is ample evidence that suggests cannabis use has a heritable component, yet the genes underlying cannabis use disorders have yet to be completely identified.[68] Existing research suggests that vulnerability to 'cannabis use initiation' as well as 'problematic use' is influenced significantly by both shared environment and unshared environments. Results from current studies indicate involvement of regions on chromosomes 1, 3, 4, 9, 14, 17, and 18; which harbor candidates of predicted biological relevance.[69] The majority of the evidence concerning high heritability comes from twin studies which have reported evidence for both genetic and environmental influences on vulnerability.[70] A study by Yücel *et al*.,[71] reported susceptibility loci for cannabis use and dependence as well as two narrower cannabis-related phenotypes of "craving" and "withdrawal" from family studies, on chromosomes 1, 3, 6, 7, and 9. Several common genetic influences may be related to other illicit drugs, but a search for specific genes underlying illicit drug use might also hold a key to understanding biological vulnerabilities, which could aid in the development of targeted interventions. Early cannabis use is a risk-modifying factor for psychosis-related outcomes in young adults. A study by Pelayo-Terán *et al*.,[64] examined the interaction between the Val158Met polymorphism of the catechol-O-methyltransferase (COMT) genotype (involved in dopamine regulation) and cannabis use in early stages of psychosis. Cannabis users had a significantly earlier age of onset. The cannabis-COMT interaction showed a significant effect on both duration of untreated psychosis and age of onset. Differences between genotypes were only present in the 'non-users' group. Use of cannabis could exert a modulator effect on the genotype, suppressing the delay effect for the age of onset in the case of the Met allele patients.

With respect to genetic factors, it is thought that cannabis dependence is highly heritable but with unknown explanations. There are several endophenotypes of cannabis dependence, for example, cannabis craving and cannabis withdrawal types which have different mechanisms underlying expression of genetic material. Some of the previously mentioned chromosomes have been identified; however, these do not work in isolation. It is likely that cannabis suppresses the 'delay effect' in gene-environment interaction in vulnerable subjects, more so at an early age and specifically in early onset psychosis.

Imaging

Neuroimaging techniques are powerful research tools used to investigate possible cannabis-induced pathophysiological changes. Imaging studies have been performed in acute administration of cannabis as well as in short- and long-term abusers and non-abusers. Furthermore, it has also been performed in patients consuming cannabis with and without psychosis in order to find out any possible anatomical or structural changes as well as changes occurring in physiological activity.[15] Most of the evidence is available from studies of first-episode schizophrenia and preliminary neuroimaging studies (in mainly nonpsychotic populations) show that cannabis does not affect gross brain anatomy, but does acutely increase cerebral blood flow; and long-term exposure causes an overall reduction of cerebral blood flow.[72]

Major studies, which have reviewed available data on neuroimaging, show a high degree of heterogeneity across studies. Most studies report no evidence of cerebral atrophy

or regional changes in tissue volumes, although some studies did not find cannabis use-related changes in brain morphology and others do suggest that long-term heavy cannabis use may lead to structural brain changes.[73,74] Functional neuroimaging studies have reported increases in neural activity in regions that may be related with cannabis intoxication or mood change effects (orbital and medial frontal lobes, insula, and anterior cingulate cortex), and decreases in activity of regions related with cognitive functions impaired during acute intoxication.[75] These functional studies also suggest that resting global and prefrontal blood flow is lower in cannabis users than in controls. Only minimal evidence of the major effects of cannabis on brain structure has been reported. Imaging studies acquired during the performance of cognitive tasks seem to confirm the vulnerability of still developing frontal lobe functioning for early-onset cannabis use. Adolescent-onset cannabis use, compared with adult-onset use, has been associated with a higher risk for developing symptoms of schizophrenia-like psychotic disorders.[76]

Studies of acute administration of THC or marijuana report increased resting activity and activation of the frontal and anterior cingulate cortex during cognitive tasks.[77] The anterior cingulate and amygdala play key roles in the inhibition of impulsive behavior and affective regulation, and studies using positron emission tomography (PET) and fMRI (functional magnetic resonance imaging) have demonstrated changes within these regions in marijuana smokers.[78] Smokers demonstrated a relative decrease in both anterior cingulate and amygdala activity during masked affective stimuli compared to controls, which showed relative increases in activation within these regions during the viewing of masked faces.[79]

This suggests that the changes in frontal cortex functioning could be responsible for the apathy that smokers feel due to reduced functioning of the frontal lobes and reduced activation of the amygdala.

Ventricular enlargement and reduced prefrontal volume are consistent findings in schizophrenia. Both are present in first-episode subjects and may be detectable before the onset of clinical disorder.[80] In a prospective cohort study; patients with substance misuse history, imaging data, and clinical information were collected on subjects with high risk of schizophrenia as well as controls.[81] Regions exhibiting a significant relationship between level of use of cannabis and structure volume were identified alcohol and cannabis misuse were associated with an increased subsequent risk of schizophrenia. This provides prospective evidence that use of cannabis or alcohol by people with a high genetic risk of schizophrenia is associated with brain abnormalities and later risk of psychosis.[81] A family history of schizophrenia may render the brain particularly sensitive to the risk-modifying effects of these substances it appears that cannabis does not cause any structural changes; however, some brain areas involved in memory and emotion do show some changes. It is not known if these changes are transitory or permanent and whether they contribute to the pathophysiology of schizophrenia.

Neurocognition

Neurocognitive changes are commonly seen in subjects that use cannabis and have been a common determinant of psychosis. The connection between cognition, cannabis, and schizophrenia is complex and not clearly understood. It has been studied in healthy volunteers, patients of schizophrenia with and without cannabis, and previous users. The current levels of information and understanding, though collected over last 25-30 years of research, are far from adequate to establish any direct relationship except a mere association. Thus, we cannot rule out that (a) certain cognitive and cerebral abnormalities existed in patients before cannabis use begins and (b) that patients suffer from subacute effects of cannabis. Though most of the studies show diminished cognitive function, it still remains undetermined and equivocal. Paradoxically, it is also shown that in a subgroup of patients cognition is enhanced by cannabis in both patients and in healthy population. There are also reports that it does not affect cognition at all. Greater adverse cognitive effects are associated with cannabis use commencing in early adolescence yet some studies have not reported any intellectual decline he evidence of cognitive effects comes from clinical, experimental human as well as animal studies; also in both acute administrations and chronic consumption these changes are consistent.

The cognitive domains which have been frequently reported to be involved are: Working memory (WM), spatial working memory, associative memory (AM), processing speed, verbal fluency, verbal learning and memory, attention, executive functions, cognitive complexity, fixation durations, word viewing times, error-proneness, prospective memory task, and object recognition memory;[82] all occurring during the period of acute intoxication and beyond, persisting for hours, days, or weeks after the last use of cannabis. Much of the explanations for the cognitive effects have been possible after CB receptors were reported. Cognitive dysfunction associated with long-term or heavy cannabis use is similar in many respects to the cognitive endophenotypes that have been proposed as vulnerability markers of schizophrenia.[83] CNS cannabinoid systems, particularly exogenous cannabinoids, play a central role in neurochemical processes for cognitive changes pharmacological challenge studies in humans are elucidating the nature and neural substrates of cognitive changes associated with various cannabinoids.

Psychosocial factors

Psychosocial factors have an important role in gene-environment interactions. Cumulative exposure to

environmental risks may increase the risk for psychosis in an additive fashion. The concept of behavioral sensitization may provide a plausible mechanism for the link between cannabis and psychosis.[84] The main stress factors studied are childhood sexual abuse (CSA) and urbanicity. Adolescent cannabis use, childhood trauma, and increased risk of later psychosis are intricately related. Significant interactions between cannabis use and childhood trauma is emerging as a potential risk factor for psychotic symptoms. One recent study has shown increased incidence of CSA in a population of schizophrenia patients.[85] It is also believed that measures to actively discourage or intensively treat cannabis use in children and adolescents who have experienced abuse may help to prevent the development of psychosis in this vulnerable group.[86] Consistent results are also seen for an increased risk for schizophrenia with urban birth and/or upbringing, especially among males. The mechanism of association is unclear but may relate to biological or social/environmental factors or both, acting considerably before psychotic symptoms manifest.

Urbanicity may have a synergistic effect with genetic vulnerability. Several factors appear to contribute in liability for psychosis, for example, the relationship between urban city and neural maldevelopment, the possibility of rural protective factors (e.g., social capital, low social fragmentation), urbanicity in developing countries, cultural variables and geographical location, and associations between urbanicity and other disorders (e.g., affective psychosis).[87] Patients suffering from psychotic disorder report using cannabis mainly for affect regulation and socialization.[88]

TRAJECTORY OF TRANSITION TO SCHIZOPHRENIA

The present paper examined the similarity between neurobiological changes due to cannabis and schizophrenia. Neurobiology of schizophrenia has advanced considerably, primarily related to development in neuroimaging, electrophysiological, and neuropathological approaches.[89] Several neurobiological alterations in the domains of brain structure, physiology, and neurochemistry have been documented; that may reflect diverse pathophysiological pathways from the "genome to the phenome" the changes which are evident from sophisticated functional and anatomical imaging have provided almost credible arguments for neuronal dysfunction and such changes are highly heritable. Research in the early phase of psychosis has also indicated that fundamental changes in neuronal architecture and integrity are possibly the most fundamental changes. The neurochemicals implicated include the dopaminergic, glutaminergic, GABAergic, cholinergic, and serotonergic systems. Neuroanatomical changes are evident and have emerged as a result of imaging and neuropathological observations of brain, structural and functional alterations have referred variously to the postulated networks thought to underlie the symptoms. Theories of pathogenesis have focused on the nature and timing of pathology.[90] These have included early neurodevelopmental models that posit an early disruption in neuronal migration or proliferation.[17,91] Abnormal gene expression, or epigenetic factors and a multitude of environmental factors are current areas of investigation in this field.

There have been a number of reasonable neurobiological advances in cannabis abuse in individuals who are diagnosed with or without schizophrenia. Some of these changes, particularly in neuroimaging and neurocognition, are fairly close to what is observed in some of the patients suffering from schizophrenia. There are inherent limitations to understanding the different research outcomes and the ability to synthesize it in order to develop a trajectory for transition to psychosis. Lack of biological longitudinal follow-ups and studies of pre- and post-cannabis use in patients with schizophrenia has been one such limitation. Neurodevelopmental views of schizophrenia have posited that the illness may result from either an early (pre or perinatally) static brain lesion with a long latency or a late (adolescent) brain disturbance of limited duration and short latency.[17,91] Therefore, the alleged role played by the endocannabinoid system in late developmental phases such as the adolescent one, prompted speculation that alterations in the endocannabinoid tone induced by cannabis consumption during the adolescent developmental window might represent a risk factor for developing schizophrenia.[33,92] THC is associated with transient exacerbation in core psychotic and cognitive deficits in schizophrenia; however, these data do not provide a reason to explain why schizophrenia patients use or misuse cannabis. Furthermore, THC might differentially affect schizophrenia patients relative to control subjects. The enhanced sensitivity to the cognitive effects of THC warrants further study into whether brain cannabinoid receptor dysfunction contributes to the pathophysiology of the cognitive deficits associated with schizophrenia.

The mechanisms by which cannabinoids produce transient psychotic symptoms are unclear but may involve dopamine, GABA, and glutamate neurotransmission. Dose, duration of exposure, and the age of first exposure to cannabinoids may be important factors as well. Genetic factors that interact with cannabinoid exposure to moderate or amplify the risk of a psychotic disorder are beginning to be elucidated. Novel hypotheses including the role of cannabinoids on neurodevelopmental processes relevant to psychotic disorders are being studied.[17] Finally, cannabis use causes cognitive changes and dysfunction in dopamine transmission in genetically vulnerable subjects, which may be responsible for the psychotic-like experience.

CONCLUSION

We have examined the neurobiological changes due to cannabis to see if these changes are similar to those seen in schizophrenic patients the findings show strange similarities; however, none of these studies have been able to establish a possible long-term longitudinal course for these changes. These mere similarities cannot establish a 'cause-effect' relationship, since a number of people with similar changes do not develop schizophrenia. Therefore, the 'transition-to-psychosis' due to cannabis, despite it being a strong risk factor, remains uncertain based upon neurobiological changes. It appears that multiple other factors might be involved in these processes which are beyond neurobiological factors. Major advances have been made in understanding the underpinning of marijuana dependence and the role of the CNS cannabinoid system, which is a major area for targeting medications to treat marijuana withdrawal and dependence, as well as other addictions is of now, it is clear that some of the similarities in neurobiology of cannabis and schizophrenia may indicate a mechanism for development of psychosis but its trajectories are undetermined.

REFERENCES

1. Varma LP. Cannabis psychosis. Indian J Psychiatry 1972;14:241-55.
2. Baldacchino A, Blair H, Scherbaum N, Grosse-Vehne E, Riglietta M, Tidone L, *et al*. Drugs and Psychosis Project: A multi-centre European study on comorbidity. Drug Alcohol Rev 2009;28:379-89.
3. Moore TH, Zammit S, Lingford-Hughes A, Barnes TR, Jones PB, Burke M, *et al*. annabis use and risk of psychotic or affective mental health outcomes: A systematic review. Lancet 2007;370:319-28.
4. Chen CY, Lin KM. Health consequences of illegal drug use. Curr Opin Psychiatry 2009;22:287-92.
5. Gregg L, Barrowlough C, Haddock G. Reasons for increased substance use in psychosis. Clin Psychol Rev 2007;27:494-510.
6. Barrigón ML, Gurpegui M, Ruiz-Veguilla M, Diaz FJ, Anguita M, Sarramea F, *et al*. Temporal relationship of first-episode non-affective psychosis with cannabis use: A clinical verification of an epidemiological hypothesis. J Psychiatr Res2010;44:413-20.
7. de la Serna E, Mayoral M, Baeza I, Arango C, Andrés P, Bombin I, *et al*. Cognitive functioning in children and adolescents in their first episode of psychosis: Differences between previous cannabis users and nonusers. J Nerv Ment Dis 2010;198:159-62.
8. Compton MT, Kelley ME, Ramsay CE, Pringle M, Goulding SM, Esterberg ML, *et al*. Association of pre-onset cannabis, alcohol, and tobacco use with age at onset of prodrome and age at onset of psychosis in first-episode patients. Am J Psychiatry 2009;166:1251-7.
9. Corcoran CM, Kimhy D, Stanford A, Khan S, Walsh J, Thompson J, *et al*. Temporal association ofcannabisuse with symptoms in individuals at clinical high risk for psychosis. Schizophr Res 2008;106:286-93.
10. Sewell RA, Skosnik PD, Garcia-Sosa I, Ranganathan M, D'Souza DC. Behavioral, cognitive and psychophysiological effects of cannabinoids: Relevance to psychosis and schizophrenia. Rev Bras Psiquiatr 2010;32 Suppl 1:S15-30.
11. Baker AL, Hides L, Lubman DI. Treatment of cannabis use among people with psychotic or depressive disorders: A systematic review. J Clin Psychiatry 2010;71:247-54.
12. Winter-van Rossum I, Boomsma MM, Tenback DE, Reed C, van Os J. The influence ofcannabison the course of bipolar disorder: A longitudinal analysis. Tijdschr Psychiatr 2010;52:287-98.
13. Schubart CD, Sommer IE, van Gastel WA, Goetgebuer RL, Kahn RS, Boks MP. Cannabis with high cannabidiol content is associated with fewerpsychoticexperiences. Schizophr Res 2011;130:216-21.
14. Wiley JL, Kendler SH, Burston JJ, Howard DR, Selley DE, Sim-Selley LJ. Antipsychotic-induced alterations in CB1 receptor-mediated G-protein signaling and *in vivo* pharmacology in rats. Neuropharmacology 2008;55:1183-90.
15. Morrison PD, Zois V, McKeown DA, Lee TD, Holt DW, Powell JF, *et al*. The acute effects of synthetic intravenous Delts9-tetrahydrocannabinol on psychosis, mood and cognitive functioning. Psychol Med 2009;31:1607-16.
16. D'Souza DC, Perry E, MacDougall L, Ammerman Y, Cooper T, Wu YT, *et al*. The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: Implications for psychosis. Neuropsychopharmacology 2004;29:1558-72.
17. D'Souza DC, Sewell RA, Ranganathan M. Cannabis and psychosis/schizophrenia: Human studies. Eur Arch Psychiatry Clin Neurosci 2009;259:413-31.
18. Le BecPY, Fatséas M, Denis C, Lavie E, Auriacombe M. Cannabis and psychosis: Search of a causal link through a critical and systematic review. Encephale 2009;35:377-85.
19. McLaren JA, Silins E, Hutchinson D, Mattick RP, Hall W. Assessing evidence for a causal link between cannabis and psychosis: A review of cohort studies. Int J Drug Policy 2010;21:10-9.
20. Kuepper R, van Os J, Lieb R, Wittchen HU, Höfler M, Henquet C. Continued cannabis use and risk of incidence and persistence of psychotic symptoms: 10 year follow-up cohort study. BMJ 2011;342:d738.
21. Malik AR, D'Souza DC. Gone to pot: The association between cannabis and psychosis. Psychiatric Times 2006;23.
22. Hambrecht M, Häfner H. Cannabis, vulnerability, and the onset of schizophrenia: An epidemiological perspective. Aust N Z J Psychiatry 2000;34:468-75.
23. Hall W, Degenhardt L, Teesson M. Cannabis use and psychotic disorders: An update. Drug Alcohol Rev 2004;23:433-43.
24. Andréasson S, Allebeck P, Rydberg U. Schizophrenia in users and nonusers of cannabis: A longitudinal study in Stockholm County. Acta Psychiatr Scand 1989;79:505-10.
25. van Os J, Bak M, Hanssen M, Bijl RV, de Graaf R, Verdoux H. Cannabis use and psychosis: A longitudinal population-based study. Am J Epidemiol 2002;156:319-27.
26. Verdoux H, Gindre C, Sorbara F, Tournier M, Swendsen JD. Effects of cannabis and psychosis vulnerability in daily life: An experience sampling test study. Psychol Med 2003;33:23-32.
27. Mathers DC, Ghodse AH. Cannabis and psychotic illness. Br J Psychiatry 1992;161:648-53.
28. Wilson RI, Nicoll RA. Endocannabinoid signaling in the brain. Science 2002;296:678-82.
29. Degenhardt L. The link between cannabis use and psychosis: Furthering the debate. Psychol Med 2003;33:3-6.
30. Henquet C, Di Forti M, Morrison P, Kuepper R, Murray RM. Gene-environment interplay between cannabis and psychosis. Schizophr Bull 2008;34 1111-21.
31. Mechoulam R, Gaoni Y. A total synthesis of DL-delta-1-tetrahydrocannabinol, the active constituent of hashish. J Am Chem Soc 1965;87:3273-5.
32. Manrique-Garcia E, Zammit S, Dalman C, Hemmingsson T, Andreasson S, Allebeck P. Cannabis, schizophrenia and other non-affective psychoses: 35 years of follow-up of a population-based cohort. Psychol Med 2012;42:1321-8.
33. Malone DT, Hill MN, Rubino T. Adolescent cannabis use and psychosis: Epidemiology and neurodevelopment models. Br J Pharmacol 2010;160:511-22.
34. Rubino T, Parolaro D. Long lasting consequences of cannabis exposure in adolescence. Mol Cell Endocrinol 2008;286 (1-2 Suppl 1):S108-13.
35. Vigano D, Guidali C, Petrosino S, Realini N, Rubino T, Di Marzo V, *et al*. Involvement of the endocannabinoid system in phencyclidine-induced cognitive deficits modelling schizophrenia. Int J Neuropsychopharmacol 2009;12:599-614.
36. Bhattacharyya S, Morrison PD, Fusar-Poli P, Martin-Santos R, Borgwardt S, Winton-Brown T, *et al*. Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. Neuropsychopharmacology 2010;35:764-74.
37. Malone DT, Jongejan D, Taylor DA. Cannabidiol reverses the reduction in social interaction produced by low dose Delta (9)-tetrahydrocannabinol in rats. Pharmacol Biochem Behav 2009;93:91-6.
38. DeRosse P, Kaplan A, Burdick KE, Lencz T, Malhotra AK. Cannabis use disorders in schizophrenia: Effects on cognition and symptoms. Schizophr Res 2010;120:95-100.
39. Hernández ML, García-Gil L, Berrendero F, Ramos JA, Fernández-Ruiz JJ. Delta 9-Tetrahydrocannabinol increases activity of tyrosine hydroxylase in cultured fetal mesencephalic neurons. J Mol Neurosci 1997;8:83-91.
40. El Marroun H, Tiemeier H, Steegers EA, Roos-Hesselink JW, Jaddoe VW, Hofman A, *et al*. A prospective study on intrauterine cannabis exposure and fetal blood flow. Early Hum Dev 2010;86:231-6.
41. Lafourcade M, Elezgarai I, Mato S, Bakiri Y, Grandes P, Manzoni OJ. Molecular components and functions of the endocannabinoid system in mouse prefrontal cortex. PLoS One 2007;2:e709.
42. Wang X, Dow-Edwards D, Anderson V, Minkoff H, Hurd YL. In utero

marijuana exposure associated with abnormal amygdala dopamine D2 gene expression in the human fetus. Biol Psychiatry 2004;56:909-15.
43. Harkany T, Guzmán M, Galve-Roperh I, Berghuis P, Devi LA, Mackie K. The emerging functions of endocannabinoid signalling during CNS development. Trends Pharmacol Sci 2007;28:83-92.
44. Huizink AC, Mulder EJ. Maternal smoking, drinking or cannabis use during pregnancy and neurobehavioral and cognitive functioning in human offspring. Neurosci Biobehav Rev 2006;30:24-41.
45. HarkanyT, Keimpema E, Barabás K, Mulder J. Endocannabinoid functions controlling neuronal specification during brain development. Mol Cell Endocrinol 2008;286 (1-2 Suppl 1):S84-90.
46. Stokes PR, Egerton A, Watson B, Reid A, Lappin J, Howes OD, *et al*. History of cannabis use is not associated with alterations in striatal dopamine D2/D3 receptor availability. J Psychopharmacol 2012;26:144-9.
47. Solowij N, Michie PT. Cannabis and cognitive dysfunction: Parallels with endophenotypes of schizophrenia? J Psychiatry Neurosci 2007;32:30-52.
48. Hurd YL, Wang X, Anderson V, Beck O, Minkoff H, Dow-Edwards D. Marijuana impairs growth in mid-gestation fetuses. Neurotoxicol Teratol 2005;27:221-9.
49. Puighermanal E, Marsicano G, Busquets-Garcia A, Lutz B, Maldonado R, Ozaita A. Cannabinoid modulation of hippocampal long-term memory is mediated by mTOR signaling. Nat Neurosci 2009;12:1152-8.
50. Katona I, Freund TF. Endocannabinoid signaling as a synaptic circuit breaker in neurological disease. Nat Med 2008;14:923-30.
51. Arseneault L, Cannon M, Poulton R, Murray R, Caspi A, Moffitt TE. Cannabis use in adolescence and risk for adult psychosis: Longitudinal prospective study. BMJ 2002;325:1212-3.
52. Dekker N, Schmitz N, Peters BD, van Amelsvoort TA, Linszen DH, de Haan L. Cannabis use and callosal white matter structure and integrity in recent-onset schizophrenia. Psychiatry Res 2010;181:51-6.
53. Campolongo P, Trezza V, Ratano P, Palmery M, Cuomo V. Developmental consequences of perinatal cannabis exposure: Behavioral and neuroendocrine effects in adult rodents. Psychopharmacology (Berl) 2011;214:5-15.
54. Zammit S, Thomas K, Thompson A, Horwood J, Menezes P, Gunnell D, *et al*. Maternal tobacco, cannabis and alcohol use during pregnancy and risk of adolescent psychotic symptoms in offspring. Br J Psychiatry 2009;195:294-300.
55. Fadda P, Robinson L, Fratta W, Pertwee RG, Riedel G. Differential effects of THC- or CBD-rich cannabis extracts on working memory in rats. Neuropharmacology 2004;47:1170-9.
56. Williamson S, Jackson L, Skeoch C, Azzim G, Anderson R. Determination of the prevalence of drug misuse by meconium analysis. Arch Dis Child Fetal Neonatal Ed 2006;91:F291-2.
57. Jutras-Aswad D, DiNieri JA, Harkany T, Hurd YL. Neurobiological consequences of maternal cannabis on human fetal development and its neuropsychiatric outcome. Eur Arch Psychiatry Clin Neurosci 2009;259:395-412.
58. Zavitsanou K, Wang H, Dalton VS, Nguyen V. Cannabinoid administration increases 5HT1A receptor binding and mRNA expression in the hippocampus of adult but not adolescent rats. Neuroscience 2010;169:315-24.
59. Verweij KJ, Zietsch BP, Lynskey MT, Medland SE, Neale MC, Martin NG, *et al*. Genetic and environmental influences on cannabis use initiation and problematic use: A meta-analysis of twin studies. Addiction 2010;105:417-30.
60. Hartman CA, Hopfer CJ, Haberstick B, Rhee SH, Crowley TJ, Corley RP, *et al*. The association between cannabinoid receptor 1 gene (CNR1) and cannabis dependence symptoms in adolescents and young adults. Drug Alcohol Depend 2009;104:11-6.
61. Huizink AC, Levälahti E, Korhonen T, Dick DM, Pulkkinen L, Rose RJ, *et al*. Tobacco, cannabis, and other illicit drug use among Finnish adolescent twins: Causal relationship or correlated liabilities? J Stud Alcohol Drugs 2010;71:5-14.
62. Jentsch JD, Andrusiak E, Tran A, Bowers MB, Roth RH. Delta9-tetrahydrocannabinol increases prefrontal cortical catecholaminergic utilization and impairs spatial working memory in the rat: Blockade of dopaminergic effects with HA966. Neuropsychopharmacology 1997;16:426-32.
63. McGrath J, Welham J, Scott J, Varghese D, Degenhardt L, Hayatbakhsh MR, *et al*. Association between cannabis use and psychosis-related outcomes using sibling pair analysis in a cohort of young adults. Arch Gen Psychiatry 2010;67:440-7.
64. Pelayo-Terán JM, Pérez-Iglesias R, Mata I, Carrasco-Marín E, Vázquez-Barquero JL, Crespo-Facorro B. Catechol-O-Methyltransferase (COMT) Val158Met variations and cannabis use in first-episode non-affective psychosis: Clinical-onset implications. Psychiatry Res 2010;179:291-6.
65. Bhattacharyya S, Crippa JA, Martin-Santos R, Winton-Brown T, Fusar-Poli P. Imaging the neural effects of cannabinoids: Current status and future opportunities for psychopharmacology. Curr Pharm Des 2009;15:2603-14.
66. Jager G, Block RI, Luijten M, Ramsey NF. Cannabis use and memory brain function in adolescent boys: A cross-sectional multicenter functional magnetic resonance imaging study. J Am Acad Child Adolesc Psychiatry 2010;49:561-72.
67. Delisi LE, Bertisch HC, Szulc KU, Majcher M, Brown K, Bappal A, *et al*. A preliminary DTI study showing no brain structural change associated with adolescent cannabis use. Harm Reduct J 2006;3:17.
68. Bolla KI, Eldreth DA, Matochik JA, Cadet JL. Neural substrates of faulty decision-making in abstinent marijuana users. Euroimage 2005;26:480-92.
69. Arnone D, Barrick TR, Chengappa S, Mackay CE, Clark CA, Abou-Saleh MT. Corpus callosum damage in heavy marijuana use: Preliminary evidence from diffusion tensor tractography and tract-based spatial statistics. Neuroimage 2008;41:1067-74.
70. van Os J, Kenis G, Rutten BP. The environment and schizophrenia. Nature 2010;468:203-12.
71. Yücel M, Solowij N, Respondek C, Whittle S, Fornito A, Pantelis C, *et al*. Regional brain abnormalities associated with long-term heavy cannabis use. Arch Gen Psychiatry 2008;65:694-701.
72. Peters BD, Blaas J, de Haan L. Diffusion tensor imaging in the early phase of schizophrenia: What have we learned? J Psychiatr Res 2010;44:993-1004.
73. Pierre JM. Psychosis associated with medical marijuana: Risk vs. benefits of medicinal cannabis use. Am J Psychiatry 2010;167:598-9.
74. Kuepper R, Morrison PD. Does dopamine mediate the psychosis-inducing effects of cannabis? A review and integration of findings across disciplines. Schizophr Res 2010;121:107-17.
75. Jockers-Scherübl MC, Rentzsch J, Danker-Hopfe H, Radzei N, Schürer F, Bahri S, *et al*. Adequate antipsychotic treatment normalizes serum nerve growth factor concentrations in schizophrenia with and without cannabis or additional substance abuse. Neurosci Lett 2006;400:262-6.
76. Stefanis NC, Delespaul P, Henquet C, Bakoula C, StefanisCN, Van Os J. Early adolescent cannabis exposure and positive and negative dimensions of psychosis. Addiction 2004;99:1333-41.
77. Martin-Santos R, Fagundo AB, Crippa JA, Atakan Z, Bhattacharyya S, Allen P, *et al*. Neuroimaging in cannabis use: A systematic review of the literature. Psychol Med 2010;40:383-98.
78. Linszen D, van Amelsvoort T. Cannabis and psychosis: An update on course and biological plausible mechanisms. Curr Opin Psychiatry 2007;20:116-20.
79. Fadda P, Scherma M, Spano MS, Salis P, Melis V, Fattore L, *et al*. Cannabinoid self-administration increases dopamine release in the nucleus accumbens. Neuroreport 2006;17:1629-32.
80. Bossong MG, van BerckelBN, Boellaard R, Zuurman L, Schuit RC, Windhorst AD, *et al*. Delta9-tetrahydrocannabinol induces dopamine release in the human striatum. Neuropsychopharmacology 2009;34:759-66.
81. Welch KA, McIntosh AM, Job DE, Whalley HC, Moorhead TW, Hall J, *et al*. The impact of substance use on brain structure in people at high risk of developing schizophrenia. Schizophr Bull 2011;37:1066-76.
82. Battisti RA, Roodenrys S, Johnstone SJ, Respondek C, Hermens DF, Solowij N. Chronic use of cannabis and poor neural efficiency in verbal memory ability. Psychopharmacology (Berl) 2010;209:319-30.
83. Shrivastava A, Johnston M, Tsuang M. Cannabis use and cognitive dysfunction. Indian J Psychiatry 2011;53:187-91.
84. Cougnard A, Marcelis M, Myin-Germeys I, De Graaf R, Vollebergh W, Krabbendam L, *et al*. Does normal developmental expression of psychosis combine with environmental risk to cause persistence of psychosis? A psychosis proneness-persistence model. Psychol Med 2007;37:513-27.
85. Hayatbakhsh MR, Najman JM, Jamrozik K, Mamun AA, O'Callaghan MJ, Williams GM. Childhood sexual abuse and cannabis use in early adulthood: Findings from an Australian birth cohort study. Arch Sex Behav 2009;38:135-42.
86. Harley M, Kelleher I, Clarke M, Lynch F, Arseneault L, Connor D, *et al*. Cannabis use and childhood trauma interacts additively to increase the risk of psychotic symptoms in adolescence. Psychol Med 2010;40:1627-34.
87. Kelly BD, O'Callaghan E, Waddington JL, Feeney L, Browne S, Scully PJ, *et al*. Schizophrenia and the city: A review of literature and prospective study of psychosis and urbanicity in Ireland. Schizophr Res 2010;116:75-89.
88. Dekker N, Linszen DH, De Haan L. Reasons for cannabis use and effects of cannabis use as reported by patients with psychotic disorders. Psychopathology 2009;42:350-60.
89. Roffman JL, Weiss AP, Goff DC, Rauch SL, Weinberger DR. Neuroimaging-genetic paradigms: A new approach to investigate the pathophysiology and treatment of cognitive deficits in schizophrenia. Harv Rev Psychiatry 2006;14:78-91.

90. Zammit S, Allebeck P, Andreasson S, Lundberg I, Lewis G. Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: Historical cohort study. BMJ 2002;325:1199.
91. Rodríguez de Fonseca F, Cebeira M, Fernández-Ruiz JJ, Navarro M, Ramos JA. Effects of pre- and perinatal exposure to hashish extract on the ontogeny of brain dopaminergic neurons. Neuroscience 1991;43:713-23.
92. Ellgren M, Artmann A, Tkalych O, Gupta A, Hansen HS, Hansen SH, *et al*. Dynamic changes of the endogenous cannabinoid and opioid mesocorticolimbic systems during adolescence: THC effects. Eur Neuropsychopharmacol 2008;18:826-34.

Source of Support: Nil, **Conflict of Interest:** None declared