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The Effect of Cannabis on the Brain: Can it cause brain anomalies that lead to increased risk for Schizophrenia?

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Abstract

Purpose of This Review—This review explores what is known about cannabis's association with schizophrenia, cannabis's effects on the brain, and whether the brain changes known to be present in schizophrenia could be caused by cannabis and thus lead to a psychosis.

Recent Findings—The heavy use of cannabis is known to be associated with some adverse consequences, such as the occurrence of acute psychotic episodes and the development of chronic schizophrenia in some people even after its use has terminated. Recent studies have produced controversy about whether cannabis in heavy use can cause irreversible brain damage, particularly to adolescents and thus, whether a chronic psychosis could be a result of brain changes caused by cannabis.

Summary—From the evidence that exists, it appears that the above view is unlikely and that cannabis may even have benign effects on brain structure, not producing deleterious damage. However, its neurochemical interactions with the dopaminergic pathway may, particularly in genetically vulnerable individuals, have adverse consequences.

Keywords

Marijuana; MRI; DTI; Adolescence; Genes; Psychosis

Introduction

Cannabis abuse is a major public health problem world-wide [1] and moreover, cannabis is the most frequent drug of abuse among adolescents [2]. Despite being illegal in many countries it is easily obtainable and even home-grown. Most people who frequently use it report a mild euphoric feeling and sense of wellbeing, a reason for its continual popularity. However in some individuals, frequent use has adverse consequences and can lead to psychotic symptoms. Adolescents may be particularly sensitive to its effects because of the continued brain growth and differentiation of higher cortical centers that occurs during these specific years of life [3], although this notion has only been conjecture. When a severe acute psychosis does occur in cannabis users, these individuals may be admitted to hospital emergency rooms, but generally clear their mental state over a few hours. In some individuals, however, a primary schizophreniform illness develops and further progresses to chronic schizophrenia. This first episode, in these cases, is often blamed on the cannabis use by patients and their families. Thus, after recovery these individuals may cease taking prescribed medication and in some instances relapse into a more severe chronic

schizophrenia illness. Few studies have examined the association of cannabis with brain structure and schizophrenia, particularly in developing adolescents. However, if cannabis can cause brain abnormalities that place an individual at greater risk for developing schizophrenia-like symptoms, then this is an important issue that needs to be resolved. Alternatively, cannabis may lead to schizophrenia-like symptoms in individuals who already are at high risk for developing schizophrenia because their brains have had some previous developmental and/or genetic insult to the brain. Nevertheless, schizophrenia is a devastating and debilitating mental disorder that has profound effects on the future occupational and social functioning of individuals who are afflicted. Likewise, heavy cannabis use has negative social, academic and future functional consequences on young people who are preoccupied with its use. It is known that heavy cannabis use is common among people with schizophrenia and also thought to lead to an elevated risk for schizophrenia. The question is whether there is currently enough evidence to suggest that there are detectable brain anomalies occurring as a consequence of cannabis use that lead to this increased risk of psychosis and schizophrenia.

Previous hypotheses about the association of cannabis and schizophrenia

There currently is considerable debate about the reasons for the association of cannabis with schizophrenia in both clinical and population based samples. Among the hypotheses proposed are that (A) common independent factors explain the co-occurrence; (B) cannabis causes psychosis that would not have occurred in the absence of cannabis use; (C) cannabis precipitates psychosis only among persons who were genetically vulnerable to developing the disorder; (D) cannabis initiates an early onset of an already predetermined psychosis and its use worsens or prolongs the psychosis; and (E) that persons with psychosis proneness are more likely to become regular or problematic cannabis users than persons without such traits —i.e. the “self-medication hypothesis”. Although some investigations seem to at least partially support the last explanation [4,5,6], there has been little evidence for it and, although implied, no current explanation has yet suggested that cannabis directly damages the brain in regions that are crucial for developing psychiatric symptoms, such as frontal and temporal cortex. Furthermore, one can hypothesize that should there be an interaction between the genetic vulnerability for schizophrenia and the heavy use of cannabis, this may be a direct consequence of both on brain structural organization in an additive or interactive fashion. Whether either is the sole factor is currently unknown.

Cannabis use in people with chronic schizophrenia

Individuals who have chronic schizophrenia and a prior history of marijuana and other drug use have an earlier age of onset of schizophrenia than those who never use any drugs [5,6,7,8,9]. They also are significantly more likely to be males than females. They have less negative and more positive symptoms compared with non-users, and they respond less well to antipsychotic treatment [6]. If they continue to use drugs once released from the hospital, their course of illness tends to be more severe than those who do not use drugs [10,11], but this is not specific to cannabis. Patients with schizophrenia who continue to abuse drugs after the first psychotic episode are also more likely to be medication non-compliant [12], which may then contribute to their poor prognosis. These non-abstinent patients also have more suicide attempts than those who abstain from cannabis use [13]. Cannabis use

additionally appears to exacerbate symptoms of schizophrenia (e.g. [14]). The above quoted studies, however, do not address causality. It is likely that cannabis potentiates a neurochemical deficit in the dopaminergic pathway that causes the above effects (see below), but whether it is causing structural damage to the already compromised brain structure of someone with chronic schizophrenia is unknown.

The Epidemiological Evidence suggesting cannabis causes psychoses

Several epidemiologic studies (reviewed in ref. [15,16]) have suggested that cannabis could cause a psychosis that would not otherwise occur. These findings have sparked recent debates. Cross-sectional, retrospective and recent prospective epidemiological studies show that individuals with psychosis use cannabis more often than other individuals in the general population. The rate of cannabis use among people with psychosis exceeded 40% in some studies (reviewed in [9,5,17]). The previously accepted explanation was the “self medication” hypothesis, but more recent studies show that cannabis exposure itself in a dose-dependent fashion is associated with an increased risk of psychosis (reviewed in [18]) and this association is independent of potential confounding factors such as exposure to other drugs and pre-existence of psychotic symptoms. However, the diagnostic specificity has also been known to be weak, as cannabis exposure may be associated with the occurrence of other psychiatric conditions, from schizophrenia to mood and anxiety disorders.

Nevertheless, the cannabis-schizophrenia association cannot be ignored. In an early well-known study from Sweden, the relative risk of schizophrenia among cannabis users in Stockholm County was calculated to be overall 4.1 (95% confidence interval 1.8–9.3) compared with non-users [19] and 6.0 (95% confidence interval 4.0–8.9) for high users (more than 50 times a year; [20]). A larger long-term follow-up study ([21]) covering the entire age period of risk for schizophrenia of Swedish military conscripts initially ages 18–20 when ascertained, showed that cannabis use at baseline was associated with an increased risk for schizophrenia, again in a dose dependent fashion. The adjusted odds ratio was 4.7 with the greatest amount of use.

Degenhardt et al. [22] proposed that the increase in cannabis use in Australia would then increase the incidence of schizophrenia if it were causal and then tested this hypothesis. They found no increase in the incidence of schizophrenia with the rise in cannabis comparing 8 different birth cohorts from 1940 to 1979. They concluded that cannabis use does not appear to be causally related to the incidence of schizophrenia, but its use may precipitate disorders in persons who are vulnerable to developing psychosis and worsen the course of the disorder among those who have already developed it. On the other hand, Arsenault et al. [23] reviewed five studies that included well-defined samples drawn from population-based registers or cohorts and that used prospective measures of cannabis use and later adult psychosis. They estimated that cannabis use confers an overall twofold increase in the relative risk for later schizophrenia and calculated that at the population level, elimination of cannabis use would reduce the incidence of schizophrenia by approximately 8%, assuming a causal relationship. Using the well-known Dunedin, New Zealand birth cohort longitudinal data [24], they then showed that cannabis use at ages 15 and 18

predicted significantly more diagnoses of schizophreniform disorder at age 26 than that found in non-users, although the sample was small and they have not yet shown that this is true for conversion to a chronic schizophrenia diagnosis.

Henquet et al. [25] in a 4-year follow-up of adolescents and young adult cannabis users found that at follow-up the cumulative lifetime incidence of at least one psychotic symptom was 17.4% and that cannabis use increased the risk for psychotic symptoms in a dose-wise fashion. In those cannabis users with personality traits characteristic of psychotic vulnerability (i.e. paranoid, schizotypy), 23.8% had at least 2 psychotic symptoms on follow-up compared with only 5.6% of those without these traits. The overall population attributable risk for psychosis in cannabis users was 6.2% and twice as much in those cannabis users with predisposing personality traits. However, this study did not fully support a self-medication hypothesis for cannabis use by psychosis-prone individuals, as prior personality traits did not predict later cannabis.

Thus, the evidence from epidemiological studies is inconsistent and not conclusive that cannabis causes schizophrenia and thus the issue is still highly controversial.

Outcome following a primarily cannabis induced 1st psychotic episode—If cannabis effects brain structure directly, one would expect that individuals with these brain changes would not have a good outcome to any developed psychotic episode and not be able to return to his/her premorbid state. Psychosis due to cannabis has long been known and reported upon (e.g. [26]) and in one study, 49% of cannabis-induced psychoses later satisfied criteria for schizophrenia [27] despite cessation of cannabis use. In a longitudinal follow-up of early phase psychosis and substance use comorbidity, Caton and colleagues [28] found that by one-year post intake, 25% of those with a baseline DSM-IV research diagnosis of substance-induced psychosis and 50% of pure cannabis users had been re-diagnosed with a primary psychotic disorder, most often of a non-affective type, i.e. schizophrenia. People with schizophrenia rarely if ever can return to their premorbid level of functioning, which leads to the belief that brain changes have occurred that make this unlikely.

Cannabinoids and their neurochemical effects—The main active component of cannabis or marijuana is THC(delta-9-tetrohydrocannibinol), a compound that activates the endogenous CB1 receptor, which is in high concentration in hippocampus, amygdala, cerebellum, basal ganglia and regions of the cerebral cortex. Recent advances in the understanding of brain cannabinoid receptor function have renewed interest in the association between cannabinoid compounds and psychosis, and some evidence exists for a “cannabinoid hypothesis” of schizophrenia (reviewed in [29]). In a 3-day, double-blind, randomized study [30], the behavioral, cognitive, and endocrine effects of 0, 2.5, and 5 mg intravenous delta-9-tetrahydrocannabinol (Delta-9-THC) were characterized in 22 healthy individuals, who had been exposed to cannabis but had never been diagnosed with a cannabis abuse disorder. Delta-9-THC produced a variety of schizophrenia-like positive and negative symptoms, altered perception, increased anxiety, and some euphoria. It caused acute disturbances in immediate and delayed verbal memory, verbal fluency and working memory, all of which are completely reversible These data suggest that Delta-9-THC can

produce many symptoms that are characteristic of schizophrenia, perhaps due to a heightened sensitivity to its effects with increased use. Also, increased endogenous cannabinoids, such as anandamide, have been reported in CSF of patients with schizophrenia who have not used cannabis [31, reviewed in 32]. Other studies examining the cannabinoid receptors suggest an association of deviance in reactivity of this system with the pathophysiology of psychotic disorders. For example, one post-mortem study found a significant increase in [3H]SR141716A specific binding to CB1 receptors in the anterior cingulated, and other cannabinoid receptors are increased in density in subregions of the prefrontal cortex, in patients with schizophrenia compared with controls [33], major sites in the brain for action of cannabis ([34]; reviewed in [32]). In addition, it was shown post-mortem that chronic cannabis abusers had a down-regulation of cannabinoid receptors as evidenced by significantly lower density of cannabinoid receptor-1 mRNA-positive neurons than in control brains in regions of the putamen, caudate, nucleus accumbens and hippocampus. Moreover, and most relevant to schizophrenia, is that cannabis has been shown to acutely result in an increased release of dopamine, which could be a biochemical basis for the positive psychotic symptoms (hallucinations and delusions) when experienced [35]. Thus, these biochemical changes are likely to interact with those already known to be present in schizophrenia (i.e. dopaminergic) to make one even more vulnerable to developing psychosis and continuing it. On the other hand, there are those who think that cannabinoids may exert a neuroprotective effect. The THC activation of the P13K/Akt/GSK-3 signaling pathway, independent of the dopamine system, may provide some support for this notion [36].

Genetics studies of liability for cannabis abuse and its association with schizophrenia—The genetic liability for mixed drug abuse has been found to be high in several studies of MZ vs. DZ twins and families [37,38,39,40], and is thought to be a non-specific genetic liability, with the possible exception of heroin dependence [41]. Family and twin studies have also specifically examined relative risks for cannabis abuse. Bierut et al [39] found a relative risk for cannabis abuse of 1.78 for siblings of cannabis-dependent probands. Genetic factors explained 44.7% of the variance in the liability for cannabis dependence among male twins in one study [42] and 59% of the variance among female twin pairs for cannabis use in another study [38]. Males had somewhat lower risk estimates for use compared with females (explaining 40% of the variance), but this risk increased with more severe use (i.e.79% for heavy users, 72% for abuse, and 62% for dependence). In another study using both male and female twin pairs [43] the heritability for cannabis abuse has been calculated at from 62 to 79% in women and a minimum of 60% for both sexes combined, although earlier studies [44] had lower heritability estimates of from 33–44%. The probandwise concordance rates in Kendler et al. [43] were 48.5% for MZ, 26.2% for DZ same-sex twin pairs and 22.6% for siblings. The non-specificity of the genetic liability suggests that the search for particular liability genes should cover classes of genes with shared effects for non-specific drug abuse, such as on the dopaminergic pathways or on response to neurotoxicity. The sex differences in familiality are not substantial, but if anything suggest higher familial tendency in females, although females have not been studied as extensively as males. Despite far fewer family and twin studies of pure cannabis use than of schizophrenia, it is interesting that these above estimates are slightly less, but

similar to the heritability and familial liability reported for schizophrenia (reviewed in [45,46]) and thus searches for genes for both of these complex disorders should benefit from common strategies. Ultimately genes uncovered may be found to influence common pathways in the brain for biochemical or structural alterations or both.

There is only one family study confined to cannabis abusers who have experienced a psychosis [47]. In this study the morbid risk for schizophrenia was elevated among first degree relatives (7.1%) as compared with controls who were psychotic but who did not use cannabis (0.7%); However, the number of probands was small (N=23), other substance abuse was not eliminated, no cannabis using non-psychotic controls or normal controls were used AND the rates for schizophrenia among the non-cannabis using psychotics is contrary to what one would expect from the known rates in schizophrenia family studies in general [48]. In other studies, schizotypal personality traits (genetically related to schizophrenia; e.g. [49,50] have been associated with cannabis use [51,52]. In one study, cannabis, as well as other drug use, was associated with the presence of psychotic symptoms in adolescents at genetic risk for schizophrenia [53], suggesting an interaction of genetic predisposition with environment. However, no carefully controlled family study of psychotic pure cannabis abusers has been performed to show that schizophrenia is increased among their first-degree relatives regardless of whether cannabis is used and also whether cannabis use is increased among these relatives independent of the schizophrenia. Such a study would suggest that the association of cannabis with schizophrenia is dependent on the inheritance of schizophrenia vulnerability genes.

The gene for the cannabinoid 1 receptor, located on chromosome 6q14-q15, near one region of linkage in schizophrenia [54] would be a likely possible candidate. Only one genetic study of this gene has been published to date and shows that the CNR1 gene, which encodes CB1 receptors, has an AAT-repeat polymorphism in the gene that may have an increased association with schizophrenia [55].

Catechol-O-methyltransferase is an enzyme that metabolizes dopamine particularly in the prefrontal cortex [56]. Thus, a genetic alteration in the gene for COMT such that it has either reduced or elevated activity could have an effect on the amount of dopamine available and could possibly increase one’s vulnerability to the effects of cannabis. The COMT gene has two common variants that consist of a difference at codon 108/158 of the gene that translates into an amino acid change in the protein, a substitution of a methionine (met) for a valine(Val), producing differences in enzymatic activity such that met-met genotypes have lower activity than val-val genotypes [57]. The high-activity Val allele for the enzyme COMT, lowers the amount of available dopamine and has been associated with working memory deficits [58], while violent and aggressive behavior are associated with the low activity MET allele in some studies of patients with schizophrenia (e.g. [59]), but neither alleles are associated with schizophrenia as a diagnosis or only very weakly so [60]. Most recently, Caspi et al. [61] found that the Val allele was associated with an increased risk for schizophreniform disorder among Caucasian adolescent cannabis users and this has partially been confirmed by other studies (i.e. [62]). They report that both Met and Val alleles were present in approximately 50% of the cohort, similar to previous Caucasian population frequencies and that 27% had the val-val genotype. Although a cohort of 803 individuals

was studied from a New Zealand birth cohort of over 1000, only 3.6% of them had a broadly diagnosed acute schizophrenic-like psychosis (N=25). Extraction from a figure within the Caspi et al. manuscript suggests that approximately 15% (approximately 8) of the 54 val/val carriers had cannabis use in adolescence and psychosis, and likewise, of the 148 val/val carriers who did not use cannabis, 2% of them had a schizophrenia-like psychosis (i.e. 3 people). Thus the number of schizophreniform subjects who used cannabis in adolescence and had the val-val or val-met alleles, although increased compared with those who did not use cannabis and those that had met-met alleles (N=approximately 4), was extremely small. This study needs replication in a much larger sample. A cautious view of the COMT data should also be taken at this time because having a high activity allele of this enzyme would be inconsistent with the notion that an excess of dopamine release leads to psychotic symptoms, rather than a deficit. Nevertheless, it is clear that genetic vulnerability may be the key to eventually identifying who among cannabis users are likely to develop a psychosis. Not just one gene variant, but several, may increase risk. Any study of the relation of brain structural deficits to cannabis use will have to consider genetic variation in pathways that influence both brain neurochemistry and structure.

The Evidence that Brain Structural Abnormalities exist in people at high genetic risk for schizophrenia and in first-episode patients

Schizophrenia is clearly a brain disorder and has consistently been shown in the chronic stages to be characterized by structural brain deficits (i.e. lateral ventricular enlargement, frontal and temporal lobe cortical reductions ([reviewed in 63]). White matter integrity, particularly of the frontal lobe and anterior cingulum also appears disturbed, as recently reported using diffusion tensor imaging (DTI; e.g. [64,65]). Numerous studies show hippocampal volume loss and cellular abnormalities in schizophrenia [66]. Other literature suggests early involvement of the parahippocampal gyrus [67, 68], the anterior cingulate [69], the uncinate fasciculus [70] and fusiform gyrus [71,72]. The anterior cingulate is interconnected to the dorsolateral prefrontal cortex and thus has a role in working memory processes [73], while the posterior cingulate is interconnected with medial temporal and temporal association cortex. The uncinate bundle contains frontal-temporal connections and the fusiform gyrus, located on the ventromedial surface of the temporal and occipital lobes, has been implicated in facial recognition [74]. The parahippocampal gyrus has dense hippocampal, amygdala, entorhinal cortex, and other temporal/frontal cortex connections [75]. The pattern that emerges most strongly from the literature is that changes in the prefrontal and temporal cortices and their connections through the limbic system are abnormal in schizophrenia and thus the structures and circuitry of the dorsolateral prefrontal cortex, cingulate, superior temporal gyrus and medial temporal lobe appear particularly involved. It is thought that these deficits arise early on in the illness and may even be present prior to the onset of schizophrenia (i.e. [76]), but that they are also progressive after the onset of illness[77]. Two recent high-risk/ prodromal studies from Scotland [78, 79, 80, 81, 82] and Australia [83, 84] focused on MRI measurements and have shown structural brain gray matter changes, particularly localized in the frontal and temporal lobes (anterior cingulate, temporal cortex, parahippocampal gyrus; frontal lobe) that are abnormal before the onset of psychotic symptoms. Some of these anomalies may be progressive over time (reviewed by [85]) and some have recently been detected to be progressive in adolescents at

high-risk for schizophrenia [83] who develop the illness. However, other than a couple of small reports [86,87], none of these abnormalities have carefully been examined in those patients who abuse substances, particularly pure cannabis users during adolescence. Since the adolescent period is the peak time when cannabis is frequently used and is a particularly vulnerable period for the development of a schizophreniform illness that could lead to chronic schizophrenia, the consequences of cannabis specifically on the adolescent brain should be carefully studied.

Is there any evidence for brain structural abnormalities in cannabis users?

Thus far, taken together, brain imaging, animal and neurocognitive studies appear inconsistent and not clearly showing lasting adverse effects of cannabis on the brain [see Table 1]. There does, however, seem to be some evidence that chronic cannabis use alters neuronal and axonal integrity as measured by MRS N-Acetylaspartate in the dorsolateral prefrontal cortex [105]. Nevertheless, there have been very few direct studies of the brain in people who use cannabis. None have large N's and specifically examine adolescent use. In the early 1970's a controversial report was published in the Lancet concluding that cannabis caused cerebral atrophy as evidenced by pneumoencephalography in a small group of male users [88]. This was followed by several refutes and CT studies in the later 1970's and 80's that failed to confirm significant effects of marijuana on the brain [89,90,91,92]. More recently, Tzilos et al. [97] reported an MRI study showing no difference in gray or white matter volumes, CSF, or hippocampus in heavy cannabis users compared with non users. However, measurements of other specific temporal cortical structures were not performed, the number of subjects was small (22 vs. 26) and no subject had experienced psychotic episodes. Another MRI report by Block et al. [95] had similar findings. Only a couple of MRI studies have been reported [86,87] of people with schizophrenia who used cannabis. The first [86] compared first-episode schizophrenic patients who did (N=27) and did not (N=20) use cannabis prior to the onset of their psychosis. This study with a relatively small number of subjects failed to find differences in brain pathology between the groups, but had no control comparison subjects. Moreover, similar to the other MRI studies, they did not examine more specific temporal and cortical brain regions and their white matter connections, but rather looked for subcortical evidence of changes—i.e. in the caudate and total gray and white matter and ventricular size. In the other study, [87], a larger group of patients and controls were used. Although no difference was found in the superior frontal or orbital gyrus, the anterior cingulate was found to have less gray matter in 1st episode patients with schizophrenia who used cannabis, compared with those who did not or normal controls. No other regions were measured for comparison. None of these studies specifically focused on individuals who used cannabis in adolescence. Other more indirect evidence does exist that suggests brain pathology can occur after cannabis use, such as reports of lowered IQ [106] particularly when used early in life [107], deficits in working memory performance [108], and other cognitive impairments [109]. However, the cognitive effects may be acute use or withdrawal effects and reversible without lasting deficits produced [110]. There are several other cognitive studies that together appear inconsistent (reviewed by Iversen, [32]). Clearly more studies are needed to determine whether cannabis can directly affect brain structure. Dean et al [111] have shown cannabis use can change the density of cannabinoid -1 receptors in both the caudate and putamen. Thus it would seem logical that subsequent to

chronic cannabis use, these structures would change in volume and this may be happening in other regions where cannabinoid receptors are prevalent (frontal and temporal cortex, hippocampus and limbic circuit) as well, but this has never been shown.

The hypothesis that cannabis directly causes neurotoxic damage to brain structures making individuals more vulnerable for psychosis was tested by Jockers-Scherubl et al. [112]. They studied levels of nerve growth factor (NGF) in a large group of schizophrenic patients who abused cannabis, showing that cannabis abusers had significantly higher serum NGF levels than nonabusers or controls. Since NGF is released after neuronal damage, they concluded that the increased serum NGF could be evidence of cannabis induced neurotoxicity. However, this study needs further replication and correlation to direct effects on brain tissue.

Nevertheless, there must be some biological explanation for the presumed increased risk for psychosis among adolescent cannabis users and yet a lack of epidemiological evidence for an overall increase in psychosis in decades when cannabis use rose in specific geographic regions.

To test the hypothesis that cannabis during adolescents can particularly disrupt the normal reorganization and growth of new neuronal axonal connections, Diffusion Tensor Imaging (DTI) may be particularly useful and has not been used before in brain studies of cannabis use. DTI is an MRI technique that measures the Brownian motion or free diffusion of water [113,114,115]. When applied to neural tissue, DTI assesses the degree to which water diffusion is constrained by barriers such as myelin sheaths, membranes or neuronal fiber tracts. Diffusion in nerve fibers/ white matter is anisotropic (i.e., in a given white matter voxel, axial diffusion is parallel to the principal fiber direction) and is much greater than radial diffusion (perpendicular to the principal fiber direction). Images obtained using DTI are used to compute a “diffusion tensor” for each voxel, which describes water diffusion modeled as an ellipsoid [116]. The “diffusion tensor” can be broken down into 3 component eigenvectors (the 3 axes of the ellipsoid) providing different anatomical information about the underlying diffusion of water along these separate axes. Diffusion anisotropy is expressed as fractional anisotropy (FA), a normalized measure derived from the 3 eigenvalues. Thus, FA is a measure of the degree of anisotropy within a voxel, a value of 0 corresponding to completely isotropic diffusion and 1 corresponding to free diffusion in one direction only. FA and the eigenvalues from which it is derived, are measures of white matter microstructure that may reflect fiber organization, fiber directional coherence, or fiber integrity. White matter abnormalities with axonal disorganization might therefore be expected to decrease FA. Beaulieu et al. [117] examined anisotropy and diffusion *in vitro* in myelinated and nonmyelinated fibers of the garfish and suggested that DTI measures do not represent myelination per se, but that variations in diffusion anisotropy are due to axonal fast transport [118]. Others have found that such variations are not due to susceptibility-induced gradients [119,120]. Beaulieu [117,118] thus suggested that axonal membrane properties might play the most important role in diffusion anisotropy, with myelin playing a modulating role. Thus, by examining FA in regions of interest (ROI’s) in white matter, it is possible to obtain information in vivo on the white matter microstructure within those areas. Variations in such measures could be relevant to psychiatric disorders. Since DTI measures have implications for the structural organization of neurons (e.g., axons, cell membranes,

and related myelin), it seems likely that DTI measures have relevance for understanding connectivity between brain regions. Several DTI studies have already been published on patients with chronic schizophrenia (e.g. [121,122,123,124]). These studies support the view that white matter microstructure is abnormal in schizophrenia, although methods for MRI acquisition, image processing and overall analytic approaches have varied considerably.

The connections of the left superior temporal gyrus (STG) are critical components of the neural network for determining the semantic/lexical content of language and speech production in response to auditory perception. Recently, two studies have demonstrated a loss of normal asymmetry in diffusion anisotropy in the uncinate fasciculus in schizophrenia [123,125]. Since the uncinate is one of the major pathways connecting frontal cortex and STG, this finding is consistent with the notion that the symptoms of schizophrenia arise from altered frontal/temporal white matter integrity. Interestingly, Ardekani et al. [121] found reductions in FA in patients with schizophrenia in the left, but not right, STG. Buchsbaum et al. [126] used both DTI and PET in the same patients concluding that both methods supported diminished fronto-striatal connectivity in schizophrenia. There have been few published DTI studies on cannabis users. One small study failed to find any changes reflecting reduced white matter integrity in young adults who were frequent cannabis users [102], although further reports using more advance DTI methods in larger group of subjects currently need to be completed.

Brain Functional abnormalities in Cannabis users

There have been several reviews of this topic already in previous literature [127,128,129,130] and one review of animal models of pre-pubertal and perinatal exposure linked to long lasting functional effects [131]. In acute cannabis use and also in acutely abstaining long term cannabis users, cerebral blood flow is increased in frontal lobes bilaterally with the greatest overall increase in the right hemisphere, left temporal lobe and cerebellum, whereas chronic abuse itself leads to overall reductions in CBF. Acute cannabis administration can also induce memory impairments that exist long after abstinence. Acute cannabis use can also increase EEG measures of impulsivity implying an underlying basis for violent activity associated with cannabis use [132]. However, there is no indication that cannabis causes longterm cognitive effects after abstinence years later. The overall behavioral effects of these changes were also minimal. The chronic effects of cannabis suggest an adaptive process where by the acute effects likely representing down regulation of the CB1 receptors are some how compensated for in the chronic state. It was shown in one study [133] that an auditory P50 sensory gating deficit is present in chronic cannabis users that is similarly present in patients with schizophrenia regardless of whether they used cannabis. Thus, chronic cannabis abuse may effect the same sensory cortical circuits that are involved in schizophrenia, although whether that signifies a consequent greater vulnerability for schizophrenia may not follow.

Jager et al. [134] using fMRI and volumetric analysis, studied associative memory and its medial temporal lobe pathways. While cannabis users showed lower activity in both the parahippocampal gyrus and right dorsolateral prefrontal cortex, they showed normal performance and had no changes in brain structure.

Conclusions

While extensive literature exists concluding that cannabis use is associated with schizophrenia, the reason for this association had never been clarified. There is some recent but weak evidence that when someone uses cannabis with genetic vulnerability for schizophrenia, they are either at ultra-high risk for this disease or it initiates the onset of the disorder that may inevitably occur at a later time. Since there is also extensive evidence that schizophrenia is a brain disease likely originating from developmental anomalies in both structure and corresponding brain function, it seems logical that cannabis use on top of an already compromised brain will lead to psychosis. However, the current literature fails to reveal any evidence that cannabis itself can cause adverse effects on the brain in an otherwise normal individual that would then lead to a chronic schizophrenia illness, despite the acute brain functional effects of cannabis on the same processes that are abnormal in schizophrenia. It is more likely that cannabis users who develop a transient psychotic episode subsequent to heavy use may have only a biochemical variant, such as low COMT activity, and thus higher dopamine that would potentiate the effects of cannabis and cause an acute psychotic reaction.

It is clear that further research is needed to determine the biological effect that cannabis has on the brain in people who do or do not develop schizophrenia. However, since cannabis use and legalization of its use is a controversial public health and political issue, caution should be exerted in either making public statements about brain imaging studies that do or do not show deleterious or even beneficial effects of cannabis. The intensive studies needed have not yet been performed.

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Table 1

Studies examining structural alteration in the brains of cannabis users in chronological order.

STUDY	METHODS	SUBJECTS	FINDINGS
Campbell et al.1971 [88]	PEG	10 Cannabis users and 13 controls	Ventricular enlargement in cannabis users
Co et al. 1977 [89]	CT	12 cannabis users, no controls	No brain changes
Keuhnle et al. 1977 [90]	CT	19 cannabis users, no controls	No brain changes
Rumbaugh et al., 1980 [91]	CT		
Hannerz and Hindmarsh 1983 [92]	CT	12 Cannabis users, no controls	No brain changes
Wiesbeck and Taeschner 1991 [93]	CT	12 Cannabis Users and 10 controls	No brain changes
Aisly et al 1993 [94]	MRI	23 cannabis users and 17 controls	Non-specific cerebral and cerebellar atrophy in cannabis users
Block et al 2000 [95]	MRI	18 cannabis users and 13 controls	No brain changes
Wilson et al 2000 [96]	MRI	59 cannabis users, no controls	
Tzilos et al 2005 [97]	MRI	22 adult cannabis users and 26 controls	No brain changes
Matochik et al 2005 [98]	MRI	11 cannabis users and 8 controls age range 21 to 35	Decreased Right parahippocampal gyrus, increased bilateral fusiform gyrus and right thalamus,
Gruber and Yurgelun-Todd 2005 [99]	fMRI and DTI	10 cannabis users and 10 controls ages 18–47	Testing inhibitory processing: Lower anterior cingulate and higher mid-cingulate. More diffuse DLPFC activation. No FA differences on DTI, but Increased trace diffusivity.
Chang et al 2006 [100 **and** 101]	FMRI-visual attention task and Proton MRS	24 Cannabis users and 19 controls	Decreased activation in attention network (right prefrontal, medial dorsal parietal cortex and vermis of cerebellum) Early age of use associated with lower BOLD signals. MRS study showed reduction of glutamate in basal ganglia.
DeLisi et al 2006 [102]	MRI and DTI	10 cannabis users and 10 controls Ages 17–30	No changes associated with cannabis use
Sneider et al 2006 [103]	MRI-CBV	12 cannabis users (32–47 age range) and 17 controls (21–31 age range)	No correlation between CBV and total cannabis use.
Medina et al. 2007 [104]	MRI	Alc users (N=16); Can+Alc (N=26); controls (N=21) Ages 15–18	Cannabis use associated with increased L Hippocampal volume and increased L>R asymmetry
Szeszko et al. 2007 [87]	MRI	1st episode Sz pts who used cannabis (N=20) Pts who did not use cannabis (N=31) Controls (N=56) Mean ages 22.4 to 25.7	Cannabis use associated with less anterior cingulated gray matter.