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Cannabis and Psychopathology: The Meandering Journey of the Last Decade

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Cannabis and Psychopathology: The Meandering Journey of the Last Decade

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Since its inception cannabis has been observed to be associated with various psycho-pathology. In this paper, the authors have reviewed the advancement made in this area over the last decade. The association between cannabis and schizophrenia has been researched more intensively. The controversy regarding the reliability, clinical utility, and the existence of a cannabis withdrawal syndrome has also been settled. Recent studies also buttressed the possibility of acute and chronic effect of cannabis on various cognitive functions. There has been a plethora of research regarding the treatment for cannabis use disorders. But the new and most interesting area of research is concentrated on the endocannabinoid system and its contribution in various psychiatric disorders.

Introduction

The use of cannabis has been known to mankind for time immemorial. As per the latest World Drug Report released by United Nations Office on Drug and Crime in June 2014, the global market for cannabis (both herb and resin) continues to expand, with two-third of the reporting countries ranking cannabis as the primary substance of abuse. [sup][1] In 2012, between 125 million and 227 million, people were estimated to have used cannabis, corresponding to between 2.7% and 4.9% of the population aged 15-64 years. There is a trend of increasing use of cannabis in America, Oceania, and several Asian countries. [sup][1] Data from the National Household Survey in India demonstrated a prevalence figure of 4% and 3.3% for lifetime and current cannabis users. [sup][2] Cannabis once thought to be a "harmless" to even as a medicinal herb, now has a cumulative evidence for its potentially damaging consequences. It has been linked to a plethora of psychopathology, cognitive dysfunction, and other psycho-social adversities. Interestingly, in recent times, especially after the discovery of endocannabinoids (eCB) system, there has been a renewed attention for the use of cannabis derivatives for therapeutic purpose.

In the year 1994, a paper titled "Cannabis-related psychiatric syndrome: A selective review" was published in this journal. [sup][3] The area was revisited in 2004, [sup][4] after a period of 10 years. Now, after yet another decade, there has been a perceived necessity to have a re-look on the entire conundrum of cannabis and related disorders. It would be useful, in fact, imperative to carry this review forward from the previous one, published in 2004. In their concluding remarks, the authors acknowledged that though there has not been any earth-shattering research in the area of cannabis, there were several large-scaled well-controlled epidemiological studies which had the potential to accept, reject or to modify the existing literature. Apart from the ever baffling phenomenon of cannabis and schizophrenia, authors had recognized several other areas of controversy, starting from cannabis withdrawal to cannabis-related cognitive impairment, eventually opening up an opportunity

to explore the enigma. In the last decade, there has been some clarification in many of these areas; there is emerging interest in some new areas; waning of interest in other few areas; and a few replication researches to substantiate the existing knowledge. The PubMed search word "cannabis" generated 5820 results during this period (2004-2013) as compared to 1879 from 1994 to 2003 and 871 from 1984 to 1993. These numbers signify an ever growing enthusiasm in cannabis research. Not only in terms of number of publications, the global community has responded to the increasing concern of cannabis use by various conferences like recently an "International Scientific Conference on Cannabis and Health" has been announced by the European Union.

Though there has been a controversy regarding cannabis policy owing to the scuffle between the liberal and the conservative lobbies, this area has been consciously overlooked in this review because the author's thought this to be beyond the purview of this article.

Data Search Methodology

The data search strategies used included electronic databases as well as hand-search of relevant publications or cross-references. The electronic search included PubMed, Google Scholar, PsychINFO, Scopus, and Ovid. Cross-searches of electronic and hand search key references yielded other relevant material. The search terms used in various combinations were cannabis, schizophrenia, cannabis withdrawal, eCB, cannabis and cognition, treatment, drugs, cannabis and India. We have purposely chosen to remain silent about the association between the externalizing psychopathology in the children and adolescent and cannabis use because we have planned to review cannabis and concurrent adult psychopathology. The data inclusion for this review was guided by the following principles. We included studies published after 2003 till December, 2013. As we intended for a narrative review, we were over-inclusive and did not restrict our data inclusion by any standardized methodology. The intent was to include as much research and as many aspects as possible. Wherever applicable, the strengths and the limitations of the cited research are also discussed. The search methodology was similar to the previous two reviews to ensure comparability and consistency. The results are discussed under two broad sections: Research to clarify confusion (which deals in the areas of past active research, with new findings over the last decade or so), and research in new domains (dealing in research frontiers that have come up actively in the past decade).

Research to Clarify Confusion

Cannabis and schizophrenia

It is well-known that regular cannabis use and psychotic disorders like schizophrenia are associated in the general population [sup][5],[6] and heavy cannabis users are over-represented among new cases of schizophrenia. [sup][7] The previous review suggested that "cannabis use might be causally related to development of schizophrenia in an indirect way, but its use may precipitate disorders in persons who are vulnerable for developing psychosis and worsen the course of the disorder among those who have already developed it." The usual confusion in this association is due to the presence of various confounding factors which can be common to both cannabis and schizophrenia. Subsequent studies endeavored to settle the confusion.

There were at least seven large-scale, prospective, population-based studies chiefly from various European countries. [sup][8],[9],[10],[11],[12],[13],[14] Three of these studies found that even after controlling for the effect of confounding variables the association of cannabis and Schizophrenia remained significant, though the strength of association decreased. There are no < 2 meta-analyses examining the association between cannabis and Schizophrenia. Moore et al . [sup][15] reported an increased risk (odds ratio = 1.4) of any psychotic outcome in individuals who had ever used cannabis. Findings were indicative of dose-response relationship of cannabis and Schizophrenia. This meta-analysis had only included studies which had adjusted for all possible confounding variables such as other substance use, personality traits, sociodemographic characteristics, intellectual functioning, and other mental health problems. To reduce or eliminate the effect further, McGrath et al . [sup][16] conducted a sibling pair analysis and found that the risk of nonaffective psychosis increases by 2 times following exposure to cannabis as young age. Another recent meta-analysis found that the age of onset of psychosis is about 2.7 years earlier in the cannabis user as compared to alcohol user. [sup][17] The same finding was replicated in another study which adjusted the potential confounding factors. [sup][18] Hence, from these findings, it is quite evident that there has been a direct association of both these conditions.

Next obvious question would be whether this association is causal? For the causality, association should be consistent, plausible, and specific. The biological plausibility of this association could be understood through the common neurobiological underpinning of these two apparently distinctive conditions. Long-term heavy cannabis use (without schizophrenia) may lead to reduced hippocampal and amygdala volume and also smaller cerebellar white matter. Smaller thalamic volume has also been reported in the heavy cannabis user. [sup][19],[20] These findings are analogous to those found in schizophrenia. But these brain abnormalities are nonspecific and are also found in subjects with other substance use disorders or even psychiatric

disorders other than schizophrenia. From the neurotransmitter perspective, dopaminergic hypothesis of schizophrenia postulates that positive symptoms are due to excess dopamine in the meso-lombic pathway. There is some evidence alluding to the disruption of the eCB system by exogenous cannabis resulting into excess dopaminergic transmission in the meso-limbic tract. [sup][21] The same eCB disruption by heavy cannabis use has also been implicated in the altered neurogenesis, neuroplasticity, maturation, migration, glia formation. As a result, there would be disordered neurodevelopment which is akin to schizophrenia. [sup][22] Electroencephalographic finding of cannabis use disorder, and Schizophrenia is also observed to be comparable. [sup][23] Decreased theta coherence is strongly associated with positive psychotic symptoms and also cannabis use. All these biological evidence to explain the association of cannabis and schizophrenia are speculative and need further replication.

Only a small fraction of people who use cannabis develop schizophrenia. This inconsistency points toward the possibility of the inherent vulnerability in this small portion of the population. Genetic susceptibility has been investigated in the last decade. The first evidence of such gene-environment interaction has been demonstrated by Caspi et al . [sup][24] who identified a functional polymorphism in the Catechol-O-methyltransferase gene which has low enzyme activity. The val homozygous allelic variant has low enzyme activity resulting into impaired degradation of monoamines and increased the level of dopamine which is implicated in the development of schizophrenia. It has been seen that people who are homozygous to val allele have 10 times higher risk of developing schizophrenia than those who have met allele. But the result of this study has not been replicated in another research. [sup][25] While many genes have been implicated, a sibling analysis and proband follow-up study conducted by van Winkel and the Genetic Risk and Outcome of Psychosis Investigators examined interactions between cannabis use and 152 single nucleotide polymorphisms in 42 candidate genes. [sup][26] The finding suggested that the variation in the AKT1 single nucleotide polymorphism may mediate both short-term as well as longer-term effects on psychosis expression associated with the use of cannabis. Dopamine (D2) receptor function has been mediated by AKT1, which is a serine-threonine kinase and acts through Glycogen synthase kinase 3 pathway. Overall, the evidence toward specific genetic vulnerability is inconclusive, and more research is warranted in this area to either accept or refute the existing knowledge.

There are some environmental factors which are postulated to mediate the effect of cannabis and influence the outcome. The presence of both childhood sexual trauma and cannabis use increases the risk of psychotic outcome. [sup][27],[28] This was recently replicated in the analysis of prospective data from two independent population-based studies. [sup][29] Urban upbringing is another social variable which also been brought into attention for increasing vulnerability toward the "psychotogenic" effect of cannabis. [sup][30],[31],[32] Like The biological explanation, this association is speculative and mostly indicative of cross-sensitization which is likely to be mediated by dopamine. [sup][33]

Though strong and conclusive evidence is yet to come, these genetic and environmental factors are expected to play a critical role in the progression of cannabis use to schizophrenia. Current consensus is that cannabis is neither necessary nor sufficient to cause schizophrenia. It is considered as a component cause for schizophrenia, including other environmental and genetic factors. Early and heavy use of cannabis compounded the risk further. [sup][34] [Panel 1] portrays the essential aspects of cannabis and schizophrenia research.

[INLINE:1]

Cannabis and other major psychiatric disorders

Another major question regarding the impact of adolescent cannabis relates to its role in negative affective disorders, like major depressive disorder, which are increasingly burdensome worldwide. Longitudinal studies reporting an association between cannabis uses and developing depression provide mixed results. In a recent meta-analysis, 57 studies were included for full-text review, of which 14 were included in the quantitative analysis (total number of subjects = 76,058). The odds ratio for developing depression in cannabis users compared with controls was 1.17. The odds ratio for heavy cannabis users developing depression was higher (1.62), compared with nonusers or light users. Meta-regression revealed no significant differences in effect based on age of subjects and the marginal difference in effect based on length of follow-up in the individual studies. [sup][35] There was large heterogeneity in the number and type of control variables in the different studies. Early cannabis use in the teens is also associated with increased suicidal ideation and attempts in the early adulthood. [sup][36] Importantly, accumulating evidence also implies that both adolescent exposure and the continued use during adulthood are required for these associations suggesting that the disease may be mitigated with cannabis cessation. [sup][37],[38]

Future longitudinal studies are clearly still needed to examine the contribution of the developmental period of onset and cessation of cannabis to the risk of negative affect. In addition, in vivo neuroimaging in humans can also offer much-needed neurobiological insights. Evidence already exists demonstrating volumetric impairments in the amygdala, a brain region central to affective and addictive disorders, in cannabis users during early [sup][39] and late [sup][40] adolescence. Similarly, structural changes in the hippocampus, which is linked to depression, [sup][41] have been reported in individuals with cannabis use

during late adolescence. [sup][42]

In the recent years, several animal studies have been conducted to explore about the negative affectivity following exposure to cannabis. Exposure to tetrahydrocannabinol (THC) in adolescent and especially female mice causes depression-like behavior in the forced swim test and sucrose preference test. [sup][43],[44] Findings suggest that adolescent cannabinoid exposure could affect the liability to mood disorders later in life, and the potential gender differences may relate in those well-documented in depression. Altered anxiety-like behavior as a consequence of adolescent cannabinoid exposure is apparent in experimental animals though the relationship is not straightforward. Anxiogenesis or anxiolysis has been reported depending on the period of cannabinoid exposure and the specific task used to model anxiety. For example, chronic exposure to cannabinoid agonists - such as THC during mid-to late-adolescence, increases social anxiety as measured with a social recognition task. Other measurements of stress that do not rely on social interaction, such as the open-field and elevated plus-maze tests, indicate varying degrees of anxiolysis, not anxiogenesis. [sup][45],[46],[47] These anxiolytic effects were observed after mid-to late-adolescent exposure, whereas earlier, prepubertal exposures were anxiogenic. [sup][48],[49]

[Panel 2] depicts the salient points with regard to cannabis and other major psychiatric disorders.

[INLINE:2]

Cannabis withdrawal syndrome

There has always been skepticism, whether cannabis can produce physiological dependence or withdrawal syndrome or even if it can, whether the syndrome is clinically significant enough to warrant a diagnosis. As a result of inconsistent or rather inadequate evidence, cannabis withdrawal syndrome (CWS) is not formally recognized in the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM IV). [sup][50] The diagnosis is listed, albeit without diagnostic criteria, in the International Statistical Classification of Diseases and Related Health Problems, tenth revision. [sup][51] Even after the publication of DSM IV-Text Revision, the confusion continued. In a review published in 2002, following pitfalls were pointed out in the existing literature. This review cited (1) the lack of controlled studies, (2) absence of definitions of withdrawal, (3) poor ecological validity, (4) failure to document severity of symptoms, and (5) inconsistent onset and offset of symptoms as the lacunae in research. [sup][52]

There are some human experimental and animal researches on this area after the review by Smith [sup][52] has been published. Three rigorous outpatient studies have been reported. These comprehensive prospective studies provided with adequate baseline data demonstrated clinically significant symptoms and a clear delineation of the time course of withdrawal. The results of these four controlled outpatient studies are remarkably consistent and provide validity for a cannabis abstinence/withdrawal syndrome. The generalizability of these studies is limited because the inclusion of only daily users likely produced more severe symptoms than if the light or nondaily users were studied. On the other hand, all four studies excluded treatment seekers, persons with significant psychiatric disorder, and persons who used other substances or abused alcohol. Exclusion of such participants likely resulted in less severe withdrawal symptoms than might have been observed if such participants were included. In addition to human subjects, discovery of the endogenous cannabinoid system, identification of cannabinoid receptors (CB1), and synthesis of a cannabinoid antagonist (SR141716A) made it possible to test for cannabinoid withdrawal in animals using a precipitated withdrawal paradigm. A review of this literature indicated that across multiple nonhuman species, the administration of SR141716A induced clear behavioral signs of precipitated withdrawal. In addition, the specific CB1 site for the action of this withdrawal effect has been determined by using CB1-knockout mice. [sup][53] These animal studies provide the biological plausibility of cannabis withdrawal. The concern regarding the reliability of CWS has also been addressed. Regarding cross-study reliability, the most consistently reported symptoms are anxiety, decreased appetite/weight loss, irritability, restlessness, sleep problems, and strange dreams. These symptoms were associated with abstinence in at least 70% of the studies in which they were measured. The common symptoms of cannabis withdrawal are primarily emotional and behavioral and do not typically cause significant physical, medical, or psychiatric disorders. However, this pattern does not mean that cannabis withdrawal is clinically unimportant. Other substance withdrawal syndromes (cocaine, nicotine) were included in the DSM in large part because of acknowledgment that behavioral and emotional withdrawal symptoms are as important, if not more important, than physical symptoms in undermining abstinence. To provide evidence on the clinical significance of CWS, observers suggested that symptoms are quite disruptive to daily living, making cessation difficult and comparable in terms of severity of tobacco withdrawal. [sup][54],[55] A recent study found out cannabis withdrawal is clinically significant because it is associated with functional impairment to normal daily activities, as well as relapse to cannabis use. Sample size in the relapse group was small, and the use of a nontreatment seeking population requires findings to be replicated in clinical samples. [sup][56] Overall, two extensive reviews on this area published in 2004 and 2006 and subsequent published studies of cannabis withdrawal substantiated the existence, biological plausibility, reliability, and clinical utility of CWS and finally, it has been formally included in DSM 5. [sup][57],[58],[59],[60],[61]

The DSM-5 differs somewhat from several prior proposed diagnostic criteria for CWS. [sup][62],[63],[64] These proposals varied in the content and length of the symptom list and the required number of symptoms. Chung et al ., [sup][64] provided a list of 22 symptoms whereas Budney and Hughes, [sup][62] proposed a list of 11 symptoms. DSM 5 resorted to seven symptoms drawing them from both the lists. The controversy is also about the threshold for diagnosis of CWS. While one study showed good concurrent and predictive validity for ≥4 symptoms, another study demonstrated ≥2 symptoms to be clinically significant. DSM 5 opted for a midway between the two and decided its threshold as ≥3 symptoms. A recent study evaluated the diagnostic criteria and findings supported predictive and concurrent validity of the same. [sup][64] But the same study suggested that the list of withdrawal symptoms and number required for diagnosis warrant further evaluation. [Panel 3] indicates the striking points for CWS.

[INLINE:3]

Cannabis and cognitive impairment

A large body of literature has accumulated over the last decade examining the effect of cannabis on cognitive performance and eventual functioning. The putative effect of cannabis on cognition is mediated by the CB1 (especially CB1) in the brain areas known to be associated with memory, attention, and other cognitive function. Discovery of the eCB system generated a new interest in this area.

Cognitive function can be affected by either acute or chronic use of cannabis. For demonstrating the acute effect of cannabis, studies have been conducted in both clinical and experimental population. Literature suggest that acute cannabis dose dependently, produces an adverse effect on a number of cognitive domains. Effects have been consistently observed on short-term memory, particularly immediate memory and recall and retrieval following a lapse of time. Cannabis also affects the ability to learn new information and sustained or divided attention. Cannabis intoxication influences the subjective perception of time too. Experimental studies have shown that cannabis can adversely impact decision making and executive function, though the results are not consistent. [sup][65] Chronic cannabis use is also associated with impairment in various cognitive domains. A recent study had demonstrated the detrimental effect on prospective memory ability in young adults using cannabis for a long time. [sup][66] But the subjects were not aware of their deficits. Many other studies additionally revealed effect on basic oculomotor control after chronic cannabis use. [sup][67] Regular cannabis user's performance on an auditory selective attention task was found to be significantly worse than the normal control. A few studies demonstrated significant deficits such as increased perseveration, decreased verbal learning and memory, and deficits in complex reaction and complex reasoning. [sup][68],[69] Early age of initiation of cannabis use and the prolong duration of use increases the possibility of such impairments. [sup][70] Chronic effect of cannabis in cognition is difficult to study because of methodological problems like effect of other confounding variables, possibility of preexisting cognitive impairment.

Next important question is whether the cognitive deficits are permanent? Available evidence has been inconsistent in this regard. Some studies have reported complete recovery of impairments even after 4 weeks of abstinence, whereas other studies describe persisting cognitive deficits in attention, memory, and executive function. [sup][71] One study suggests partial recovery. [sup][72] In a meta-analysis, residual impairment in verbal memory has most consistently been demonstrated. [sup][73]

The most intriguing question still remains. Whether there has been any functional significance of these cognitive deficits? The impact of cannabis intoxication on driving performance in real life setting is difficult and often impossible to determine. Studies using driving simulators and road tests have produced mixed results. Overall, driving skills and behavioral deficits have been encountered in close temporal proximity with cannabis ingestion and these are dose dependent. Combination of cannabis and alcohol which is a common pattern of use in the youth and young adult population clearly increases the risk of unsafe driving. [sup][74],[75],[76] In addition, cannabis has also been linked to low-grade point average, decreased academic satisfaction, poor overall performance in school, and absenteeism. But studies statistically controlled for the confounding variables produced mixed results. [sup][77] [Panel 4] suggests the relevant points regarding cannabis and cognitive impairment.

[INLINE:4]

New Domains of Research

Treatment for cannabis dependence/use disorders

In the last decade, there has been significant interest in cannabis treatment related research. The amount of pharmacological

treatment research overshadows the research in psycho-social intervention. Because of the understanding and acceptability of the existence, clinical importance, and reliability of cannabis withdrawal, treatment directed against withdrawal provides a new thrust in research.

Cannabis withdrawal symptoms are largely nonspecific and mostly begin during the 1 [sup]st week of abstinence and resolve after a few weeks. Because symptoms of cannabis withdrawal may serve as negative reinforcement for relapse to cannabis use in individuals trying to abstain, pharmacological treatment aimed at alleviating cannabis withdrawal might prevent relapse and reduce. Approaches to treat cannabis withdrawal can be classified into two broad groups: Treating withdrawal with agonist or treating by modulation of the neurotransmitter responsible for the symptoms. There were three published randomized trials on efficacy of dronabinol, which is a CB1 agonist. All these studies are in experimental subjects. Findings suggest that dronabinol is efficacious in ameliorating withdrawal symptoms. The dose range was variable, and sample size was very small except one study. Hence, the results are difficult to generalize. Divalproex, nefazodone, and bupropion were also tried in randomized trials, even in a clinical sample. The results were mostly negative. [sup][78],[80],[81]

Management of cannabis dependence aims at maintaining abstinence or through "harm reduction." Ongoing research is evaluating 3 major strategies for treatment: Agonist substitution, antagonist, and modulation of other neurotransmitter systems. Agonist substitution has been accomplished with dronabinol. There has been one randomized controlled trial (RCT) with dronabinol which did not improve abstinence but improved treatment retention. Neuromodulation has been carried out by various psychotropics. There were two RCTs of buspirone and fluoxetine each. Though the effect of buspirone is somewhat encouraging in reducing craving and improving abstinence, the effect of fluoxetine has been inconsistent. Naltrexone has also been tried in double-blind-RCTs with negative results. In an open-label trial, baclofen was observed to be effective for maintaining abstinence. N-acetyl cysteine is another medication which was used in another open-label study. Though there was a reduction in the self-reported use, urine cannabinoid levels did not replicate the subjective reporting. As an antagonist approach, rimonabant has been tried in a double-blind parallel group study and found to have a transient effect. Overall, neither a specific approach nor any particular medication has any unequivocal evidence. Duration of treatment is not well-defined. Even studies which have shown some positive results, generalization of those are limited by inadequate statistical power. Most of the studies have included psychosocial management in conjunction with pharmacotherapy. Hence, the relative contribution of each of these approaches is difficult to ascertain. [sup][82],[83],[84],[85],[86],[87],[88],[89],[90],[91],[92],[93],[94]

Various psychosocial interventions have been researched in the last decade. Perhaps, motivation enhancement therapy (MET) and contingency management (CM) were mostly investigated. For MET, number of sessions ranged from 2 to 4, and it is found to be effective in both short and mid-term (3-6 months) in reducing the use of cannabis. Randomized trials showed increased abstinence rate when CM is added to other psycho-social interventions like MET or cognitive behavior therapy. [sup][95],[96],[97] Sample size for these psycho-social interventions was reasonably large, and evidence is also consistent. But further replication is required. [Panel 5] refers to the salient points on the management of cannabis use disorders.

[INLINE:5]

Endo-cannabinoid system

Electronic search in the PubMed database with the search word "Endocannabinoids" yielded 186 results over the last decade as compared to the 50 results from 1993 to 2003. This figure itself indicates recent interest on this area. The eCB system modulates the neurotransmission at inhibitory and excitatory synapses in brain regions relevant to the regulation of pain, emotion, motivation, and cognition. [sup][98],[99],[100],[101],[102] In the last decades, investigation of the eCB system had considerably increased, and our understanding of this system has achieved remarkable aims. [sup][103] Endocannabinoids, the endogenous ligands, are polyunsaturated fatty acid derivatives that bind to CB1. Specifically, the two most common investigated endocannabinoids are the anandamide and the 2-arachidonoylglycerol which is synthesized "on demand" by the cell membrane in a tissue-specific manner, having prompt agonistic effects on the CB1 via., autocrine or paracrine mediated pathways. These eCB are released from the postsynaptic cell on demand in response to increase of intracellular calcium (Ca2 [sup]+). Triggered by either depolarization or activation of metabotropic glutamate receptors, and finally acting on the presynaptic terminals as a "retrograde messengers." The releasing mechanism is through an unknown mechanism. Therefore, endocannabinoids include many different types which are synthesized on demand, are not stored in vesicles; are not released from presynaptic terminals, and are not specific. [sup][104] Two types of CB1 have been characterized to date: CB1 and CB2 receptors, both metabotropic receptors coupled to Gai/o proteins. Though CB1 receptors are located ubiquitously throughout the brain, CB2 receptors, which were once thought to be located in the extra brain areas, are now known to be present in different brain regions under normal physiologic conditions. [sup][105],[106] The role of eCB system in various psychiatric disorders has been investigated. Disequilibrium or malfunctioning of the eCB system might contribute to the etiology of anxiety-related disorders, [sup][104],[107] whereas the pharmacological enhancement of e-CB activation may provide a promising therapeutic

tool for the management of such disorders. [sup][107] Given the successful results accomplished in animal studies, great expectations exist for the future clinical exploitation of this system. As for anxiety disorders, a dysfunction of the eCB system has been proposed to be in the bases of depression. [sup][109],[110],[111] Enhancing the levels of eCBs by inhibiting their deactivation has become a promising antidepressant strategy. [sup][108],[112] In contrast, inactivation of CB1Rs can have detrimental consequences provoking depressive-like symptoms. In fact, rimonabant adverse effects included not only increased anxiety, but also depression and suicidal ideations. [sup][113],[114],[115],[116] For Schizophrenia, there has been accumulating evidence from the animal research. In spite of the current discrepancies regarding CB1R changes in animal models of schizophrenia, present findings point to the eCB system as a pivotal neuromodulatory pathway that may have a critical relevance in the psychotic-related behaviors observed in these animals, that is, altered emotionality and social and cognitive deficits. [sup][117]

The distinctive role of cannabidiol (CBD) has also been examined. CBD is the main nonpsychotropic phyto cannabinoid found in the Cannabis sativa plant, constituting up to 40% of its extract. Recent comprehensive reviews indicate that CBD is one of the most promising candidates for therapeutic use in a wide range of disorders, including neuropsychiatric. [sup][118],[119],[120] Leweke et al . [sup][120] found that CBD significantly reduced psychotic symptoms in acute schizophrenia with potency similar to amisulpride but with fewer side effects such as extrapyramidal symptoms, increase in prolactin, and weight gain. The mechanism of its antipsychotic action is still elusive. [Panel 6] alludes to the summary of eCB system in psychiatry.

[INLINE:6]

Though there are fleeting reviews on amotivation syndrome, [sup][121] overall the interest has waned off in this domain. Even a recent paper on this area concluded "cannabis does not impair motivation. Its impact on subjective well-being is small and may actually reflect lower well-being due to medical symptoms rather than actual consumption of the plant." [sup][122] Cannabis psychosis, another area which had gained special attention in the previous decades, has been ignored largely of late. Acknowledging the same, a recent review failed to find out any distinctive psychopathology in cannabis psychosis as compared to the other forms of psychosis. However, they were guarded in their interpretation and had proposed further research in this area to make conclusive remarks on the existence and validity of cannabis psychosis. [sup][123] Cannabis-induced flashback is the other area which has been seldom discussed in the last decade.

Indian research

There has been only a handful of research on cannabis from India in the last decade. One study attempted to research the clinical presentation of cannabis-related psychosis and effect of abstinence. 22 consecutive male subjects were recruited for the purpose of the study, and they were followed-up in a controlled environment for the next 7 days. Assessment was done with Brief Psychiatric Rating Scale. Results demonstrated that the cannabis-related psychosis presented with a predominantly affective psychosis and prominent thought disorder, excitement, and violence. All subjects showed improvement in symptoms with abstinence from cannabis. [sup][124] Another study aimed to understand the influence of cannabis on cerebral glucose metabolism in certain predetermined regions of interest. 2-fluoro, 2-deoxy-glucose-positron emission tomography (FDG-PET) has been carried out in 16 cannabis-dependent subjects who had recently consumed cannabis and an equal number of noncannabis using volunteers. The two groups differed in their lateral and medial temporal glucose uptakes by approximately 16-24%. Significant differences in inter-regional correlations in the medial temporo-frontal and parieto-thalamic were noted between the two groups. These results suggested that at least a part of the cortico-subcortical relationship is altered among cannabis users. [sup][125] A similar study by the same group of researchers using FDG-PET purported to understand the patterns of glucose uptake in important brain regions among individuals with cannabis dependence and schizophrenia. Significant differences were noted among individuals with cannabis dependence and schizophrenia in the medial and lateral temporal regions. Study findings suggested that cannabis dependence can alter interregional relationships in a manner similar to schizophrenia. [sup][126]

Conclusion

In the last 10 years, in addition to the usual clinical and phenomenological research, there has been an upsurge of biological research in cannabis. By and large, it is in concordance with the research interest in addiction. Nevertheless, the discovery of e-CB system as a neuromodulator has opened up an opportunity for additional research for the understanding of neurobiology and treatment of various psychiatric and addictive disorders. The existence, validity, reliability, and clinical importance of cannabis withdrawal have been acknowledged, and it has found a place in the current psychiatric nosology. The association of cannabis and Schizophrenia has been studied further. There has been better-controlled longitudinal research, including meta-analysis to explore the baffling association. Current consensus alludes to the possibility of "component causality." There has also been

some research to find out the genetic vulnerability for the development of Schizophrenia following cannabis use. Cannabis and cognitive impairment has been investigated further. Though there is unequivocal evidence of acute and chronic effect of cannabis in cognitive function and the domains of cognition affected, evidence for the reversibility of these dysfunctions is mixed. Moreover, the effect of such cognitive impairment in functionality is also a matter of controversy. Though there are various treatment-related researches, the evidence for drug treatment to maintain cannabis abstinence is still preliminary and inconclusive.

Overall, the journey of cannabis research in the last decade was innovative enough to excite the scientific community, conclusive enough at least in some areas to settle down controversy and still uncertain enough in few domains to keep the quest for answers alive.

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Cannabis Dependence: Effects of Cannabis Consumption on Inter-Regional Cerebral Metabolic Relationships in an Indian Population

By Parkar, Shubhangi; Ramanathan, Seethalakshmi; Nair, Narendra; Batra, Shefali; Adarkar, Shilpa; Pandit, Anirudh; Kund, Purushottam; Baghel, Nawab

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Background: The effects of cannabis consumption on neurophysiological function have been a matter of considerable debate. With the legalization of medical marijuana, understanding the consequences of cannabis dependence has become extremely important. Aim: We attempted to understand the influence of cannabis on cerebral glucose metabolism in certain predetermined regions of interest (ROIs). Furthermore, we also explored inter-regional metabolic relationships between ROIs forming the "addiction" and "cognitive dysmetria" circuit. Materials and Me thods: 2-fluoro, 2-deoxy-glucose positron emission tomography (FDG PET) scans were carried out in 16 male patients (age: 25.3[+ or -]10.38 years) with cannabis dependence, 8-12 hours after the last cannabis consumption. Resting glucose uptake in 14 pre-determined ROIs was compared with glucose uptake in 16 non-drug using volunteers (age: 29.2[+ or -]8.39 years). Results: The two groups differed in their lateral and medial temporal glucose uptakes by approximately 16-24%. The relationships between inter-regional glucose uptakes in the two circuits were compared using the Chow Test. Significant differences in inter-regional correlations in the medial temporo-frontal and parieto-thalamic were noted between the two groups. Conclusion: The altered metabolic relationships among various brain regions can have potentially important implications for understanding cannabis dependence and cannabis-induced psychopathology.

Introduction

The effect of cannabis on neurophysiological functioning has been a topic of interest for many years. Recent evidence of possible schizophrenogenic potential has brought cannabis back into the limelight. On the other hand, medical marijuana is also gaining rapid interest for its "neuroprotective" properties. It has, therefore, become essential to affirm the neuropsychiatric effects of cannabis. Furthermore, in some developing societies such as India, the use of cannabis enjoys religious sanction. Indeed, India has seen a significant rise in the prevalence of cannabis dependence. A national survey, carried out in 2003, noted that approximately 8.75 million people reported using cannabis. Of these, only a quarter (or 2.3 million) had ever sought

treatment for cannabis use. [sup][1] Considering the magnitude of cannabis dependence and possible serious neuropsychiatric consequences, a neuroimaging study examining the influence of cannabis on cerebral glucose metabolism in an Indian population is clearly warranted; however, none has been carried out till date.

Effects of cannabis on glucose metabolism

Cannabis acts through CB1 receptors that have been identified in varied regions of the brain, including the cerebellum, basal ganglia and the hippocampus. [sup][2] A number of functional imaging studies have identified a wide range of changes in cerebral functioning in cannabis users in various stages of cannabis use and dependence. [sup][3],[4] Functional imaging studies examining individuals with cannabis dependence during periods of withdrawal are few. Block et al . [sup][5] examined cerebral metabolic rate in cannabis users following 26 hours of abstinence, a period that can be considered as subclinical withdrawal. They noticed that on a memory-based task, individuals with cannabis dependence demonstrate different activation patterns as compared to non-using controls. A second functional magnetic resonance imaging (fMRI) study [sup][6] conducted within 6-26 hours of last cannabis consumption noted that individuals with cannabis dependence recruit more areas on a spatial working memory task as compared to normal non-drug using controls. Based on these, we formed our first hypothesis.

Hypothesis 1

Individuals with cannabis dependence have different regional glucose metabolisms as compared to non-drug using controls. As we planned to avoid the immediate effects of cannabis intoxication, we selected a time frame of 8-10 hours after last cannabis consumption.

Influence of cannabis on neural networks

Cannabis has been identified as having "seemingly contradictory neurotoxic and neuroprotective effects". [sup][7] It has been suggested that cannabis can act as a modulator of synapses and, thus, potentially disrupts neural networks. Most studies examining neural networks have primarily used blood oxygenation-level dependent-fMRI (BOLD-fMRI) measurements. For our 2-fluoro, 2-deoxy-glucose positron emission tomography (FDG PET) measurements, we assumed that regions that are part of a circuit/network would share a specific and directional metabolic relationship that enables adequate functioning of the circuit. We explored regions involved in two circuits. The first one is the circuit involving the frontal, medial temporal and thalamus that has been implicated in substance dependence. [sup][8] Further, considering the controversial role of cannabis in schizophrenia, we investigated the circuit for cognitive dysmetria in schizophrenia - cortical-subcortical-cerebellar circuitry. [sup][9] This forms the basis of our next three hypotheses.

Hypothesis 2

There would be significant differences in inter-regional metabolic patterns between individuals with cannabis dependence and non-drug using volunteers in the substance dependence circuit.

Hypothesis 3

As neither individuals with cannabis dependence nor non-drug using volunteers have any symptoms suggestive of schizophrenia, there should be no differences in the cortical-subcortical-cerebellar circuitry.

Materials and Methods

The study was conducted by the de-addiction center (psychiatry department) of a tertiary care hospital in collaboration with the Radiation Medicine Centre, Bhabha Atomic Research Centre, during January 2004 - December 2005. Approval for the study was obtained from the Institutional Review Boards of both the institutions.

Subjects

Sixteen male patients with a DSM-IV diagnosis of cannabis dependence [sup][10] and ongoing cannabis consumption were invited to participate in the study (Group I). The diagnosis was made by two qualified psychiatrists using a semi-structured interview of the participant and corroborated with a reliable family member/guardian. Comorbid Axis I diagnosis, benzodiazepine intake in the last 6 months, past or current history of any neurological or medical illness were ruled out. The control group (Group II) comprised 16 consenting right-handed, non-drug using male volunteers with no history of past or present Axis I diagnosis. Only males were invited to participate in the study to avoid all possible gender confound.

Consenting participants completed a semi-structured questionnaire detailing duration and amount of cannabis consumption. Cannabis consumption was confirmed by urine thin layer chromatography, prior to participation in the study. No quantitative assessment was, however, carried out. All the participants smoked cannabis in cigarettes. None of the participants in either group had any past or present history of other substance dependence, except nicotine. Exclusion of other substance dependence, including opiates and alcohol, was confirmed by urine drug screening. Further, as the participants were not in a controlled environment prior to the scan, these urine toxicology screens were repeated prior to the scan.

Study participants continued their ongoing pattern of consumption, their last consumption varying from 10 to 12 hours prior to the scan. At the time of the scan, none of the participants reported any symptoms of cannabis intoxication or withdrawal. Subjects were also requested to refrain from nicotine and caffeine for at least 8 hours prior to the scan.

FDG PET procedure

The standard FDG PET protocol was followed. F18-FDG [sup][11] is produced in a 16.5-MeV Medical Cyclotron Facility located in the center that hosts the scanner (Radiation Medicine Center, BARC, Mumbai). Participants were fasting for at least 8 hours prior to the scan and showed a blood glucose level of <150 mg/dl. An average dose of 200 MBq (160-230) of F18-FDG was injected. Acquisition was carried out 30 minutes after the injection. Positioning was achieved with the help of LASER align lights and head was secured with restraints to minimize artifacts due to movement. The pattern of cerebral glucose metabolism was examined using F-18-FDG with a GE Advance PET System scanner NXI (General Electric Medical Systems, Milwaukee, WI, USA). The scanner has a transaxial resolution of 4.8-6.2 mm full width half maximum (FWHM) depending upon the distance from the center and an axial resolution of 4.0-6.6 mm FWHM. Emission scans of 70 slices were obtained parallel to the cantho-meatal line from vertex to the neck. Transmission scans were obtained for the same region using Ge-68 rod sources to carry out measured attenuation correction. The images were reconstructed using the Ordered Subsets Extraction Maximization (OSEM) algorithm. These images were reformatted and converted into 35 transaxial slices of 4.25 mm thickness.

Analyses

Regional glucose metabolism was examined in 14 pre-determined Regions of Interest (ROIs) - elliptical ROIs for cortical and subcortical structures and circular ROIs for cerebellar hemispheres. For the purpose of selection of ROIs, the slice of the brain through the basal ganglia was taken as reference slice. One slice above and below was checked for maximum uptake values (mUVs) for each ROIs. For the cerebellum, midcerebellar slice was selected. ROIs considered were the following:

*prefrontal regions (right and left), *temporal (right, left, medial and lateral), *parietal (right and left), *occipital (right and left), *basal ganglia (right and left), *thalamus (right and left) and *cerebellum (right and left).

The regional activity in a given ROI was measured as the mUVs in that ROI (kBq/ml).

During qualitative assessment, it was observed that in a majority of the patients, the occipital lobes showed maximum FDG uptake. Additionally, most studies examining influence of cannabis on Cerebral blood flow have failed to report any changes in the occipital lobe in cannabis users [Table 1]. [Figure 1] provides illustrative images from each group demonstrating the uptakes in the various brain regions. These are not SPM images. These are normalized images, however from single participants of each group. Hence, the average of the occipital lobe activity uptake values was taken as the normalizing factor. Hence, results related to these regions were not reported. The glucose uptakes in the other ROIs were expressed as relative uptake values (rUVs) - ratio of uptake value for ROI to average uptake value for the occipital lobes. Analysis was carried out using these rUVs in the various ROIs.{Table 1}{Figure 1}

Data were analyzed using STATA/SE 9.2 (Stata Corporation, College Station, TX, USA).

Finally, in order to understand differences in the inter-regional correlations of the rUVs, we used linear regressions combined with Chow Tests to test if the correlation between two regions were different between cannabis users and non-drug using controls. As an example, when examining the efferent relationship from frontal to medial temporal ROIs, we fitted two linear regressions, one for each group, with frontal rUVs as the independent variable and medial temporal rUVs as the dependent variable with an age correction (the age correction was used to avoid any confounding influences of age on inter-regional metabolic relationships). The Chow Test is a Chi-square test used to test whether the slope coefficients in these two regressions are statistically different. In the above example then, a positive test indicates that the efferent relationship from the frontal ROI to the medial temporal ROI is statistically different between the two groups.

Results

Sample characteristics

The mean age in both groups [Group I: 25.25 years (SD: 10.38, range: 16-50); Group II: 29.55 years (SD: 8.39, range: 18-48)] was comparable (P >0.05). The mean age at onset of cannabis consumption was 16.2 years (SD: 3.6 years, range: 10-23 years); duration of consumption varied from 6 months to 40 years (mean: 8.6 years). All participants smoked cannabis in cigarettes. The patients spent an average of Rs. 60.60 per day (Rs. 20-Rs. 150) (1 British pound was approximately Rs 80 during the period of the study). This amount spent on cannabis is reflective of the quantity of cannabis consumed, in terms of potency. We have chosen not to involve the amount of cannabis consumed in weight as this would not have been a true reflection of the potency of cannabis. In India, the rates of cannabis (at the time of this study) ranged from Rs. 10 to Rs. 50 for 10 g depending on the quality of cannabis. In other words, a user might be consuming smaller quantities of unadulterated, yet pure, cannabis with higher potency. Daily consumption in our sample ranged from 10 to 30 g of cannabis.

Regional glucose metabolism in cannabis users compared to non-drug using controls (independent sample t -test with Bonferroni correction)

Mean rUVs were higher in bilateral lateral temporal regions in the cannabis dependent group as compared to non-drug using controls. The higher metabolism in the left lateral temporal region remained statistically significant with the Bonferroni correction (P 0.003). In all the other ROIs examined, rUVs were lower in the cannabis dependent group than in the non-drug using controls. After correcting for multiple comparisons, this decrease was statistically significant in the medial temporal regions (P 0.003, 0.007). We further ascertained that these differences were not influenced by age, using regression analysis [Table 1] [Figure 1].

Influence of duration and amount of cannabis consumption on glucose uptake (Group I) (Pearson's correlation with Bonferroni correction)

Significant correlations were noted between duration of cannabis consumption and right cerebellar uptake; amount of cannabis consumption correlated significantly with right parietal and occipital glucose uptake values. However, none of these significances survived Bonferroni correction for multiple comparisons. An additional correlation was attempted with a composite cannabis consumption (CCC) value (a measure of estimated lifetime cannabis consumption). This was derived as the product of amount of cannabis consumption with duration of cannabis consumption. No significant correlations were noted between this CCC and glucose uptake in any of the ROIs. Age at first consumption did not influence glucose uptake in any ROI.

Inter-group differences in metabolic relationships among the different ROIs

Metabolic relationship between the frontal-medial temporal-thalamus ROIs implicated in addiction

When we examined the relationships between regions implicated in addiction (frontal-medial temporal and frontal-thalamus), the afferent and efferent relationships between frontal, medial temporal regions and the thalamus were significantly different. However, after correcting for multiple comparisons (Bonferroni correction), only the relationship between the frontal and the medial temporal regions (P 0.05, 0.02) remained significant, albeit with a hemispheric difference [Table 2].{Table 2}

Metabolic relationship in the cortical-subcortical-cerebellar circuitry implicated in cognitive dysmetria

In the unidirectional relationship between the cerebellum-thalamus-frontal and parietal cortices, significant differences were noted in the subcortical-cortical relationships (i.e., the thalamus-parietal relationships) [Table 3]. This difference in parietal-thalamic relationship (P - 0.01, 0.001) persisted after correcting for multiple comparisons.{Table 3}

[Figure 2] illustrates the afferent (upper row) and efferent (lower row) relationship of the frontal region with the medial temporal region. Each graph in upper row of [Figure 2] plots the rUVs of the frontal region (dependent variable) on the Y -axis and rUVs of the medial temporal region (independent variable) on the X -axis. In addition, it also includes two linear best fits based on linear regressions, one for each group. [Figure 3] provides similar plots for the unidirectional relationships from the cerebellum-thalamus-frontal and parietal regions (independent variable on the X -axis) to other ROIs (dependent variable on the Y -axis). In all these, the inter-regional relationships were more negative in the cannabis users. In other words, cannabis users showed a significantly smaller correlation (as measured by the slope-coefficient of the regression) between the various ROIs than the control group.{Figure 2}{Figure 3}

In order to understand the influence of amount of cannabis consumption on the results that were statistically significant, we divided individuals with cannabis dependence into two groups based their CCC (high and low). The results were mixed and not statistically significant. In the substance dependence circuit, the significance was positively correlated with increasing CCC, while no trends emerged in the cognitive dysmetria circuit. These results need to be interpreted with great caution as the sample sizes in the two groups were very small.

Discussion

Lower resting global cerebral blood flow has been reported in abstinent cannabis users as compared to non-users. [sup][12] Similar to this, in our study, we noted decreased glucose uptake in most brain regions among cannabis users. Additionally, we also noted differences in the lateral temporal uptakes, consistent with the effects of cannabis effect on temporal auditory areas. [sup][13] However, some of our findings were contrary to earlier observations. For example, increased bilateral medial temporal uptake has been reported in cannabis intoxication [sup][13],[14] and supports the effects of cannabis on emotions and mood. In our study, glucose uptake was significantly lower in the medial temporal lobes among cannabis users as compared to non-drug using controls. Another consistent finding that was not replicated in our study is difference in cerebellar uptake. [sup][14],[15] The most likely explanation for these differences is that our study differs from the earlier mentioned studies in the temporal stage of cannabis use. The last cannabis consumption in our study was 10-12 hours prior to the scan, while in the earlier studies, patients were scanned within 30-40 minutes of cannabis consumption. This difference in time from cannabis consumption is most likely responsible for the differences in metabolism that we noticed in our study. It can be speculated that the subjects in our study were in a stage of subclinical cannabis withdrawal (subjects denied any subjective withdrawal symptoms), which is reflected in a decreased medial temporal uptake.

Cannabis intoxication has been known to result in dose-dependent changes in regional blood flow. [sup][16] In our study, however, the uptake values were not influenced by either the duration or the amount of cannabis consumed. Further, Chang et al . [sup][17] have suggested that age at first consumption may affect neural changes noted in cannabis users. We were, however, not able to replicate this observation.

Neuronal integrity is important for a number of cognitive and emotional tasks. Neural pathways in the medial temporal structures (nucleus accumbens, amygdala), frontal and ventral tegmental areas have also been identified in the mechanisms of substance dependence. A number of pathways involving the medial temporal, frontal, parietal and cerebellar structures (limbic, neocortical and cortical-subcortical-cerebellar networks) [sup][9],[17] have been implicated in various symptoms of schizophrenia. These formed the basis of our remaining hypotheses. In agreement with our second hypothesis and consistent with the diagnosis of substance dependence, cannabis users exhibited different metabolic relationships between the frontal and medial temporal regions. Surprisingly, differences were also noted in the parieto-thalamic portion of the cortical-subcortical-cerebellar circuit, suggesting that at least a part of the cortico-subcortical relationship is altered among cannabis users. This disproves our third hypothesis.

A Diffusion tensor imaging study by DeLisi et al.[18] concluded that moderate cannabis use does not affect neuronal integrity in growing adolescent brains. More recent work by Ashtari et al.[19] contradicts this and suggests that cannabis can indeed affect developing neurons particularly in the fronto-temporal connection. Chang et al . [sup][20] noted that individuals with cannabis dependence recruit cognitive "reserve" regions to compensate for disrupted visual attention networks. Our findings of impaired cortical-subcortical-cerebellar circuit indicate toward a disruption in one of the cognitive networks, more specifically cognitive dysmetria. While this finding suggests that cannabis dependence can lead to cognitive dysmetria similar to schizophrenia, it does not conclusively establish that cannabis use leads to schizophrenia.

Influence of nicotine

One factor that needs to be considered while interpreting these results is the role of nicotine. Nicotine use decreases global cerebral metabolism and increases normalized glucose metabolism in the inferior frontal cortex, posterior cingulate gyri, and the thalamus. [sup][21] In order to examine the influence of nicotine on our results, we decided to conservatively assume that comorbid nicotine use indeed influenced the differences in metabolism between cannabis users and non-drug users and that nicotine was being abused only by individuals with cannabis dependence. Considering this, nicotine could have contributed to the global decrease in metabolism. However, the influence of nicotine on individual ROIs can be ruled out to some extent. Glucose uptake in the thalamus and medial temporal regions was low in cannabis users as compared to the normal individuals, which is contrary to the effects of nicotine. Nicotine has a half-life of 1 hour, and most work [sup][22] on the influence of nicotine on cerebral blood flow and metabolism have assumed that the influence of nicotine wears off in approximately this time period. Participants were instructed to refrain from nicotine use in the 8-10 hours prior to the scanning process; however, nicotine dependence was not strictly controlled for. However, regional metabolism in our study could have been influenced by a

craving for nicotine, although patients denied any subjective experience of craving.

Limitations

The study was limited in that details regarding cannabis consumption were based on participant self-report. [sup][23] Further, we have reported the quantity of cannabis in terms of amount of money spent rather than the weight, as the amount spent reflects the true potency. The most accurate assessment would have been plasma Tetrahydrocannabinol levels, which we were unable to perform. This study is also technically limited by the application of the manual method of analysis instead of Statistical Parametric Mapping (SPM), which also constrains anatomical micro-definitions. The main reason for this was that our images were not in the DICOM format essential for using SPM. However, in order to avoid the operator-based errors of this method, we ensured that the same blinded neurodiagnostician reported all the scans. Additionally, some studies [sup][20],[24] have suggested that the neurotoxic effects of cannabis may be reversible. The present study is a cross-sectional one; hence, definite conclusions regarding causality cannot be drawn. Longitudinal studies examining these relationships are required to clarify if the alterations in neuronal relationships are the result of cannabis use.

To conclude, the study reaffirms the global decrease in glucose metabolism associated with cannabis consumption. Importantly, this study confirms that cannabis dependence can alter metabolic relationships between important cerebral regions, indicating changes in neuronal circuits. If the disruption in relationships between the various regions noted in cannabis users in our study persisted as long-term changes, this could explain not only cannabis dependence but also the cognitive and emotional disorders arising from cannabis use.