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Abstract

*Background*: Marijuana is the most widely used illicit substance in the United States and self-reported use has remained steady over the past decade. Numerous publications examine the influence of marijuana use on various facets of human physiology including neurocognitive function, immune function, and illness symptom control, each discussing marijuana's influence in a narrow or compartmentalized fashion. However, there is a scant literature discussing the empirical and clinical implications of the intersection of these constructs. The primary objective of this review is to review and synthesize this disparate literature and propose future research directions. Thus, this review examines the literature that relates the influence of marijuana on (1) neurocognitive function; (2) immune function; and (3) treatment uses and (4) propose future directions. *Methods*: Clinical and non-clinical empirical studies were collected and utilized to inform this review. The authors used PubMed search engine as the primary mechanism used to identify relevant articles. *Conclusion*: Given the legalization efforts of recreational marijuana use, there is a need to discuss health and treatment effects of marijuana use from a more comprehensive, psychoneuroimmunological, or biopsychosocial framework. We will discuss the need for an interdisciplinary research and future steps regarding the examination of marijuana use.



Keywords (separated by "-")

Marijuana - Immune function - Cytokine - Cognitive function - Imaging - Cannabinoids

# The Psychoneuroimmunological Influences of Recreational Marijuana

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**Keywords** Marijuana • Immune function • Cytokine • Cognitive function • Imaging • Cannabinoids

# 1 Introduction

## *1.1 Foundation and Statistics*

Marijuana is the most widely used illicit drug in the United States, with approximately 5.7 million people above the age of 12 reporting daily marijuana use over the past year [1]. Approximately 19 million individuals report using marijuana in the past 30 days [1] and nearly 9% of individuals who use marijuana meet the criteria for dependence or abuse [2]. Marijuana has been used for various recreational and medicinal reasons for over 200 years [3]. In fact, it is possible that the cannabis plant has been used for medical purposes since 2737 BC [4] and may be the oldest psychotropic drug [5].

Given the recent movement for the legalization of marijuana in the United States over the last decade, 23 states and the District of Columbia have legalized marijuana in some form, which portends an increase in marijuana users in the coming years. This forecast is based on the idea that marijuana use is directly related to changes in the risk of legal punishment [6]. With decreases in legal ramifications for marijuana use or possession, more individuals may report using. As the routes of administration expand from smoking marijuana to utilizing edibles and vaporizing butane hash oil, marijuana use is becoming widely more acceptable than in previous decades. Additionally, the National Institute on Drug Abuse has suggested that given the evolution of marijuana growth, marijuana may actually be increasing in Delta 9-tetrahydrocannabinol (THC), the main psychoactive compound in marijuana [2]. This idea has not been well examined in the epidemiological or psychopharmacological literature, as many studies are focusing on any use of marijuana and not examining the specified types used recreationally. This suggests that individuals who are newly initiated into marijuana use may be at higher risk for any negative effects of the drug [2].

In general, marijuana is seen as a "gateway" drug, leading to subjectively more harmful drugs [7]. However, this position has become more controversial, given competing theories [8, 9]. Empirically, there have been many studies examining marijuana's influence on various physiological states [10], pathological conditions [11], and neurocognitive outcomes [12]. However, to date, researchers have not examined the intersection among these constructs and their subsequent potential influences on health outcomes. This notion is substantiated by a PubMed search using keywords representing each field, such as "marijuana," "immune function,"

and "cognition" (and their variants), yielding less than eight results. None of which examine the intersection of these constructs relative to epidemiological constructs or health outcomes. This is imperative, as fields become more interdisciplinary and treatment or care programs are looking to generate more comprehensive forms of care.

### *1.2 Theoretical Framework*

Overall, there is a large amount of research that examines marijuana use with decision-making processes [13], a cellular literature that examines marijuana use and disease susceptibility [14], but the authors are unaware of any current studies that incorporate each of these components in the same statistical or theoretical model. Historically, previous research has attempted to provide interdisciplinary models, such as the psychoimmunological model, which calls for an integration of psychological factors in addition to immune factors to elucidate the mechanisms involved in disease conditions [15]. There are models that include the physiological systems needed for a comprehensive view of marijuana's influence on the human body, such as Maier and Watkins. Maier and Watkins [16] posited bidirectional pathway that connects the immune system to the brain. The authors suggest that through this bidirectional pathway, much of the complex interplay between psychological phenomena and adaptive immune response can be examined. Unfortunately these authors did not include an environmental or behavioral component that could account for substance use. There are conceptual models that would fit this paradigm, such as the biopsychosocial model, which attempts to integrate various mechanisms in order to mitigate disease or identify primary vectors [17]. The current review looks to present different components in the empirical literature to in hopes of substantiating a psychoneuroimmunological model of recreational marijuana use and infectious disease susceptibility.

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## 2 Marijuana and Neurocognitive Function

### *2.1 Marijuana Constituents and Function in CB1Saturated Cortical Regions*

Marijuana contains over 60 different cannabinoids, but only two constituents are currently the main focus of research: Delta 9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Previous research suggests this is due the role of THC as the main psychoactive constituent and CBD's role as the most abundant naturally occurring constituent [18, 19]. While CBD does not appear to impair cognition [20, 21], THC is thought to be the primary constituent that influences neurocognitive

performance [22, 23]. THC binds to the Cannabinoid-1 receptors (CB1), which are distributed in various areas of the central nervous system. Generally, CB1 receptors are found presynaptically in cortical areas that are responsible for the behavioral and pharmacological effects of marijuana use. These areas include the dorsolateral prefrontal and orbitofrontal regions, motor areas, hippocampus, amygdala, the striatum, and the cerebellum [19, 24]. The preponderance of CB1 receptors in the central nervous system suggests that the introduction of exogenous cannabinoids in the human body would interfere with normal neurocognitive processes governed by these brain regions when levels of this substance exceeded values required for normal functioning of the cannabinergic system [22, 25]. For example, due to the high densities of the CB1 in the cerebral cortex, the hippocampus, and the basal ganglia, previous research suggests cannabinoids are involved in attentional and memory processes, as well as executive functions as these areas are the neural substrates for these specific neurocognitive domains [12, 26–28]. Much of the early research into the neurocognitive consequences of marijuana use focused on acute intoxication with the inference that it lead to impairments in memory and attention (see [29, 30] *for review*). However, later examinations, as with this review, focus more on the non-acute effects, which are less clear cut, but show more diffuse deficits.

## 2.2 *Marijuana and Neuroimaging Studies Findings*

Neuroimaging studies have begun to examine the neural substrates underlying the neurocognitive consequences of marijuana use, with varying results. Specifically, resting state examinations using positron emission tomography (PET) during acute intoxication have shown an increase in global metabolism and regional metabolic increases in the orbitofrontal cortex, prefrontal cortex, and basal ganglia in long-term marijuana users that was not seen in non-users [31–35]. Moreover, while there were minimal to no differences between groups on task performance, PET and functional magnetic resonance imaging (fMRI) studies involving neurocognitive challenge have reported differential activation during executive functioning and memory tasks between recently abstinent marijuana users and non-drug using controls. For example, PET examinations have indicated that chronic marijuana users show decreased blood flow in the prefrontal cortex (PFC), increased blood flow in the cerebellum, and altered lateralization of the hippocampus for memory tasks when compared to non-drug using controls [36]. Previous research utilizing PET also suggests hypoactivity in the anterior cingulate and prefrontal cortices, and hyperactivity in the hippocampus during executive functioning tasks [37]. Interestingly, neither Block (nor [37]) found differences in the actual performance on the neurocognitive tasks, despite the differential activation in different cortical regions. Examinations of brain activation in recently abstinent chronic marijuana users using fMRI indicate increased activation in the PFC, anterior cingulate, and basal ganglia when compared to controls ([38–40]. This line of research posits that both resting state and activated neuroimaging paradigms indicate changes in metabolism and

**Table 1** Marijuana's influence on cortical regions and structures

| Type of study | Duration | Outcome | Source | |
|---|---|---|---|---|
| Resting state PET | Acute | Increases in global brain glucose metabolism with marked increases in the specific regions of the orbitofrontal cortex, prefrontal cortex, and basal ganglia | [31–33, 35] | t3.1 |
| Resting state PET | Acute | Global increases in cerebral blood flow with marked increases in the regions of the prefrontal cortex, anterior cingulate, and the insular cortex | [32–34] | t3.2 |
| PET with memory task | Non-acute | Decreased cerebral blood flow in the prefrontal cortex, increased cerebral blood flow in the cerebellum, and altered lateralization of the hippocampus | [36] | t3.3 |
| PET with executive function task | Non-acute | Hypoactivity in the anterior cingulate and prefrontal cortices, and hyperactivity in the hippocampus | [37] | t3.4 |
| fMRI with memory task | Non-acute | Increased global brain activation with marked increases in the prefrontal cortex, anterior cingulate, and basal ganglia | [38, 39] | t3.5 |
| fMRI with executive function task | Non-acute | Increased activation in the prefrontal, insular, and parietal cortices | [40] | t3.6 |

*PET* positron emission tomography scan, *fMRI* functional magnetic resonance imaging



activation in cortical areas responsible for neurocognitive processes in marijuana users [12]. Similarly, heavy, long-term recently abstinent marijuana users show more widespread brain activation than controls when attempting a spatial working memory task [39]. These results suggest that even in the absence of performance differences, marijuana users display persistent metabolic and activation alterations in the brain. The results of neuroimaging research that demonstrate the effects of marijuana on the brain are presented in Table 1.

Previous research suggests that the enhanced brain activity demonstrated by marijuana users indicates a need for increased neural effort or a change in strategy to meet task demands and maintain good task performance [41]. This would account for the lack of differences reported between marijuana users and controls to be subtle. Neurocognitive examinations of marijuana use's consequences posit deficits in attention [42–45], memory [21, 39, 46], processing speed [43], verbal learning [43, 47–52], and executive function [46, 49, 53–59].

## 2.3 *Marijuana, Neurocognition, and Study Discrepancies*

Most researchers agree that the neurocognitive dysfunction related to marijuana use extends beyond the period of intoxication, but how far beyond that period has less of a consensus. Some findings suggest that the negative impact of marijuana

use on cognition is temporary and reversible [60–62], while others indicate that impairments are still seen 28 days to 3 months after last marijuana use and that deficits may increase as years of regular marijuana use increases [37, 45, 63]. These inconsistencies may stem from differences in methodology. For example, it has been indicated that examinations of non-acute effects of marijuana on cognition suffer from possible methodological issues surrounding the parameters of marijuana use. The specific parameters mentioned were frequency of marijuana use, duration of marijuana use, and age of onset of marijuana use [64]. Each of these parameters is associated with neurocognitive dysfunction when examined separately; therefore examining a population that is heterogeneous on any of these parameters could confound results. However, the more likely culprit in these inconsistencies may be the subtlety of deficits shown by marijuana users, especially given that neuroimaging research indicates that marijuana users show metabolic and activation differences even in the absence of performance differences. Moreover, adult marijuana users who initiated use before 16 years of age have been associated with increased cortical activation possibly reflecting more effort due to suboptimal cortical efficiency during neurocognitive challenge [65]. These results coupled with findings that memory deficits are more pronounced in younger marijuana samples suggest that the maturing brains of teenagers may be more vulnerable to the harmful effects of marijuana use on the brain and show lasting effects [22]. Overall, the considerable variability among the findings presented in the literature regarding the long-term effects of marijuana use on cognition sets a solid foundation to begin exploring the potential moderators or more proximal factors in this relationship.

## 3 Marijuana and the Immune System

### *3.1 Marijuana and Cannabinoids*

Numerous researchers have explored the relationship between marijuana (or its constituents) and immune function over the past 35 years. Most of the literature is based on experimental research in laboratory settings that involve in human and murine vitro studies (for review, see [14, 66]). Previous research points to the inhibitory influence of cannabinoids anti-inflammatory or modulatory properties on the cytokine network. The endocannabinoid system has been suggested to be associated with the modulation of the cytokine network. However, the literature also points to the exogenous cannabinoids as the potential immunosuppressant [67]. Very few studies have examined the acute effects for marijuana smoking on immune cells, but there is also a dearth of literature examining long-term effects of marijuana use on immune system cells or function [68]. This is imperative to examine, given marijuana is used recreationally by many with age of initiation of use as early as 12 years old [1]. With so many individuals using marijuana recreationally, even inconsistent use or sporadic use, researchers should explore marijuana use

in the context of subsequent immunological effects. Differences in patterns of use may predict future infections or conditions comprised of proinflammatory cytokine dysfunction. Overall, this body of research has focused on the marijuana and immune system relationship at the cellular level.

Immune cells express both CB1 (primarily in the central nervous system) and CB2 (primarily in the peripheral nervous system) receptors, suggesting a physiological connection between the endocannabinoid system and the immune system. This endocannabinoid system plays a pivotal role in the mitigation of functional immunity do to its direct ties to the hypothalamic pituitary axis and influence on the proliferation of natural killer cells and other adaptive immune cells [69, 70]. However, the exact role or connection between these two systems is still controversial [71]. In exploring the potential physiological overlap between these two systems, researchers have found that the cannabinoid system influences the production and proliferation of some immune cells, specifically cytokines. Comparison among many of the published findings is problematic, given the different types of experimental methodologies and quantification of outcomes [72].

CB2 are in close relation to various cells of the immune system and are typically seen in the pancreas and the lymphoid system [73]. CB2 are suggested to act as a function of immunosuppressant or modulation [74]. In both animal and human models, the majority of the literature suggests CB2 as anti-inflammatory based on various types of immune cells and health conditions [19]. Though THC is known to activate the CB1 and CB2 receptors and use them to signal throughout the endocannabinoid network, CBD, the non-psychoactive component in marijuana, does not typically activate these receptors. Interestingly, CBD is suggested to have anti-inflammatory effects [75].



### *3.2 Marijuana and Immunity*

Marijuana and its biologically active constituents have been associated with various types of immune cells (for review, see [76]). Overall, marijuana is associated with decreases in lymphocyte function [77], lung alveolar macrophage function, and granulocyte-macrophage colony-stimulating factor [78], TNF-alpha [78, 79], IL-6 [78, 80, 81], IL-8 and neutrophils [82], natural killer cells (NK) function [83–85], IL-2 [83, 84], and IL-10 [83], Transforming Growth Factor B-1 [84], IL-17 [81]. Interestingly, Monnet-Tschudi et al. [86] reported an upregulation of IL-6 48 h after a single administration of THC within a murine model. Cannabidiol and THC both have been suggested to have immunosuppressive effects as constituents of marijuana. However, the literature suggests that immune cells, or systems they directly influence, may be slightly different [87].

THC, the psychoactive constituent of marijuana, is associated with various agents within the immune system (for review, see [88]). THC is associated with suppressed natural killer cells (NK) function [89], CD40 ligand [90], IL-8, TNF, IFN [91], T cells, IFN, and mRNA related to Th1 cytokine production [92], IL-12 [93, 94], TNF

[95, 96], T cells and mRNA related to Th1 cytokine production [92]. In murine models, researchers have reported an inverse relationship between THC and IL-2 [97], natural killer cells [98], increases in Th2 antibodies and decreases in Th1 antibodies [99], NK cells, IFN, IL-2, T and B lymphocytes [100], IL-12 and IFN [101, 102], IFN [103, 104], IL-6 [105], and Th1 related dendritic cells [106].

Verhoeckx et al. [107] discussed the potential damage done by THC through marijuana use and suggested exploring THC-acid as it may be metabolized via a different pathway. THC-acid is a chemical, when burned, converts to THC. These researchers reported that THC-acid not only inhibited TNF levels, but did so for a longer period of time than THC.

THC was not associated with IL-2 function [77]. THC and CBD have also been show to increase the expression of IL-10, an anti-inflammatory cytokine [81]. Moreover, THC was reported to increase mRNA levels for Th2 cytokine levels [92]. In murine models, THC is reported to up-regulate IL-4 and IL-10 [108, 109], IL-4 [101], IL-10 and TGF-β [104]. See Table 2 for a listing of the cells influenced by marijuana.

To date, very few published studies have explored this relationship at the epidemiological level. Among these studies, self-reported lifetime use of marijuana use was found to be associated with lower levels of IL-6 [80] and TNF [79]. In addition, there are very few epidemiological studies that have explored the relationship between marijuana use and inflammatory markers, specifically [79, 80, 110–112]. Of these, Alshaarawy and Anthony [110] have the largest sample, utilizing a population-based sample. These researchers reported recent marijuana use was associated with lower C-Reactive Protein (CRP) levels in a non-clinical, predominately White sample. In contrast to Alshaarawy and Anthony [110], Costello et al. [112] reported a positive association between CRP and marijuana use in the past 3 months among children aged 9 through 21 years in a longitudinal examination. However, these researchers also reported that this association did not survive correction for covariates. Additionally, Rajavashisth et al. [113] found higher levels of CRP were associated with non-marijuana users in comparison to former and frequent users in a sample of predominately White, middle-aged population-based study. In contrast to these inverse associations between marijuana use and inflammatory markers, Muniyappa et al. [111] reported that chronic marijuana users have higher CRP levels than their non-marijuana using counterparts in a small sample matched on age, sex, and BMI. Taken together, these studies begin a foundation for epidemiological exploration of marijuana and immune function. This line of research will allow for the examination of incidence of infectious disease conditions associated various patterns of marijuana use. Potential findings could inform clinical trials and subsequent prevention or intervention programs that are based on biobehavioral processes and not just pure epidemiological constructs.

**Table 2** Marijuana's influence on Th1 and Th2 immune cells

| Cellular structure | Influence | Source | |
|---|---|---|---|
| Lymphocyte | Decrease | [77] | t6.1 |
| Alveolar macrophage (lung) | Decrease | [78] | t6.2 |
| Granulocyte-macrophage colony-stimulating factor | Decrease | [78] | t6.3 |
| CRP | Decrease | [110, 111] | t6.4 |
| CRP | Increase | [112] | t6.5 |
| TNF-alpha | Decrease | [78, 79, 91, 95, 96] | t6.6 |
| IL-6 | Decrease | [78, 80, 81, 105] | t6.7 |
| IL-8 | Decrease | [82, 91] | t6.8 |
| Neutrophils | Decrease | [82] | t6.9 |
| NK cells | Decrease | [85] | t6.10 |
| NK cells | Decrease | [83, 84] | t6.11 |
| NK cells | Decrease | [89] | t6.12 |
| IL-2 | Decrease | [83, 84] | t6.13 |
| IL-10 | Decrease | [83] | t6.14 |
| TGF B-1 | Decrease | [84] | t6.15 |
| IL-17 | Decrease | [81] | t6.16 |
| CD40 ligand | Decrease | [90] | t6.17 |
| IFN | Decrease | [91, 92] | t6.18 |
| T cells mRNA | Decrease | [92] | t6.19 |
| IL-12 | Decrease | [93, 94] | t6.20 |
| IL-2 | Increase | [97, 100] | t6.21 |
| NK cells | Decrease | [98] | t6.22 |
| Th1 antibodies | Decrease | [99] | t6.23 |
| Th2 antibodies | Increase | [99] | t6.24 |
| NK cells, IFN, T & B lymphocytes | Decrease | [100] | t6.25 |
| IL-12, IFN | Decrease | [101, 102] | t6.26 |
| IFN | Decrease | [103, 104] | t6.27 |
| Th1 dendritic cells | Decrease | [106] | t6.28 |
| IL-10 | Increase | [81] | t6.29 |
| mRNA (Th2) | Increase | [92] | t6.30 |
| IL-4, IL-10 | Increase | [108, 109] | t6.31 |
| IL-4 | Increase | [101] | t6.32 |
| IL-10 and TGF-B | Increase | [104] | t6.33 |

*CRP* C-reactive protein, *TNF* tumor necrosis factor, *IL-6* interleukin 6, *IL-8* interleukin-8, *NK Cells* natural killer cells, *IL-2* interleukin 2, *IL-10* interleukin 10, *IL-17* interleukin 17, *CD40 Ligand* cluster of differentiation 40, *IFN* interferon, *mRNA* messenger ribonucleic acid, *IL-2* interleukin 2, *IL-4* interleukin 4, *IL-12* interleukin 12, *TGF-B* transforming growth factor



## 3.3 *Marijuana Use and Infection Susceptibility* 274

Marijuana is commonly used in combination with illicit substances. In accordance 275
with this, individuals who inject drugs may leave themselves more susceptible 276
to various diseases due to the immunosuppressive influence of marijuana in 277

conjunction with opiates or stimulants [114]. Specifically, some researchers suggest that marijuana use exacerbates vascular and proinflammatory symptomatology in immunity-based conditions, such as HIV [91]. Moreover, marijuana use (either medical or recreational) has been reported to be associated with the development of invasive pulmonary aspergillosis [115–117]. This finding suggests how the immunosuppression produced by marijuana use may function in individuals who are already at risk for immune dysfunction. Cabral and Pettit [118] discuss this issue, suggesting cannabinoids increase susceptibility to infectious diseases. Moreover, Huemer et al. [119] reported the use of marijuana a day before infection augmented the severity of the subsequent cowpox infection in a group of mice. Though these researchers focus on animal-based models, this sets a strong foundation for future research to begin exploring this research question in humans, even at the epidemiological or global level.

## 4 Marijuana Use and Symptom Palliation

In 1964, THC was isolated and utilized to control nausea during chemotherapy [3]. After the discovery of the endocannabinoid system [120], clinicians and researchers began to elucidate the therapeutic nature of marijuana and its constituents [72]. Moreover, with the budding exploration of marijuana as a therapeutic agent, few regions of the United States have begun employing medical marijuana programs to distribute marijuana for medicinal purposes. Medicinal marijuana users who are approved for these programs: (1) are individuals with more severe symptomatology or diseases; (2) may be individuals with a history of substance use; (3) may potentially develop dependence or have negative health outcomes based on the medicinal marijuana use [121]. In addition to the decreases in physiological symptomatology, improving the quality of life for patients with severe or chronic conditions may also play a critical role in the rise of medicinal marijuana usage. In the alleviation of pain, palliative care looks to improve the quality of life for the patient as much as possible. This raises a very interesting discussion, as there are two clear sides to the conversation regarding medicinal marijuana use. One side cites various side effects and the potential harmful effects of marijuana use in any capacity. While the other speaks to the quality of life for the truly suffering patients and weights the alleviation of disease symptomatology more than the short term effects of marijuana use. Philipsen et al. [122] coin this debate Nonmalfeasance ("First, do no harm") versus Beneficence ("Do all the good you can").

Overall, literature exploring the therapeutic potential for marijuana and its constituents is growing. Such conditions include, but are not limited to neurodegeneration, irritable bowel syndrome, brain injury, arthritis, and vascular inflammation (for review, see [123, 124]). The underlying theme for the relationship between marijuana's therapeutic utility and these conditions is the inflammatory function proximal to each condition.

Endocannabinoids controls various central nervous system and peripheral nervous system functions, such as movement, memory, cognitive function, neuroendocrine secretion, and immune system modulation [72]. Endocannabinoids also have the ability to regulate neurotransmission, which may be key in neurological diseases such as Multiple Sclerosis or Parkinson's disease where you have overactive neurotransmission. Previous research posits that marijuana does not present harmful or negative outcomes, as long as it is used in moderation [125]. Much of the focus has been on marijuana's mitigating influence on various disease symptoms (nausea, appetite, etc.), however, there is a growing literature examining the antitumoral function of THC within cancer [126].

Given the anti-inflammatory effects of THC, various medical fields have begun exploring the treatment usages. For example, Gaffal et al. [103] reported that topically applied THC may attenuate inflammation related to allergy in an experimental murine sample in the field of dermatology. Previous research has reported that marijuana use may improve Hepatitis C virus treatment adherence and reduce the likelihood of virologic relapse after treatments [125]. Marijuana has been reported to decrease disease activity and even reduce the need for prescribed medication in individuals with Crohn's Disease [127]. Further, within the Naftali et al. [127] examination of marijuana's influence on Crohn's Disease, researchers posited that it was not only the anti-inflammatory effects of marijuana that aided in disease symptoms amelioration, but the gastrointestinal effects (i.e., reduction in diarrhea) as well. Interestingly, a recent study reveals that an ultra-low dose of THC may reduce myocardial damage if administered before or up to 24 h after induced myocardial infarction in mice [128]. This finding suggests a potential cardioprotective component of marijuana use, seemingly in dose–response relationship.

Utilizing smoking marijuana as the primary route of administration may deter various health professionals from promoting its health benefits. In the addiction literature, one commonly sees the use of marijuana paired with other illicit drugs or legal substances such as alcohol. However, smoking may be the preferred route of administration due to the efficiency in receiving the desired effect. Specifically, smoking introduces the exogenous cannabinoids to the bloodstream faster, yielding the sought anti-inflammatory effect. Nevertheless, some researchers suggest that consuming marijuana orally may have the same potent influence as smoking [127]. This may be critical if the goal is to alleviate pain, nausea, or any other symptoms in the gut.

## 5 Conclusions

Taken together, this literature presents a pattern in the effects of marijuana on immune function. Specifically, marijuana seems to suppress the Th1 branch of the immune system, while potentially augmenting various agents within the Th2 branch of the immune system. Given the abundance of CB1 receptors in the central nervous system and majority of the CB2 receptors are in the periphery,

marijuana seems to have a concomitant effect on the human physiology. Marijuana also influences the central nervous system; cerebral and subcortical structures involved in memory, decision-making, processing speed, and autonomic regulation are all affected by marijuana use. The potential bidirectional influence of marijuana can be traced throughout the nervous system with the principles outlined in psychoneuroimmunology [129]. Specifically, the alteration of cortical activation relating to the HPA axis and the autonomic nervous system in addition to the various neurocognitive effects portray a comprehensive portrayal of marijuana's influence on human physiology. Identifying the psychoneuroimmunological influences of marijuana use will aid in examining and evaluating both deleterious and health promoting effects to the human physiology and behavior. However, the complex interplay between the peripheral and central nervous systems altered by marijuana use may vary based on an individual's health status (see Fig. 1).

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The number of individuals using marijuana will continue to increase with various states choosing to legalize the recreational use. With legalization, come the use of



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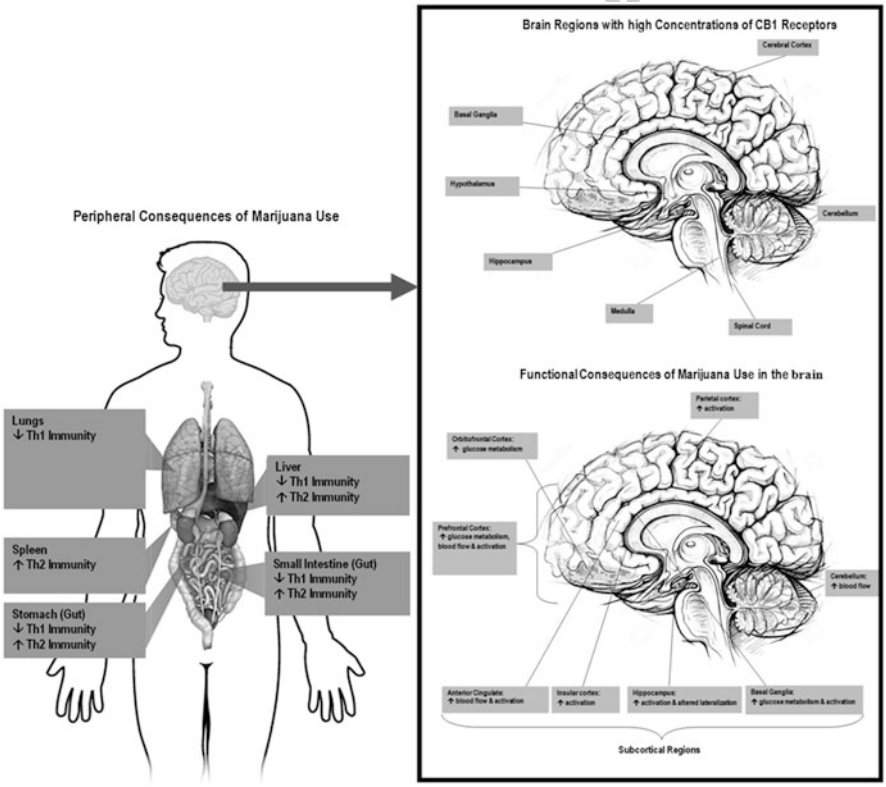


**Fig. 1** The influence of marijuana on the peripheral and central nervous systems. This figure details cortical immune functions in each region or area

edibles and other variation in routes of administration. Though these items are safe for consumption, the dosage of THC and other chemicals must be regulated and studied further. As individuals are gaining freedom to access/use marijuana legally in various forms, policy makers and individuals involved in regulating marijuana in the United States may need to examine if there are increases in polysubstance uses. Marijuana use is associated with the constructs reported in this review, however, the literature does not discuss how polysubstance users immune, neurocognitive, and disease susceptibility vary by substance grouping. Recreational use of marijuana has varied effects on the human anatomy. Identifying different mechanisms from various fields of research may elucidate the nexus of influence that surrounds recreational marijuana use. This identification may work through models such as the biopsychosocial model, which incorporates physiological, psychological, and social factors that that may be applied to the examination of marijuana and potential disease effects or development. At a cellular level, marijuana has both immunosuppressive and anti-inflammatory effects. However, negative effects of marijuana use include risk of opportunistic infections among individuals with impaired cell-mediated immunity as well as impaired neurocognitive functioning across recreational and chronic users. Although there is a growing body of literature highlighting these cellular, clinical, and population-based effects, there is an extremely scant amount of research, to our knowledge, that examines the psychoneuroimmunological effects of marijuana use.

There is a large literature on the influence of marijuana uniquely on immunosuppression at the cellular level, neuropsychological processes, and potential treatment and disease utilities. However, much of this literature does not empirically intersect. Future research should begin to discuss marijuana use from a psychoneuroimmunological perspective in order to provide comprehensive understanding of data and performance from various samples. Moreover, negative data reporting is a phenomenon that has limited the progression of the literature. Researchers must attempt to report null findings as well as significant findings in order to provide a more complete picture of the influence of recreational marijuana use. Having a comprehensive literature that intersects multiple fields would allow for a clear presentation of marijuana's' effects, further informing policy and legalization efforts.

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AUTHOR QUERIES

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