



“The Impact of Cannabis Abuse on cognition: a comprehensive Review”

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ABSTRACT:

Introduction: This review article explores the multifaceted impact of cannabis abuse on cognition, encompassing various aspects such as attention, perception, memory, motor skills, executive functioning, and language skills. The primary psychoactive component responsible for these effects is delta-9-tetrahydrocannabinol (THC), with its immediate impact felt post-smoking. The age of initiation plays a crucial role, with earlier use linked to more significant cognitive impairment, particularly during adolescence. Studies have shown that THC exposure in adolescent rats affects memory, while chronic use in adults leads to depressive behaviour. Human studies suggest temporary cognitive impairments in attention, executive functions, and learning among cannabis users, especially in young adults. Cannabis intoxication compromises attention and creates biases, with sub-acute effects on learning and memory. However, research indicates potential recovery with abstinence. Decision-making is also influenced by cannabis use, with studies revealing altered risk-taking behaviours. Context and emotion play a vital role, with peer influence, stress, and emotional processing impacting cognitive performance.

Introduction

Numerous investigations have explored the cognitive impairments linked to substance use disorders, especially in the recent two decades, propelled by advances in cognitive and computational neuroscience, along with neuroimaging methods. Substance misuse poses a significant health challenge, entailing various clinical implications. Among adolescents, cognitive impairments emerge as some of the most significant health issues related to substance misuse. Cognition, an intricate and multi-dimensional concept, refers to the brain's capacity for acquiring, processing, preserving, and recalling information. It encompasses critical elements such as attention, perception, memory, motor skills, executive functioning, and verbal and language skills.[1] Cognition encompasses both the conscious and subconscious activities involved in gathering knowledge, including perception, recognition, understanding, and thinking. The core of cognition lies in making judgments, which happens when we identify an item as distinct from others and describe it using one or more concepts. Psychologists

focus on cognitive processes because they influence both learning and behaviour.

Substance abuse, also known as drug abuse, is the misuse of drugs in manners or quantities that are harmful to the individual or others. It is a grave issue with far-reaching consequences, including exacerbating mental health conditions, contributing to premature mortality, and escalating violent crimes. Differing definitions of drug abuse are used in public health, medical, and criminal justice contexts. occur.[2] From a basic understanding, impaired cognitive function is a major characteristic of substance-use disorders. Changes in critical cognitive abilities like working memory, self-control, concentration, and decision-making are part of this. A person's daily activities and decisions may be impacted by these changes.[3] Persistent use of drugs can lead to cognitive impairments that make it challenging to maintain long-term sobriety. The brain, especially during its developmental stages, is highly vulnerable to the impact of substance abuse. Exposures during prenatal stages, as well as in childhood and adolescence, can result in enduring cognitive alterations. These changes



can significantly affect an individual's ability to function and adapt, underscoring the importance of addressing substance abuse early and effectively. The most common physical or mental health problems, experienced by 22% of users were acute anxiety or panic attacks following cannabis use. Fifteen percent reported psychotic symptoms following use.[4] Alcohol, amphetamines, barbiturates, benzodiazepines, cannabis, cocaine, hallucinogens, methaqualone, and opioids are the drugs most frequently linked to this phrase. Although the precise cause of substance abuse is unknown, two main explanations exist: either a habit picked up from others or a hereditary predisposition. If addiction develops, the habit becomes a chronic, crippling condition.

'According to the National Institute of Drug Abuse, 7 million people were taking prescription drugs for nonmedical use in 2010'

'Among 12th graders, nonmedical prescription drug use is now second only to cannabis.[5]

History of Cannabis use

One of the oldest crops ever farmed, cannabis has long been associated with religion in many cultures for its therapeutic properties, even before it was introduced to Western medicine. Since the discovery of cannabis some 12,000 years ago in the Altai Mountains of Central Asia, the seeds of the plant have travelled with nomadic peoples. Cannabis was used medicinally in China, Egypt, and Greece before the Common Era, and then in the Roman Empire.

'Cannabis sativa, commonly known as cannabis (Family: Cannabaceae), is one of the oldest crops cultivated and has various religious and medicinal values.'[6]. Long before cannabis was included in Western medical systems, it was used medicinally in India and China to treat a wide range of conditions, including fever, urinary tract infections, inflammation, meningitis, gastrointestinal issues, and dermatological conditions. 'Later, during the 19th century, multiple extracts and tinctures of cannabis were used to treat pain, whooping cough, and asthma, and used as a sedative or hypnotic.'[7] Only a small number of neurological conditions are approved, such as rare forms of epilepsy or spasticity in multiple sclerosis. Beyond that, though, medical cannabis is used to treat a range of neurological conditions and symptoms. In India, the sacred scripture

"Atharva Veda" claimed cannabis as an herb of happiness, as it elicited joy and pleasure, and hence used in ritualistic activities. The Ayurvedic system of medicine also described the use of cannabis for treating various gastrointestinal, respiratory, and urinary disorders.[8],[9]

Mechanisms/Pathophysiology

The brain's response to Cannabis Use Disorder (CUD) is explored through both preclinical and clinical studies, which delve into the effects of THC on the brain and behaviour. Despite the ongoing debate about the usefulness of animal models in addiction research, these models have been instrumental in unravelling the intricate processes involved in substance use disorders (SUDs). Human studies, encompassing genetic, imaging, pharmacological, and randomized clinical trials, have also shed light on changes in brain activity and functional networks in the development and persistence of CUD.

The endocannabinoid system is pivotal in mediating the addictive properties of cannabis. THC, the main psychoactive compound, interacts with cannabinoid receptors, predominantly CB1 and CB2. CB1 receptors are plentiful in the brain and are the primary target for THC. THC acts as a partial agonist of both CB1 and CB2 receptors.

Cannabinoids typically interact with cannabis receptors (CB). The primary cannabis receptors, CB1 and CB2, are part of the G-protein-coupled receptors (GPCR) family and can be activated by endogenous endocannabinoids, Phyto cannabinoids, or synthetic cannabinoids. Endogenous cannabinoids, such as anandamide and 2-arachidonoylglycerol, are neurotransmitters produced by specific enzymes and play a role in modulating brain function.

'THC and endogenous cannabinoids mainly modulate brain function through the CB1 receptor.'

The intracellular processes involve the inhibition of adenylyl cyclase activity through the activation of Gi/o protein. CB1 can also activate other cellular targets, leading to a complex response that depends on the type of neurons involved. CB1 receptors are found not only on presynaptic terminals but also in other cellular compartments like astrocytes, mitochondria, and somatodentritic regions of neurons. Presynaptic CB1 receptors, especially in glutamate and GABAergic



neurons, play a vital role in retrograde signalling, where endogenous cannabinoids released from post-synaptic neurons act on these receptors to reduce neurotransmitter release. The retrograde signalling process involving CB1 receptors aims to regulate neuronal excitability in brain circuits by modulating both GABA and glutamate release. The overall impact depends on various factors, including the expression of CB1 in different neuron types, local circuit anatomy, and signalling efficacy. Through negative feedback mechanisms on neurotransmitter release, the endocannabinoid system physiologically contributes to both short- and long-term depression at excitatory and inhibitory synapses in the brain. CB1-mediated self-inhibition has been described in neurons of the CA1 area in the hippocampus and in neocortical interneurons and some pyramidal neurons. In the brain, endocannabinoid signalling has been implicated in sleep regulation, reward response, anxiety control, appetite control, neuroprotection, and neural development. In the cardiovascular system, negative inotropy and vasodilation have been associated with cannabinoids. In the gastrointestinal tract, motility and enteroendocrine functions appear to be influenced.

Therapeutic use of medical *Cannabis* in neurological diseases

'*Cannabis sativa* and *Cannabis indica* plants have been used for medicinal purposes for thousands of years.'

[10] Many chemicals, including terpenes, flavonoids, phytosterols, and Phyto cannabinoids, are present in the plants; nevertheless, the two most significant compounds in terms of pharmacology are tetrahydrocannabinol (THC) and cannabidiol (CBD). The Narcotics Law only applies to the prescription of THC and its analogues because, in contrast to CBD, it has a psychoactive impact. Through the G protein-coupled cannabinoid receptors CB1 and CB2, THC and CBD can have the same effects as endogenous cannabinoids (such as anandamide).[11] The central nervous system, including the spinal cord, limbic system, and basal ganglia, and the cardiovascular system are the primary locations of CB1 receptors. Hematopoietic and immune-regulatory cells, as well as to a lesser degree, the central nervous system, are known to contain CB2 receptors.[12] Cannabis is a medicinal substance that is used to alleviate emesis and discomfort. Certain cannabinoids are used in clinical settings to treat chronic pain, especially pain related to

cancer and multiple sclerosis; to stimulate appetite and prevent vomiting in patients with HIV/AIDS and cancer; and to treat spasticity in patients with multiple sclerosis and epilepsy. The absorption and toxicity of cannabinoids can be affected by the several ways that herbal cannabis and cannabis-based therapy are taken, including smoking, vaporisation, oral, oro-mucosal, and others. For chronic illnesses, long-acting oral preparations are the backbone of treatment; vaporisation can be used as an adjunctive measure for acute symptoms. 'The primary cause of cannabis side effects is THC.' There are several preparations of *C. sativa*, which can be smoked by a cigarette or a hash pipe, inhaled, or ingested in the form of candy or brownies; the most common is marijuana (dried, crushed flower tops, stems, and leaves of *C. sativa* plant), and hashish (resins of the flowering tops of *C. sativa* plant).[13]

Pain Treatment with Cannabis

Chronic pain is a serious health issue that is frequently linked to diseases including multiple sclerosis, neuropathy, and cancer. Opioids, antidepressants, and anticonvulsants are usually used to treat it; however, these can cause problems like as drug dependence and a variety of negative effects. In light of these difficulties, cannabis is being investigated as a potential substitute for opioids in pain management, and its legalisation in certain areas has coincided with a drop in opioid-related deaths. These days, a lot of research is being done on cannabis for treating many forms of pain, including nociceptive, neuropathic, and central. Endocannabinoids, such as anandamide and 2-AG, are produced by injured tissues of neuronal and non-neural cells. These compounds modify pain signals by activating cannabinoid receptors. Nociceptive and non-nociceptive sensory neurons of the brain, spinal cord, dorsal root ganglion (DRG), mast cells, macrophage defence cells, trigeminal ganglion (TG), and epidermal keratinocytes are rich in CB1 receptors. These areas have low expression levels of CB2 receptors, but when peripheral nerve injury occurs, these expression levels rise.[14] Different mechanisms allow cannabinoids to control pain. For instance, THC can stimulate lipoxygenase and inhibit prostaglandin E-2 synthesis, reduce 5-hydroxytryptamine (5-HT) release from platelets and synaptosomal uptake while increasing cerebral production, and influence the trigeminovascular system in migraines. TNF- α , pro-inflammatory



cytokines, reactive oxygen species (ROS), T cell apoptosis, T cell proliferation inhibition, immune cell migration and adhesion reduction, and inducing T cell apoptosis are some of the ways that CBD may enhance anti-inflammatory effects. All of these processes reduce inflammation and oxidative stress.[15]

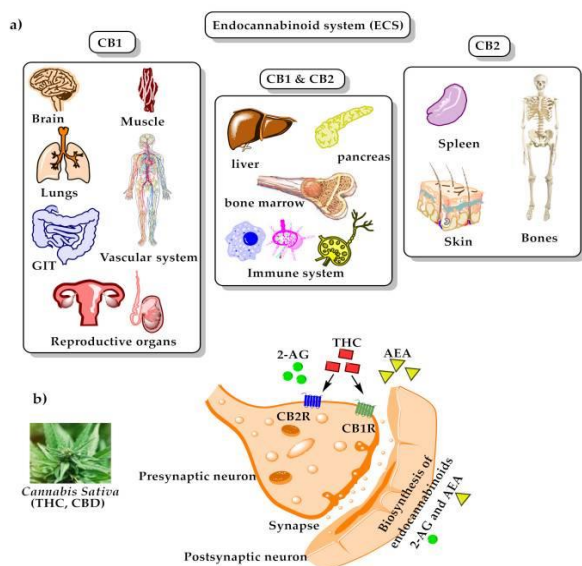


Figure 1[16] The endocannabinoid system; (a) distribution of endocannabinoids receptors through human body; (b) binding of endogenous anandamide (AEA), 2-arachidonoylsn-glycerol (2-AG), and exogenous Δ^9 -tetrahydrocannabinol (Δ^9 -THC) with cannabinoid receptors type 1 (CB1) and type 2 (CB2).

Cannabis and Multiple Sclerosis (MS)

MS patients use a variety of cannabis drugs (legally or over-the-counter) for a range of purposes, including pain management, anxiety, tremors, spasticity, relaxation, and sleep. By lowering inflammatory factors, the anti-inflammatory properties of cannabis may aid in the suppression of disease activity in multiple sclerosis.

‘Recent studies showed that 20–60% of MS patients are currently using cannabis, and 50–90% are willing to consider its usage if it was legal.’[17]

Cancer Treatment by Cannabis

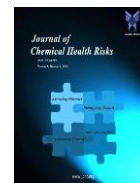
In cancer patients, cannabinoids are mostly used in palliative care to reduce pain, increase appetite, and reduce nausea. The potential use of cannabis as anticancer and symptomatic relief medicines in cancer patients has been the subject of increased research in

recent years. Cannabinoids have been found to inhibit tumour cell proliferation, angiogenesis, tumor invasion, and induce apoptosis in vitro and in vivo by the activation of cannabinoid receptors.[18]

Effect of cannabis use on cognition

Important components of cognition include motor skills, executive functioning, attention, perception, memory, and linguistic and language abilities. The use of cannabis has been shown to impact cognitive capacities on a number of different levels, from simple motor coordination to more complex activities related to executive functioning. Planning, organising, problem-solving, decision-making, memory recall, and emotional and behavioural management are a few of these skills. The amount and frequency of cannabis use, the age at which use started, and the length of use are some of the variables that can affect how severe these deficits are. The main psychoactive component of the cannabis sativa plant, delta 9-tetrahydrocannabinol (THC), is thought to be mostly in charge of the cognitive effects and potentially addictive qualities of smoked cannabis. THC levels in blood plasma are produced by smoking cannabis; these levels are almost instantly detectable and peak in a matter of minutes. Since THC dissolves in fat, it can be readily retained and released into the bloodstream. The psychoactive effects of cannabis are experienced immediately after smoking, with peak levels of intoxication occurring after approximately 30 minutes and lasting several hours.[19]

Research indicates that the age at which an individual first uses cannabis is a critical factor in determining its impact on cognitive functions. Participants who began the use before 18 years were more cognitively impaired than those who entertained the use in their later years. Moreover, cannabis produced higher detrimental effects on cognition in teens than alcohol, affecting the neuronal brain tissue accountable for memory.[20] The brain undergoes significant development up to approximately 25 years of age. Advances in MRI technology have shed light on the dynamic changes in grey and white matter from birth through to adulthood. During adolescence, the brain experiences a decrease in superfluous grey matter alongside an augmentation in white matter. The early stages of life witness a substantial surge in synapse formation, especially within the cortex. As one progresses into later stages, a refinement process takes



place, characterized by the elimination of underutilized neural connections and the enhancement of active synapses. This process, from a histological perspective, is integral to learning and serves to heighten the brain's efficiency. During this process, many neurons are lost, so that the adult has about 41% fewer neurons than the new born. Increased loss of grey matter in the medial prefrontal cortex was found in drug users, in particular in those who used multiple drugs.

A study by Cohen et al. (2021) showed that THC exposure in adolescent rats affected memory and plasticity through the hippocampal-accumbens pathway.[21]

Another study, by Tagne et al. (2021), demonstrated that frequent exposure to THC in male mice during adolescence resulted in dormant dysfunction in social behaviour.[22]

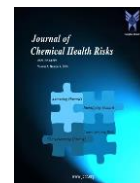
Furthermore, persistent THC treatment in adult rodents led to depressive behaviour and suicidal thoughts, which is associated with younger rats' lower serotonergic brain activity than that of adult rats. This is due to the fact that the primary psychoactive ingredient in marijuana, THC, acts by binding to receptors in the hippocampus, amygdala, and cerebral cortex—three areas of the brain critical for memory formation. It is unknown to what degree regular marijuana use—whether for medicinal or recreational purposes—causes long-term cognitive issues. In younger populations, particularly adolescents and young adults, cannabis consumption has been linked to minor cognitive declines. However, these declines are not typically enduring after ceasing cannabis use. Studies indicate that cannabis differentially influences immediate recall and verbal reasoning in young adults, whereas spatial working memory is more significantly impacted in adolescents. This suggests that cannabis may have a unique effect on the maturing brains of these distinct age demographics. Both adults and adolescents have attention problems when under the influence of cannabis, and these problems might persist for several weeks. Additionally, acute vs chronic cannabis use has varied effects on executive functions as inhibition and problem-solving. It remains unclear how likely these impairments are to persist after a period of abstinence.[23]

Attention and Concentration

The frontal lobes are the brain's primary mediator of attentional processing, which is the capacity to focus both divided and sustained attention on a stimulus. A key component of focus and attention as well as the foundation of higher order cognitive processing is information processing. examined how long-term, heavy cannabis users processed information when compared to controls who did not use cannabis. Cannabis users completed a task when abstinent and then attempted the same task 30 minutes after smoking their “regular” amount of cannabis.[24] The amount of THC ingested has a direct correlation to the reduction in attentional focus that results from cannabis intoxication. Regular cannabis users have grown tolerant to the drug's rapid attention-boosting effects. This tolerance is associated with a decreased reward system response in the brain after cannabis usage. Basically, heavy cannabis users might not feel the same amount of benefit or impairment in attention as infrequent users do.[25] Heavy cannabis users may exhibit an attentional bias for cannabis-related cues, potentially affecting their cognitive processes. This bias, although subtle, is evident in the way these individuals respond more intensely and quickly to cannabis-related stimuli, which correlates with the severity of Cannabis Use Disorder (CUD). Essentially, their attention is involuntarily drawn to such cues, as indicated by heightened and earlier brain activity, specifically the N1 component, during exposure to these stimuli.

Cannabis Learning and Memory

Cannabis intoxication can impair learning and memory, with the severity of impairment depending on the amount consumed. However, individuals react differently to cannabis use. Research on heavy users shows inconsistent results, but difficulties with learning and immediate memory recall are the most frequently observed issues among active users. A recent study on adolescents suggests that cannabis use may cause problems with immediate memory recall during memory tasks, although it doesn't seem to affect delayed recall. Additionally, another study found that cannabis users learn verbal information more slowly than non-users, which may be due to changes in brain function, particularly in areas like the para-hippocampal gyrus, thalamus, and midbrain.[26] Furthermore, impairments may not be relegated to only memory of real experiences. Kloft *et al.* showed that cannabis intoxication increased



susceptibility to false memory, an effect that appeared most prominent at immediate compared to delayed recall.[27] The consequences of cannabis usage that have been reported most likely stem from sub-acute intoxication effects. Abstinence from cannabis causes the effects on memory function and related changes in brain activity to disappear. Cannabis use-related learning and memory issues could have a significant negative influence on heavy cannabis users' everyday functioning, including their performance at work or in school, despite the documented deficiencies varied and perhaps time-limited nature. Research in the fields of psychology, neurology, and neurobiology is essential to understanding the seemingly intricate mechanisms underlying cannabis's memory-enhancing effects.

Decision-making

Decision-making is a complex cognitive function that builds upon more basic cognitive abilities. If these foundational abilities are impaired, it can lead to poor choices, such as the decision to use substances. The intricate nature of these cognitive processes might be why studies have found inconsistent results regarding the impact of cannabis use on decision-making. However, recent research has shed light on this issue, revealing that heavy cannabis users tend to make riskier decisions. For instance, studies have found that such individuals are more likely to choose smaller immediate rewards over larger delayed ones, a behaviour known as financial delay discounting. This suggests that heavy cannabis users are more drawn to immediate gratification and less deterred by potential losses.[28]

The importance of context and emotion

Research on how cannabis affects the brain and cognition is a fast-moving field that has shown evidence of a complex interplay between psychological and physiological processes. Acute, residual, and long-term alterations in brain activity are brought on by cannabis use, and these effects are felt throughout the body and include changes in emotional behaviour and executive function measurements, as well as changes in appetite and food intake.[29] Given the involvement of the endocannabinoid system in stress responses and general emotional states, there is conflicting information about the effects of cannabis on mood states and emotional processing in the brain. For instance, it has been proposed that cannabis use elevates mood states that are

both pleasant and negative.[30] While a popular peer's cannabis use may influence an occasional user's decisions, those with CUD may be especially vulnerable to cannabis-related cues that influence their decisions. Similar to attentional bias, heavy cannabis users may experience an approach bias towards cannabis when they are exposed to stimuli connected to cannabis. Furthermore, acute stress could affect one's ability to think clearly. For instance, both heavy cannabis users and controls experience higher impacts from acute stress on prospective memory function. Conversely, higher working memory capacity appears to shield heavy cannabis users from cravings during stressful situations. All things considered, potential cognitive deficiencies in heavy cannabis users may show up in different situations. The influence of cannabis consumption on the processing of emotions warrants attention. While research is scarce, the effects of cannabis intoxication could potentially impair the ability to identify emotions, particularly negative ones. This impairment is likely connected to diminished neural activity in areas of the brain associated with reward and cognitive control, especially when encountering negative facial expressions.[31] A novel investigation into gender variances has unveiled intricate correlations between genders and patterns of cannabis consumption concerning the initial response to emotional triggers (EEG, ERP: P1 and P3). This underscores the critical necessity of evaluating gender disparities in the impact of cannabis usage. This matter is especially pertinent in the realm of research on emotion processing due to the substantial comorbidity rates between cannabis utilization and conditions linked to emotion processing (for instance, anxiety) and the frequently observed gender disparity in the incidence of these disorders.

Conclusion

In summary, cannabis abuse has a multifaceted impact on cognition, affecting attention, perception, memory, motor skills, executive functioning, and language skills. Delta 9-tetrahydrocannabinol (THC) is the primary psychoactive component responsible for these effects, with immediate impact post-smoking. Onset age is crucial, with early use before 18 linked to more significant cognitive impairment, especially during adolescence. THC exposure in adolescent rats affects memory, while chronic use in adults leads to depressive behaviour. Human studies suggest temporary cognitive



impairments in attention, executive functions, and learning among cannabis users, particularly in young adults.

Cannabis intoxication compromises attention and creates biases, with sub-acute effects on learning and memory. However, research indicates potential recovery with abstinence. Decision-making is influenced by cannabis use, showing altered risk-taking behaviours. Context and emotion play a vital role, with peer influence, stress, and emotional processing impacting cognitive performance. In conclusion, cannabis-induced cognitive impairments, notably in attention, memory, and decision-making, may be reversible with abstinence. The complex interplay between cannabis, cognition, and contextual factors highlights the need for further research to fully comprehend the nuanced effects on the brain.

Future study recommendations (concise):

- Explore effects on specific populations (age, gender, pre-existing conditions).
- Examine different consumption methods (edibles, vaping, concentrates).
- Consider the role of other cannabinoids (e.g., CBD) on cognition.

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