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Cannabinoids impact on cognition: A review from the neurobiological perspective

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ABSTRACT

Cannabis is a widely used psychoactive substance in society, especially among the youngest. The use of this substance has been consistently associated with various health problems, many of which have in common an alteration in the cognitive manifestations of behavior, including memory, attention, emotion and decision-making. Evidence was found that cannabinoids, the active substance in Cannabis, negatively impact short-term memory, working memory, and decision-making. Likewise, cannabinoids affect attention and the interaction between cognitive events and emotion. This information can be used as a biological plausibility argument to interpret a series of clinical and epidemiological findings in which the use of Cannabis has been shown to be related to problems such as traffic accidents, psychosis, depression, poor academic performance, among others.

1. Introduction

Cannabis (substance subtracted from the Cannabis plant) is the most widely used illegal psychoactive substance in the world. The United Nations Organization (UNODC) has estimated that in 2009, between 125 and 203 million people in the world used this substance, with the annual prevalence of drug use being 2.8-4.5% of the population. world population between 15 and 64 years [1]. In Peru, the annual prevalence of Cannabis use has been reported to be around 0.7%, which is a fairly low prevalence compared to other neighboring countries, such as Colombia, Bolivia and Chile, where the annual prevalence of use of Cannabis is 2.3, 4.3 and 6.7%, respectively. This discrepancy between countries with similar socioeconomic characteristics in the same region may be due to methodological differences, which in this case may mean for Peru an underreporting of Cannabis use (especially when the UNODC published an annual prevalence for 2005 of 3.3%). The truth is that from global trends it is known that in general the consumption of Cannabis increases as the development of the countries grows [1,2]. If there are several countries in Latin America that are growing steadily in their economy, including Peru, then it is to be expected that the trend of Cannabis use will also grow in the coming years.

There are many health problems for which the use of Cannabis has been suggested to have a contributing role, including pulmonary, cardiovascular, reproductive, teratogenic, and oncological problems, although without conclusive evidence. Other health problems with greater evidence of association, possibly causal, include neurological problems, such as acute deterioration of neuromotor manipulation skills that are necessary, for example, to drive vehicles (such as information processing, temporal reaction, perceptual-motor coordination, motor action, working memory and attention) [3]. The epidemiological literature is consistent with this, showing an association between traffic accidents and the use of Cannabis [4-8], although more studies are needed to accurately identify independent effects of this substance with respect to other substances, mainly alcohol, since the Concomitant use is very common [9].

In addition to abuse and dependence, for which Cannabis is a necessary cause, it has been suggested that there are other mental health problems that could also be caused by this substance, and mainly include non-

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affective psychosis (especially schizophrenia). [10-12] and depression [10,13]. Among the psychosocial problems associated with Cannabis and that have most interested researchers is the failure to achieve academic goals. There is evidence showing an association between Cannabis use and low academic achievement, especially failure to complete high school on time, and lower academic grade level attained in adulthood [14-19].

So, the consumption of Cannabis may be having serious consequences in society, although still little known. A considerable part of the health and psychosocial problems that the use of Cannabis could be causing, such as the greater probability of suffering traffic accidents, psychosis, depression, and educational problems, involve in some way the neuropsychological construct known as cognition. Cognition is understood as the intermediate behavior between sensation (information that we receive through our sensory system) and action (which is our final response to said sensations). Thus, cognition involves the interaction of various behavioral manifestations such as memory, attention, emotion, language, thought and consciousness [20,21]. A disruption in any area could translate into some of the health and psychosocial problems we have described and that have been related to Cannabis use.

The objective of this review is to make a compilation of the most solid findings regarding the effect that Cannabis has on the different manifestations of cognition, focusing on memory, attention, emotion and decision making, since they are the most directly neuropsychological functions. related to the health problems associated with Cannabis, described previously. To do this, a search for reviews and original articles from the last 20 years was carried out using the ISIWeb of Science biomedical bibliography search engine, and the references were ordered by number of citations, choosing for this review those with a proven level of impact. (defined by a number of citations greater than 20 since the publication appeared in the indexed journals). Findings were divided into four sections reflecting the search criteria used, which meant the intersection of Cannabis with memory, attention, emotion, and decision making.

2. Cannabinoids impacts on Cognition

2.1. Cannabis and Memory

Before discussing the impact of Cannabis on memory, it might be in the interest of the non-neuroscience reader to describe aspects of memory that are very important to study. Memory has three aspects that make it possible: (i) Encoding or registration, which is the process by which the brain captures an event through sensory pathways; (ii) Consolidation, which means the creation of new neurocircuits from the previously captured event; and (iii) the ability to retrieve information through neurochemical events that occur in these neurocircuits, which translates into the experience of "remembering" the fixed event [22]. Memory is the foundation of cognitive processes, and supposes an efficiency in neuronal plasticity with respect to electrical activity, neurotransmitters, second messengers, and in some modifications of synaptic proteins, for a healthy gearing of the three aforementioned aspects.

The different classifications of memory derive from aspects such as its duration, the type of information stored or in which brain structures are involved. In this review, we will focus on memory duration, which is the most typically used in their study. Thus, memory can be long or short term.

Long-term memory (LTM) is distinguished by its ability to store a large amount of information, indefinitely. It is further divided into declarative MLP and non-declarative MLP. Explicit or declarative MLP retrieves events or experiences from the past, a historical fact or a family event, and can be measured by the request for memory or its identification; it can, in turn, be differentiated into semantic memory (meaning of words, facts, norms), and episodic memory (dates of events, place and some associated emotions). Implicit or non-declarative MLP allows performance even in the absence of consciousness, which is colloquially recognized as “I did it out of inertia”, for example when riding a bicycle [22].

For its part, short-term memory (STM), lasts approximately less than a minute, has a capacity limit and corresponds to about five or six words, or seven digits. It can be erased by head trauma or electroconvulsions, which would not affect long-term memory. Working memory is a special type of MCP, as it also has a limited ability to store and manipulate information in a short time, but it differs in that it manipulates the information it stores. This means that working memory not only has the image of the information as a mental representation in its current state, but also represents a possible future situation in order to work on it [22].

Animal and human volunteer studies show that cannabinoids, which are the active substance in Cannabis, primarily have observable effects on both MCP and working memory [23-26]. However, the evidence is still controversial since the studies evaluating the effects of cannabinoids on memory are highly complex and a consensus has not yet been reached. It's hard to tell in studies which are substance effects and which are due to other factors that researchers can't control or identify. Thus, for example, in these studies it must be ensured that there is no condition in the individual that is impairing their ability to remember information and that there is good performance in the three memory events (registration,

consolidation and recall) before administration of the drug.

Another intervening variable in studies on the effect of cannabinoids on memory is the quantity and quality of the drug to be ingested and its administration route. Cannabinoids can be used orally, sublingually, by inhalation, intramuscularly, and intravenously. For the purposes of this review, we will focus on the administration of smoke inhalation (cigarette), as it is the most frequent means of Cannabis use in our setting. A typical cigarette may contain around 0.35g of Cannabis, which contains 0.3-10% of the active ingredient delta-9-THC. When smoking, only 10-25% of the active ingredient enters the circulation, reaching a maximum concentration peak at 3-10 min. However, the psychotropic effects can begin a few seconds after smoking, reaching their maximum expression at 15-30 min and lasting between 2 and 3 h. All of these effects will depend on the weight of the cigarette, the frequency of inhalation, the depth of the puff, the extent of how long the breath is held after inhaling, and even the vital lung capacity of the individual [22].

Some studies of the effect of cannabinoids on memory have been carried out, which take into account methodological aspects, the administered dose and the existence of tolerance, which is one of the most important characteristics to define drug dependence [27,28]. For example, in a case-control study with Cannabis-using and non-using volunteer subjects conducted to measure the impact of Cannabis on basic CPM skills, a consistent association was found between being a substance user and impaired cognitive abilities. of the different memory pathways [27].

Block et al.,[27] have also described that for frequent chronic consumers (seven or more times a week) deficiencies are observed in tests of mathematical abilities and verbal expression. and using more specific tests (Buschke's test, which measures learning and recall), significant flaws in the recall pathway of memory are found. However, in less frequent consumers, no association was found between substance use and memory deficiencies, and the subjects only showed confusion about some concepts. These results clearly show an effect of cannabinoids at high doses on specific recall abilities, but the evidence is not clear at low doses. However, it is not yet completely clear whether these are lifetime cumulative dose effects, recent use effects, or pre-existing characteristics of the individual.

For its part, the evidence that cannabinoids negatively affect working memory is relatively solid [27,29-33], which is especially relevant given that working memory is altered in schizophrenia [34], thus being a link more with this disease. In addition, the findings suggest that the effects of cannabinoids in adults are greater due to long-term dose accumulation and that there are differences between men and women in terms of the effects of cannabinoids on working memory processes [26.35]. These findings may be adding useful evidence for the study of the Cannabis-schizophrenia association.

At the molecular level, the effect of cannabinoids on both short-term memory and working memory can be explained by specifically affecting the CB1 receptor, which plays an important role in memory and other aspects of cognition , as well as in the perception of pain [22,36]. The CB1 receptor that binds endogenous cannabinoids (endocannabinoids), is a G-protein-linked receptor, distributed mainly in the prefrontal cortex, with high density in the basal ganglia and hippocampus [22]. They also participate in the regulation of the basal ganglia that comes from the cerebellum, where the endocannabinoids would affect the glutamateric synapses, suppressing their excitation when they return to the presynaptic neuron [36]. In addition, it is the function of the endocannabinoids to act as retrograde messengers for presynaptic neurons, modulating the release of the neurotransmitters GABA and glutamate, which, having opposite effects, will in turn regulate the activation of postsynaptic neural projections. Endocannabinoids manage to inhibit the release of presynaptic neurotransmitters by acting on calcium channels by activating the CB1 receptor, and can give two different forms of short-term plasticity if GABA or glutamate transmission is involved, respectively [37]. .

GABA is an inhibitor par excellence and is responsible for regulating different processes, such as sleep, pain modulation, anxiety, among others. Before explaining the role of endocannabinoids in the GABA pathway, we must explain the concept of “depolarization-induced inhibition suppression” (SIID). The SIID accounts for the suppression of GABA release by the presynaptic neuron after the postsynaptic neuron, previously activated, sent a message to suppress GABA release to said presynaptic neuron, which initially generated the activation of the postsynaptic neuron. This removal of inhibition results in the postsynaptic neuron continuing to make plasticity. This effect seems to predominate in the hippocampus and cerebellum [37-39]. Endocannabinoids appear to be the messengers that activate this pathway, thus resulting in long-term, unordered potentiation and generation of plasticity in postsynaptic neurons [36].

On the other hand, and before explaining the role of endocannabinoids in the glutamate pathway, which is the activator par excellence of the nervous system, we must explain the concept of “depolarization-induced excitation suppression” (SEID). In this case, the messenger sent by the postsynaptic neuron inhibits the release of glutamate from the presynaptic, which was intended to keep postsynaptic plasticity going. This

phenomenon, which occurs predominantly in the cerebellum, has the net effect of controlling the plasticity of the postsynaptic neuron (an effect that is contrary to that produced by SIID). Again, the retrograde messenger that makes SEID possible, as in the case of SIID, is an endocannabinoid [37]. So, both forms of control in synaptic plasticity are induced by endocannabinoids, so they would have the function of regulating and coordinating the neural networks involved in physiological processes such as memory or motor coordination [37,40,41].

The hippocampus plays a very important role in memory formation, and the fact that endocannabinoids generate an uncontrolled proliferation of neuronal plasticity through SIID may partly explain the findings that Cannabis use is associated with a condition of the MCP. For example, some studies designed to observe learning efficiency under the influence of Cannabis have shown that individuals under the influence of the substance have problems remembering what they learned minutes before consumption; that is, they have problems fixing the information in short-term memory until it is consolidated (depending on the time elapsed between the consumption and the moment in which the information was received). If cannabinoids promote neuronal plasticity, how it is that individuals would have problems fixing short-term memory would be associated with the fact that these new connections have been formed by altered plasticity, which are not necessarily congruent in the routes of new learning [22 .27]. As Cannabis allows promiscuous plasticity, there will be deficits in cognition and memory. In experiments in CB1 receptor knock-out mice, both MCP and long-term potentiation failures have been observed, probably due to the instability of the neural connections formed [36].

There are two other receptors for cannabinoids: CB2 and CB3. The first, CB2, is mainly distributed in the peripheral nervous system and lymphoid organs, and is only found in small amounts at the glial level, so it is not relevant for cognitive studies [22-37]. CB3 does appear in the central nervous system, and its ligands inhibit both glutamate release and long-term potentiation. As glutamate is not released, the postsynaptic neuron fails to depolarize sufficiently to unblock Mg2+ from NMDA (N-methyl-Daspartate) receptors, thus affecting neuronal plasticity and, therefore, memory. However, delta-9-THC does not seem to be a good ligand for CB3, so the effects of Cannabis on memory seem to be due only to CB1 receptors [36].

In working memory, the literature describes certain effects of cannabinoids by directly altering the hippocampal complex by reducing its coding ability, resulting in clumsiness and inaccuracy [42,43]. Interestingly, due to the potential impact on the learning of people of school age, Pattij [26] has observed that when rimonabant is used (a molecule that is commercially used to inhibit appetite and, being a CB1 antagonist, allows measuring their performance), failures in working memory measured by recognition tests have more acute results in adolescents than in adults. finally, for a better understanding of cognition reproduced by working memory, it should be taken into account that it is regulated by emotion and attention [44,45], processes that will be described later.

2.2. Cannabis and Concentration

The human brain, in its animal evolutionary origin, seeks to behave with a regulation that Miller [28] calls “bottom-up”, in which the process goes from molecular mechanisms (given by physical and chemical interactions), to levels of cellular communication, until reaching the control of human behavior. In this way, our homeostatic functions that adjust our biological functions to environmental needs (which some call "instinct"), govern our behavior and development. However, as social beings, most of our behaviors are regulated by the nature of the sensory stimuli that connect with the respective neuronal response pathways, that is, “top down”. Being our external environment and the interaction with our peers that allows us to have cognitive control to select responses according to our interests (selective attention) and mediate our behavior [28].

When there is a conflict between different pathways with different sources of information, a competition for behavioral expression is created and that stimulus with the strongest source of support will win. This is clearly expressed using neuropsychological measures, such as the Stroop technique, in which conflicts in attention are created by writing the name of a color in letters of another color and a subject is asked to say the color of what is written. The strongest way is the already developed cognitive part, which leads the subject to read the word instead of letting himself be guided by the visual sense only and mentioning the color he is seeing, but not the one he is reading. If the individual has paid attention to the indications, no matter how slight the conflict, he will be able to respond to what has been requested by using the sensory pathway over the cognitive one [28]. The competition between these cognitive and sensory pathways is the unique evolutionary result in humans, responding to specific situations, such as social pressure, perception of external objects, body action, including social interactions [46].

Regarding the effect of Cannabis on attention, studies show that Cannabis causes transient attention disturbance that is evident within seven days of use but disappears by 28 days [47,48]. In addition, studies with cannabis users compared to non-users found no differences in neuropsychological tests with attention attributable to chronic use [49]. These latter findings

have been consistent with subsequent neurobiological findings. For example, Jager [24] conducted studies to see the effect of Cannabis on associative memory and attention tasks, using a morphometry technique, in which differences in tissue composition by region are identified by tissue density via functional magnetic resonance, in which it could be demonstrated if there is any type of morphometric change in the three-dimensionality of the neurons. The study compared performance during attention and associative memory tasks, by asking individuals (consumer and non-consumer) to connect two figures. No significant differences were found, which would be consistent with the hypothesis that Cannabis does not impair attention [24]. However, although it is not yet clear that Cannabis use affects attention specifically, since it is related to other neurocognitive processes, attention could be affected as a secondary effect of failures in memory or regulation of emotion, as will be reviewed below. continuation.

2.3. Cannabis and Emotions

All events and objects that are part of our daily lives occur in neural representations of various modalities. The interactions between perception, the action of the body, the environment, the state of mind and other agents will be of great importance when performing an action [46].

Currently, it is known that emotions influence attention and perception according to social stimuli and response feedback. Phelps [44], describes the objective of cognitive psychology as "the way in which man collects, stores, modifies and interprets information; or the information already stored internally". To this concept must be added the role of emotion, whose neurosubstrate is the limbic system: the amygdala, mainly. Neural circuits of emotion and cognition have been described as constantly interacting, from the most primitive perceptual systems to those of decision making and reasoning [44]. In cognition, emotion is a very important component that intervenes in the formation and collection of episodic memory, altering the three components of memory (registration, encoding and recall) [28].

The amygdala regulates the registration of the stimulus to be remembered, limiting attention only to the internal details that each person considers most important to themselves (according to their own needs, gaps or satisfactions that they have as an individual personality). So, the function of the amygdala would not be the recording itself, but the modulation (or modification) of the neurocircuitry that allows memory. A clear and very typical example of this are the events that result from an emotional response and that, being very important for survival, are more difficult to forget [44]. For example, those who survived the last earthquake in Pisco (Ica-Peru) in 2007 will clearly remember where and what they were doing at the time of the earthquake. This has been proven so much that episodic memory cannot be measured in the precision of the memory, since there is a high degree of emotionality in the circuit of memory retrieval that it may not reflect with real and exact precision what happened, since In addition, it will integrate what is subjectively lived into the memory, which can add embellishments and fantasies to the memory [28,44,46].

Among the various functions of endogenous cannabinoids is the homeostatic control of emotions and the regulation of motivated behavior which, as described above, is guided by attention [37]. The natural cannabinoid system is distributed in the amygdalar complex and its control over emotions has been confirmed by behavioral studies after administration of cannabinoid receptor antagonists and reward deficits observed in CB1 knockout mice[37] . Sanchis et al.,[50] have described that the control exerted by CB1 receptors would not only be given to reward systems as motivated behavior, but that CB1 receptors would also be involved in the control of homeostatic reward, satisfaction of basic needs (eating, sleeping, for example). Therefore, cannabinoid receptors would be associated not only with disturbances in motivation, but also with the emotional process of information perceived from the environment [50-64]. This finding is especially interesting since it has been postulated that one of the mechanisms by which Cannabis is associated with a poor educational trajectory is through the so-called amotivational syndrome, where the individual loses interest in things of daily life as an effect of chronic substance use [18,51].

The way in which endocannabinoids can cause demotivation is through a decrease in the release of glutamate and corticotropin-releasing factors, reducing the entry pathways to the amygdalar complex. The limit between exposure to a significant dose of cannabinoids for the final balance of this system would lead to anxiety or anxiolysis, depending on the activation rate of the amygdala with projections to the hippocampus and the brain stem, with anxiolysis being the most common response. likely to an increase in cannabinoid transmission in this system [37].

2.4. Cannabis and Decision-making

Decision making is defined as a mental process, of high cognitive order, in which an appropriate action must be selected from among different alternative scenarios and inappropriate behaviors must be inhibited [26]. This cognitive process is of great importance in cognition, since failures in this system could lead to impulsive behaviors or attention and hyperactivity disorders.

To measure these processes, most studies use the immediate reward and impulsivity systems, measuring in the tests the inability to inhibit the behavior in such a

way that the preference for the reward increases. Chronic Cannabis use has been reported to increase the likelihood of engaging in behaviors associated with higher risk. For example, when choosing between two options to increase monetary gains, subjects who use Cannabis tend to choose the options associated with large monetary losses, a behavior that suggests that these subjects make risky decisions impulsively [52-54].

Churchwell et al. provide an anatomical-morphological explanation for this impulsive behavior, with the findings of a sophisticated study based on the findings of fuster et al. and Ellgren et al. The first, Fuster et al., found that morphogenesis in the prefrontal cortex enhances the ability to temporarily organize action plans and choices when achieving goals [55]. For their part, Ellgren et al., found in animal models that the density of the CB1 receptor in the prefrontal cortex changes during adolescence, suggesting that this stage represents a period of morphological vulnerability to Cannabis [56]. On this basis, Churchwell et al. [57], found that the volume of the mid-orbital prefrontal cortex of subjects who abuse Cannabis use is lower compared to controls without this substance abuse. This finding also converged with a lower capacity in the neuropsychological function of future orientation in subjects who abuse Cannabis, who do not. All this is strong behavioral evidence that has a neurobiological substrate that those who abuse Cannabis have a poor ability to control impulses. Furthermore, if the abuse occurs in adolescence, when the prefrontal cortex is still in the process of maturation, then this capacity may be more affected [57].

However, studies do not yet reveal a clear effect on decision-making in casual users, frequent low-dose users, or long-term high-dose users. Kelleher et al., describe results that indicate that long-term Cannabis users have a deficit in the development of information processing tasks (they are slow to decide), but that this deficiency seems to normalize when the effects of acute intoxication pass. [25]. More research is needed in this area, since this may be related to a greater ease of young people who initiate Cannabis to relate to peers with behavioral problems or to engage in marginal behaviors.

4. Conclusion

Cannabis is a widely used psychoactive substance in society, especially among the youngest. The use of this substance has been consistently associated with various health problems, many of which have in common an alteration in the cognitive manifestations of behavior, including memory, attention, emotion and decision-making. There is well-documented evidence that cannabinoids, the active substance in Cannabis, negatively impact short-term memory, working memory, and decision-making. Likewise, cannabinoids temporarily affect attention and the interaction between cognitive events and emotion. These findings help interpret clinical and epidemiological evidence of problems such as traffic accidents, psychosis, depression, poor educational background, among other difficulties with which Cannabis use has been found to be associated.

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