

# Cannabis impact on working memory, inhibitory response and risk decision making in people under 30 years of age: A systematic review

## Impacto del cannabis sobre la memoria de trabajo, la respuesta inhibitoria y la toma de decisiones de riesgo en personas menores de 30 años: Una revisión sistemática

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### ABSTRACT

**Introduction:** marijuana is the third most consumed substance in the country, after tobacco and alcohol, with a worrying increase in consumption in young people, who are the most vulnerable to neurological damage, since the prefrontal cortex is the last to mature, and is one of the brain regions where there is a greater impact on the consumption of various drugs, especially cannabis. Although there are no studies in which deaths caused by marijuana overdose have been reported, little is said about how executive functions are affected, especially: working memory, risk decision making and the inhibitory response.

**Objective:** evaluation of the impact on working memory, inhibitory response and risk decision making, in cannabis users under thirty years of age

**Method:** a systematic review was carried out, through the collection of data in the Pubmed search portal, referring to the last 20 years, which has measured the damage of marijuana on executive functions.

**Results:** working memory, decision making, and inhibitory response are affected in cannabis users. Not only are there alterations in the cognitive tests, but also structural brain changes are evident. These alterations are associated with starting consumption at an early age and exposure to high doses of THC.

**Conclusion:** the implementation of measures to promote abstinence from this drug for as long as possible in this vulnerable group must be necessary, since some changes could be irreversible.

### KEYWORDS

Cannabis, Marijuana Abuse, Executive Function, Brain, Prefrontal Cortex.

### RESUMEN

**Introducción:** la marihuana es la tercera sustancia más consumida en el país, después del tabaco y el alcohol, con un incremento preocupante en el consumo en jóvenes, quienes son los más vulnerables al daño neurológico, ya que la corteza prefrontal es la última en madurar, y es una de las regiones cerebrales donde hay un mayor impacto por el consumo de diversas drogas, especialmente el cannabis. Aunque no existen estudios en los que se hayan reportado muertes por sobredosis de marihuana, poco se habla de cómo se ven afectadas las funciones ejecutivas, especialmente: la memoria de trabajo, la toma de decisiones de riesgo y la respuesta inhibitoria.

**Objetivo:** evaluación del impacto sobre la memoria de trabajo, la respuesta inhibitoria y la toma de decisiones de

riesgo, en consumidores de cannabis menores de treinta años

**Método:** se realizó una revisión sistemática, a través de la recopilación de datos en el portal de búsqueda Pubmed, referidos a los últimos 20 años, que han medido el daño de la marihuana sobre las funciones ejecutivas.

**Resultados:** la memoria de trabajo, la toma de decisiones y la respuesta inhibitoria se ven afectadas en los consumidores de cannabis. No sólo hay alteraciones en las pruebas cognitivas, sino que también se evidencian cambios estructurales cerebrales. Estas alteraciones se asocian al inicio del consumo a edades tempranas y a la exposición a altas dosis de THC.

**Conclusiones:** debe ser necesaria la implementación de medidas que promuevan la abstinencia de esta droga durante el mayor tiempo posible en este grupo vulnerable, ya que algunos cambios podrían ser irreversibles.

## PALABRAS CLAVE

Cannabis, Abuso de Marihuana, Función Ejecutiva, Cerebro, Corteza Prefrontal.

## INTRODUCTION

Marijuana is the most widely consumed illicit drug in Argentina, and the third most consumed substance, after tobacco and alcohol. An increase in cannabis consumption has been noted between 2010 and 2017, in all age groups and in both sexes, with young people between 18 and 24 years old showing the highest rates of consumption.<sup>(1)</sup> There is an idea of the benevolence of marijuana compared to other recreational drugs, and although there are no reported cases of deaths due to overdose, little is said about the impact it can cause on a neurological level.

The two most important components of cannabis are delta-9tetrahydrocannabinol (THC) and cannabidiol (CBD), which are very fat-soluble, allowing rapid diffusion to the central nervous system. These components interact in the presynaptic space, as exogenous agonists of the endocannabinoid system, which plays an important role in the control of neural circuits, especially in the prefrontal cortex and the hippocampus. The receptors that are involved are the cannabinoid receptor type 1 (CB1) and the cannabinoid receptor type 2 (CB2), which are coupled to G protein, associated with GABAergic release.<sup>(2,3)</sup> The neurotransmitter GABA acts as an inhibitor of neuronal activation. When endocannabinoid receptors are activated, especially CB1, by THC and CBD, they produce an inhibition in GABAergic neurons, decreasing this neurotransmitter, and producing neuronal activation, increasing the release of other neurotransmitters. It is here that the reward system, which consists of dopaminergic fibers that project from the ventral tegmental area to the nucleus accumbens, is affected.<sup>(4)</sup> The consumption of the drug produces hyperactivity of this system, at the expense of the release of dopamine. With repeated consumption of the drug, the dopamine signal decreases, leading to a lack of natural motivation, and the need for more drug to increase the availability of this neurotransmitter.<sup>(5)</sup> In this way, acutely the consumer can feel pleasure and a decrease in stress due to this increase in the bioavailability of dopamine in the reward circuit and a decrease in the release of cortisol through the hypothalamic-pituitary axis, but the Chronic consumer due to the downregulation of CB1 receptors, contributes to the alteration of the sensitivity of the reward and stress system, with the appearance of depressive symptoms such as anhedonia and lack of motivation.<sup>(6)</sup>

Adolescents are the most vulnerable to the effects of marijuana. Throughout life, from fetal life to late adolescence, our brain matures through modifications and increases in myelination, given by stimuli and experiences, which are then converted into more efficient dendritic connections through a process called synaptic pruning. The last brain region that ends up fully maturing is the prefrontal cortex, and this happens in late adolescence. This region is responsible for the integration of information from stimuli, reasoning, and executive functions.<sup>(7)</sup>

In the following work we are going to investigate the impact of cannabis on executive functions, especially working memory, inhibitory response and risk decision making. Executive functions are a set of top-down mental processes, necessary to concentrate and pay attention or other goal-directed behavior, being essential when it would be insufficient or impossible to rely on instinct or intuition.<sup>(8)</sup>

Working memory is the domain that involves actively retaining information, to be able to work with it mentally, without it being perceptual. Not only is that information retained, but it is manipulated, unlike short-term memory, where there is no manipulation of the information, it only involves retention.<sup>(8)</sup>

The inhibitory response, for its part, is the ability to suppress unwanted or inappropriate behaviors or impulses and is an important component of flexible and directed behavior.<sup>(9)</sup>

Regarding risk decision making, they are a type of uncertain decision making, where the probability of the different results that could be obtained are known.<sup>(10)</sup>

Given an alteration in executive functions in marijuana consumers, the implementation of measures should be necessary to prevent and discourage the use of this drug, as well as educate people about the effects it may be having on their health. Adolescents should be encouraged, by public health organizations, to abstain from this and other drugs for as long as possible.

**METHOD**

In the present work, a systematic review was carried out using the guidelines of the PRISMA Declaration.<sup>(11)</sup> To search for works, the PICO method was applied: studies with samples of cannabis users under 30 years of age (P) were included; not subjected to any intervention; compared to a control group, non-consumers (C); that evaluate alterations in executive functions (working memory, inhibitory response and risk decision making) in consumers (O). The question posed was: Do marijuana users under 30 years of age have alterations in working memory, risk decision making, and inhibitory response, compared to non-consumers?

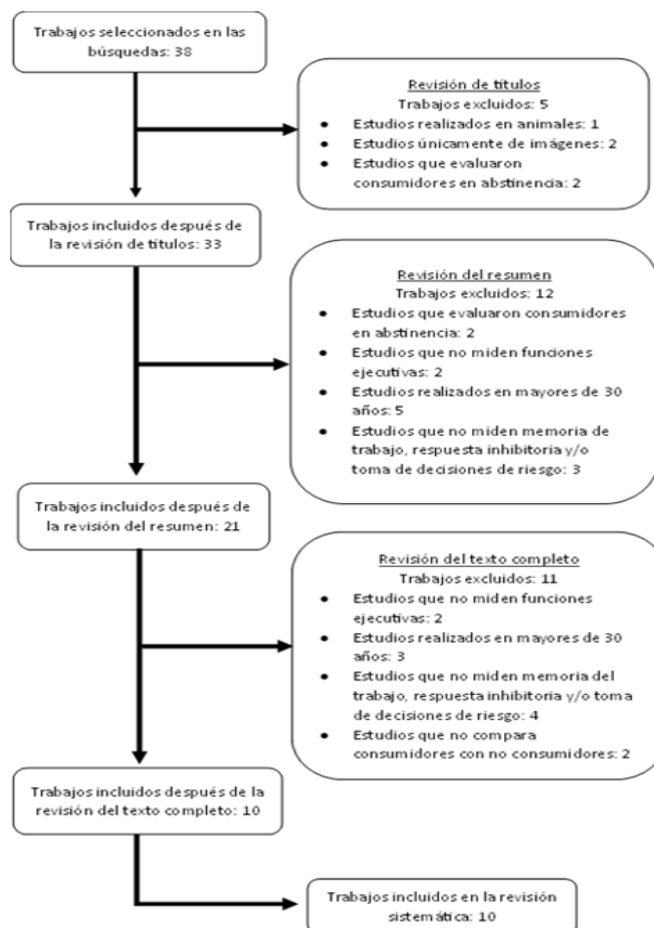
**Inclusion criteria**

- Studies carried out in humans.
- Papers that have been published in the last 20 years.
- Papers where working memory, inhibitory response and/or risk decision making are measured.
- Works that compare groups of cannabis consumers and non-consumers.
- Age of participants (consumers and non-consumers) less than 30 years old.
- Group of consumers, who have consumed products with THC a minimum of 25 times in the last year, or a minimum of 50 times in their life; or failing that, the test is double-blind, where THC is administered to this group.

**Exclusion criteria**

- Marijuana users with detectable alcohol in urine or breath prior to testing.
- Those with a substance abuse disorder (other than cannabis, alcohol, or nicotine); or failing that, these other substances are not detectable in urine, blood or breath, before carrying out the tests.
- History of psychiatric pathology, or who has been treated with psychotropic medication.
- History of neurological disorders.
- Abstinent cannabis users.

**Literature search procedure**



**Figure 1.** Selection process PRISMA

The searches were carried out in the Pubmed database, during the months of June to August 2023, using filters of publications between the years 2003 and 2023. The keywords used were cannabis, brain, marijuana abuse, executive function, memory, cognition, adolescent, and young adults. These searches were interleaved using the Boolean operator AND or OR. The study identification and selection process were performed during the same period, being later placed in common findings to verify that the selected studies met the inclusion criteria.

After the searches, a total of thirty articles could be identified, without considering systematic reviews, reviews, and meta-analyses. Three articles were then removed after title review, leaving a total of twenty-seven. When analyzing the abstract of each work, another nine were excluded, leaving a total of eighteen works. Immediately afterwards, after reviewing the full text, another eight articles were excluded, leaving ten remaining articles, which were the ones that were finally used for the development of this systematic review.

The PRISMA flow diagram is presented in figure 1, where this selection process is shown, with the number of papers included and excluded, according to the analysis of the title, abstract and full text of each paper; and the reasons why they were excluded were also detailed.

## RESULTS

The ten selected works are shown in table 1. Each work is distinguished by the title and first author that appears in the publication, the age of the sample, the executive functions that were measured in each work, the test that was used to measure each executive domain, and the results reached in each article.

**Table 1.** Selected works

Titel and author	Sample age	Executive function measured	Task	Results
Adolescents are more sensitive than adults to acute behavioral and cognitive effects of THC (Conor H. Murray) <sup>(12)</sup>	Adolescent group: 18-20 years old Adult group: 30-40 years old	Inhibitory response	Stop Task	Alteration in response accuracy in adolescents, but not in adults
		Working memory	N-back Task	Dose-dependent condition in adolescents and adults alike
Are adolescents more vulnerable to the harmful effects of cannabis than adults? A placebo-controlled study in human males (C. Mokrysz) <sup>(13)</sup>	Adolescent group: 16-17 years old Adult group: 24-28 years old	Inhibitory response	Stop signal	Less accuracy in adolescents exposed to cannabis compared to the control group. No alteration in accuracy was observed in adults
		Working memory	Spatial N-back	Discriminability was worse in cannabis than in placebo, and worse in high doses than in low doses. Adults exposed to cannabis had a prolonged reaction time compared to placebo
Cognitive control in young adults with cannabis use disorder: An event-related brain potential study (David LR Maij) <sup>(14)</sup>	Group between 18-25 years old	Inhibitory response	Go/NoGo Task	Participants with cannabis use disorders (CUD) showed less accuracy on the NoGo tasks (difficulties inhibiting their response), unlike controls. Furthermore, this group had less reaction time (they were slower) in the Go tasks, compared to the control groups.
Effects of Marijuana Use on Prefrontal and Parietal Volumes and Cognition in Emerging Adults (Jenessa S. Price) <sup>(15)</sup>	Group between 18-25 years old	Working memory	Paced Auditory Serial Attention Test	In cannabis users, a decrease in the medial orbitofrontal cortex was related to worse working memory. It is considered that the decrease in the prefrontal cortex, in young adults, may be associated with chronic exposure to cannabis for at least 4 years
			Letter Number Sequencing	

Impulsivity, Attention, Memory, and Decision-Making among Adolescent Marijuana Users (Donald M. Dougherty) <sup>(16)</sup>	Group between 14-17 years old	Inhibitory response (impulsivity)	GoStop Task Immediate Memory Task Two Choice Impulsivity Paradigm Single Key Impulsivity Paradigm	Greater impulsivity (lower inhibitory response) in users compared to the control group
		Risky decision making	Iowa Gambling Task Intradimensional/ Extradimensional Shift	Higher rate of errors in decision making in consumers, compared to the control group
Neurocognition in College-Aged Daily Marijuana Users (Mary P. Becker) <sup>(17)</sup>	Group between 18-20 years old	Working memory	Digit Span	Marijuana users tended to perform worse, with lower accuracy and longer response latency.
		Risky decision making	Iowa Gambling Task	Marijuana users showed worse performance. Marijuana users failed to acquire an effective strategy, showing relatively less consistency in responses than non-users. Test choice patterns suggest that, for marijuana users, rewarding feedback, that is, potential gratification, is more compelling than punishing feedback.
Response inhibition and elevated parietal-cerebellar correlations in chronic adolescent cannabis users (B. Behan) <sup>(18)</sup>	Group between 14-19 years old	Inhibitory response	Go/No-Go Task	Cannabis users performed worse with a low number of successful inhibitions. The worse inhibitory control could be related to aberrant connections between nodes of the response inhibition circuit, observed in fMRI.
Performance of Young Adult Cannabis Users on Neurocognitive Measures of Impulsive Behavior and their Relationship to Symptoms of Cannabis Use Disorders (Raul Gonzalez) <sup>(19)</sup>	Group between 17-24 years old	Risky decision making	Iowa Gambling Task	Worse performance (worse decision making) was associated, within the group of users, with those who had more symptoms within the cannabis use disorder (DSM IV)
		Inhibitory response (impulsivity)	The GoStop Task	No significant differences were evident between the consumer group and the control group. This result could be associated with the strict inclusion criteria proposed by the research, and the age at which consumption began.
Testing the association between tobacco and cannabis use and cognitive functioning: Findings from an observational and Mendelian randomization study (Liam Mahedy) <sup>(20)</sup>	Cohort study evaluated from 13 to 18 years and 24 years	Working memory	N-back Task	Worse performance in cannabis users, compared to the control group. The worst performance is associated with the beginning of consumption at an early age
		Inhibitory response	The Stop Signal Task	Worse performance, reflected in a slower ability to inhibit responses, and worse accuracy in the test in cannabis users, compared to the control group. The worst performance was associated with the beginning of consumption at an early age

Working memory-related brain activity in cannabis use disorder: The role of cross-cultural differences in cannabis attitudes (Emese Kroon) <sup>(21)</sup>	Study groups with a mean age of 24 years	Working memory	N-back Task	Worse results in cannabis users, unlike the control group. The deterioration in working memory was associated with the complexity of the task
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In “Adolescents are more sensitive than adults to acute behavioral and cognitive effects of THC”<sup>(12)</sup> the objective was to determine if adolescents were more sensitive than adults to the acute effects of THC, measuring, among other things, the inhibitory response and working memory. It was concluded that adolescents are more sensitive than adults to the effects of THC, presenting alterations in the inhibitory response; and dose-dependent alterations in working memory.

“Are adolescents more vulnerable to the harmful effects of cannabis than adults? A placebo-controlled study in human males”<sup>(13)</sup> proposed to evaluate the different effects that cannabis produces in adolescents and adults, also measuring the inhibitory response and working memory. Alterations were observed in people exposed to cannabis, with a lower precision in adolescents in the inhibitory response tests, and worse discriminability at high doses, in the working memory test. Furthermore, it was observed that the adolescents did not show satiety after the administration of the drug; Instead, they wanted more cannabis, regardless of whether they received cannabis or placebo.

In the article “Cognitive control in young adults with cannabis use disorder: An event-related brain potential study”<sup>(14)</sup> the objective was to measure, among other cognitive aspects, the inhibitory response, in a group of young people with cannabis use disorder and compare the results with two other control groups (one tobacco smoker and a non-smoker). It was concluded that the cannabis consumer group had difficulties inhibiting their response (NoGo test), with a longer reaction time (Go test). It is believed that this delay in reaction time was intended to avoid errors in the inhibitory part.

In “Effects of Marijuana Use on Prefrontal and Parietal Volumes and Cognition in Emerging Adults”<sup>(15)</sup> prefrontal and parietal volumes and working memory were investigated in young adult cannabis users. A decrease in the volumes of the inferior parietal cortex and the medial orbitofrontal cortex was demonstrated in cannabis users, the latter being associated with a deterioration in working memory. Furthermore, it was proposed that a decrease in volume in the prefrontal cortex in young adults may be related to a disruption of the neurological development process, after chronic exposure to cannabis for at least 4 years.

In the article “Impulsivity, Attention, Memory, and Decision-Making among Adolescent Marijuana Users”<sup>(16)</sup> the objective was to determine the performance of adolescent marijuana users and non-users in several executive domains, among which were the inhibitory response or impulsivity and risky decision making. As a result, it was obtained that the consumer group presented greater impulsivity with a lower inhibitory response, and a higher rate of errors when making decisions compared to the control group.

In the article “Neurocognition in College-Aged Daily Marijuana Users”<sup>(17)</sup> it was proposed to determine the neurocognitive profile in young adult marijuana users, who started using before the age of seventeen, and compare them with a control group. Working memory and risk decision making were evaluated, concluding that consumers showed a tendency towards worse performance in the working memory test, and worse performance in the test that measured risk decision making, without being able to achieve an efficient strategy. Furthermore, according to the choice patterns in this last test, it was possible to identify that rewarding feedback is more convincing for the group of consumers than punishing feedback.

The objective of the work “Response inhibition and elevated parietal-cerebellar correlations in chronic adolescent cannabis users”<sup>(18)</sup> was to evaluate at a neurocognitive level the inhibitory response in adolescent marijuana users and relate the findings to imaging studies (fMRI). A worse performance was concluded in the inhibitory control test, which is related to aberrant connections between nodes in the response inhibition circuit.

In “Performance of Young Adult Cannabis Users on Neurocognitive Measures of Impulsive Behavior and their Relationship to Symptoms of Cannabis Use Disorders”<sup>(19)</sup> it was proposed to investigate risk decision making and impulsivity, through the inhibitory response, in young adult cannabis users, compared to a control group. The consumer group, which was more symptomatic, showed worse decision making. On the other hand, no differences were observed with the control group in the inhibitory response. This could be associated with the strict inclusion criteria proposed by the researchers, and the age at which consumption began.

The article “Testing the association between tobacco and cannabis use and cognitive functioning: Findings from an observational and Mendelian randomized study”<sup>(20)</sup> aimed to establish a possible relationship between the age of initiation of consumption and the habitual use of marijuana and tobacco, with some cognitive functions, among which were working memory and inhibitory response. The findings showed worse performance in the working memory test and worse performance and accuracy in the inhibitory response test, in the cannabis consuming group. Furthermore, poorer performance was associated with starting cannabis use at an early age.

The article “Working memory-related brain activity in cannabis use disorder: The role of cross-cultural differences

in cannabis attitudes”,<sup>(21)</sup> proposed to evaluate possible conditions in neurological processes in cannabis users in comparison to a control group. In this case, working memory was evaluated, and showed that there is a worse result in the test in those who consume marijuana, and that the deterioration of this executive function is associated with the complexity of the task.

## DISCUSION

The objective of the present systematic review was to determine if there was any alteration in working memory, inhibitory response and risk decision making in cannabis users under thirty years of age. The findings allowed us to confirm the condition of the named executive functions.

Among the limitations that were presented to us in carrying out the work, there is comorbidity in the consumption of other drugs, such as alcohol and tobacco. In most of the articles, cannabis users also consumed tobacco and alcohol, but these substances are not quantified or determined in this study group.

With respect to working memory, an alteration was seen in both precision and reaction time. This worse performance has a dose-dependent relationship and is associated with an early age of initiation of cannabis use. These results can be objectivized with functional imaging studies (fMRI), carried out during the tests, where an excessive increase in activity in the prefrontal cortex is observed in groups of adolescent marijuana users.<sup>(22)</sup>

The inhibitory response was altered, leading to an increase in impulsivity. In general terms, consumers had a slower ability to inhibit responses, and worse accuracy and precision. This alteration in the executive domain is associated with adolescent consumer groups, with an early start in cannabis consumption, and is also associated with high levels of marijuana consumed.<sup>(23)</sup> An early start in the consumption of this drug is associated with greater adverse effects on the brain and a worse inhibitory response, compared to consumers who had a later start.<sup>(24)</sup> Drug craving is directly related to excessive daily use, and this is linked to an alteration in the inhibitory response.<sup>(25)</sup>

This disorder is not limited only to cognitive tests, but aberrant alterations are evident in the connections between nodes of the response inhibition circuit, objectified through functional imaging tests.<sup>(26)</sup> Furthermore, greater activation is observed in regions of the prefrontal cortex, which suggests that additional neural resources are required to maintain correct executive control.<sup>(22)</sup>

In only one study were no differences observed between the consumer and non-user groups, but in this case, we must keep in mind the strict inclusion criteria proposed by the researchers, and the age of start of marijuana consumption. Risk decision making shows worse performance in the consumer group, with a higher error rate and difficulty in establishing an effective strategy. In consumers, this alteration is associated with a greater sensitivity to immediate gain, which is accompanied by a lower sensitivity to loss.<sup>(25)</sup> Furthermore, as happens with the inhibitory response, the alteration in this domain is associated with an early age of initiation of drug consumption, compared to consumers who started later.<sup>(23)</sup> Similarly, there is an association between the presence of more symptoms of cannabis use disorder and impaired decision-making.

Both adolescents and young adults are a vulnerable group to the effects of marijuana. It is evident that the alteration in executive functions is related to an early age of initiation of drug consumption.<sup>(6)</sup> As this is a stage of brain maturation, chronic exposure to cannabis induces changes in brain morphology. Imaging studies show a reduction in gray matter volume in regions with high concentrations of the CB1R receptor (hippocampus, prefrontal cortex, amygdala, and cerebellum).<sup>(26)</sup>

The recovery of cognitive functions and morphological alterations are incongruent. An improvement in working memory is reflected after three weeks of abstinence in a group of adolescent consumers.<sup>(27)</sup> Furthermore, it is suggested that abstinence could recover part of the alterations produced in the endogenous cannabinoid system, although other works propose that those consumers who started using cannabis at a young age never completely recover their cognitive function prior to exposure to marijuana, not even with abstinence in adult life.<sup>(28)</sup>

With these findings, it is evident that marijuana users not only present alterations in executive functions, but also present alterations at the brain morphological level. In this context, it is necessary to promote drug abstinence by public health organizations for as long as possible, trying as much as possible to discourage consumption in adolescents and young adults; warning and educating this vulnerable group about the neurological effects of cannabis.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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