Effects of marijuana consumption in students on brain functions demonstrated by means of neuropsychological tests and neuro-SPECT imaging

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Original article

SUMMARY

Comparative study based on 565 school adolescents coming from four schools in the metropolitan area of Santiago, Chile. All were interviewed in order to select a sample that was stratified by sex, class and condition of users or non users. The variables of intelligence quotient and socioeconomic status were maintained constant. Two groups were made: 40 marijuana-only users and 40 non users. We compared the results obtained in both groups in the neuropsychological tests while the neuroSPECT studies of users were compared against a normal database for the same age group.

Adolescent marijuana users demonstrate less cognitive capacity related to the process of learning such as attention, concentration, ranking, visuo-spatial integration, immediate retention and visual memory. The differences between both groups are statistically significant.

The findings of neuroSPECT show subgenual bilateral hypoperfusion, more marked on the left side (Brodmann's area 25), frontal bilateral hypoperfusion (Brodmann's areas 10 and 32), front cingulate *gyrus* hypoperfusion (Brodmann's area 24) and hypoperfusion of Brodmann's area 36 that projects over the hippocampus.

Students that were only-marijuana users demonstrate coincident abnormal findings of neuroimages and neuropsychological tests in brain learning-related areas and also significant differences between users with non users in the neuropsychological tests.

Key words: Cannabis, marijuana, adolescents, NeuroSPECT, HM-PAO, neuropsychological tests.

RESUMEN

Estudio comparativo basado en 565 escolares adolescentes pertenecientes a cuatro colegios de Santiago, Chile. Fueron encuestados todos para seleccionar una muestra estratificada por sexo, curso y condición de consumidores o no consumidores, manteniendo constante las variables coeficiente intelectual y nivel socioeconómico. Se conforman dos grupos: 40 consumidores exclusivos de marihuana y 40 no consumidores. Se comparan los resultados obtenidos en ambos grupos en los Test Neuropsicológios y del NeuroSPECT de consumidores con una base de datos considerados normales para el mismo grupo etario.

Los adolescentes consumidores de marihuana evidencian menores habilidades cognitivas asociadas al proceso de aprendizaje, tales como atención, concentración, jerarquización, integración viso-espacial, retención inmediata y memoria visual. Las diferencias entre ambos grupos son estadísticamente significativas.

Los hallazgos del NeuroSPECT muestran hipoperfusión subgenual bilateral, más marcada en el hemisferio izquierdo (área 25 de Brodmann), hipoperfusión frontal bilateral (areas 10 y 32 de Brodmann), hipoperfusión del *gyrus* cingulado anterior (área 24 de Brodmann) e hipoperfusión del área 36 de Brodmann que proyecta sobre el hipocampo.

Los estudiantes consumidores exclusivamente de marihuana muestran compromiso coincidente en neuroimágenes y test neuropsicológicos en áreas del cerebro relacionadas con el aprendizaje y se diferencian significativamente de los no-consumidores en las pruebas neuropsicológicas.

Palabras claves: *Cannabis*, marihuana, adolescentes, NeuroSPECT, HMPAO, pruebas neuropsicológicas.

Translation of the original version published in spanish in: Salud Mental 2013, Vol. 36 Issue No. 5.

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INTRODUCTION

Social impression in Chile about the harmlessness of marijuana consumption led us to investigate its effect on cognitive functions necessary for school learning, especially because of the worrying statistics showing this country as the major Latin-American user of marijuana in students, as well as a continuing trend towards the increasingly younger onset age of users: according to the 2010 World Drug Report 15.6% of users were between 13 and 18 years old.[1]

The National Drug School Survey concluded in an increase of 4.4 percentage points in the last two years of experimental use of marijuana among students from 8th grade of middle school to 4th grade of high school,* going from 15.6% in 2009 to 19.1% in 2011.

The same report states that the lack of risk perception among the students on the frequent use of marijuana (once or twice a week), increased 10.2 percentage points, that is, from 37.8% to 48%.[2]

These data are coincident and corroborate recent research findings, such as the survey on marijuana and learning disorders conducted in 2007, in which the hazard perception associated to consumption was very low: in the marijuana-using group only 7% disapproves of its usual consumption, and in contrast 74% disapproves of cigarette use.[3,4] If we consider that education is the most effective way to pull out of the vicious circle of poverty and that most consumption happens in low socio-economic status, the fact of consuming without risk perception becomes even more concerning, thus the young user is exposed to a more vulnerable situation.

The 2010 World Drug Report states that *cannabis* continues to be the most produced drug worldwide as well as the most illicit substance used in almost all countries around the world. Today, between 130 and 190 million people smoke it at least once a year. Although this consumption level may be considered low, it is important to recall that the risk of addiction not only depends on the amount but also on genetic-social factors and on the onset age of use, in addition to the personal susceptibility.[5] Likewise, global trends show that as economic development of countries improves, marijuana use increases.[1,6]

The possibility of legalizing marijuana and other illicit drug use has brought this topic at the centre of attention of the media. However, in the discussion there are no considerations about marijuana effects in the most vulnerable segments of population, such as school adolescents, who use it without being labeled as regular users or addicts. They —while not being categorized as "addicts"— are not considered in public health policies and, therefore, do not have any social, school, family or medical support.

Numerous authors have referred to the negative impact of marijuana in school learning and performance, emphasizing that either "pleasant" or "unpleasant" effects, such as risk of addiction and damage, depend on individual sensitivity.[3,7-10]

Other reported damages are those that affect prefrontal cortex functions, like the ability of planning, purpose-driven work and control and inhibition of responses.[11-13]

An additional effect, regarding school performance, is amotivational syndrome or decrease of personal initiative.[14] This sign is pathognomonic of the adolescent user. It is characterized by deterioration in behavior, loss of energy and aboulia with an important limitation of regular activities, which relates to the inability organizing time efficiently in pursuit of certain objective. Also, a state of passivity and indifference characterized by widespread dysfunction of social skills is common.[15] The amotivational syndrome has important effects within what could be classified as emotional factors in school performance as a whole.

Neuroimages have caused abnormalities of structures, of functions at rest or under stimulus, of receptors and neurotransmitters in illicit substances users, including marijuana.[11,16]

Especially, with NeuroSPECT functional imaging the irreversible neuro-toxic effect of cocaine with multifocal alterations in cerebral blood flow, of disorganized distribution and associated with cerebral functional abnormalities.[17-19]

When using in the analysis the Brodmann's areas, it is possible to correlate imaging findings with the relevant functions.[20]

Cannabis affects indirectly the dopamine production and interacts with specific CB1 receptors, which are intensely expressed in the hippocampus and in the cerebellum, which explains the implication of such areas within the functional alterations associated with the use of this drug.[12,21]

Studies with transcranial magnetic stimulation techniques showed that when the prefrontal system fails, subjects start making decisions bound for obtaining instant satisfaction, without assessing consequences. This would correspond to behaviors preferably led from the limbic system.[22,23] Adolescents, due to age-related immaturity of prefrontal lobes, are more vulnerable to prefrontal hypofunction caused by marijuana and thus to the determination of their behavior by the limbic system, with the aforementioned characteristics.[24]

Delta-9-tetrahydrocannabinol (THC) modifies the grasping and processing of the information made by the hippocampus, which is crucial for learning, memory, integration of sensory experiences and motivations.[25,26] THC is a lipophilic molecule that easily crosses the blood-brain and placental barriers. Due to this affinity with lipids it is accumulated in body fat, from where it is gradually released causing an extension of the effects. Therefore, after smoking a marijuana cigarette, it is possible to detect the existence

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* Translator's note: Generally, every country has its own school grade nomenclature. This is the Chilean grade system.

of metabolites in the urine during a week. In chronic users, urine may be THC positive for over a month after stopping use.[5] The effect of the drug on cognitive functions remains in user, even after a withdrawal of several days.

Our objective was assessing the effects on the only-marijuana use cerebral function, excluding poly-drug use, in school adolescents not labeled as addicts, through neuropsychological tests and NeuroSPECT functional cerebral imaging.

METHODOLOGY

Sample Selection

The sample was selected from a population made up by 565 students (1st – 4th year of high school from three public schools located at the peripheral areas of Santiago, stratified by sex, course and marijuana consumption/non-consumption status. The following variables are kept constant: a) medium-low income and b) cognitive development level, within ranges of normality.[27]

For the purposes of this survey a *user* is considered as the student who declares a minimum of four *cannabis*-only using episodes during the last month and a minimum regular use of 18 months. The sample to be individually assessed is made up by 40 subjects who only use marijuana and 40 subjects of the control group with no drug use background. Only 29 from the 40 users were also surveyed with neuroSPECT. In both groups the sex variable was proportionally distributed.

Instruments and Procedures

Collective application (n=565)

a) Informed consent of the address of each of the participating establishments for the group evaluation of the 565 students.
b) Psychosocial and Consumption Assessment Questionnaire of Dörr et. al abridged and adapted, for the demographic data collection, using behaviors and other information required, in order to determine the sample composition.[3]
c) Questionnaire about morbid background of the student, his/her family and regarding the final grade point average during the last four years.
d) Domino Test (D-48).

Individual application of neuropsychological tests to the using group (n=40) and to the non-using control group (n=40)

a) Informed consent/informed assent from students and their parents for the individual neuropsychological assessment and neuroSPECT application. The procedures had the formal approval from the Bioethics Committee of the School of Medicine of the University

of Chile as well as from the Ethics Committee of the Clínica Las Condes.
b) Benton Visual Retention Test (Benton, 1965).
c) Rey Word Memory (Rey, 1959).
d) Rey Complex Figure Test (Rey, 1959).
e) Wisconsin Test (WSCT, 2001). Only applied to users.

NeuroSPECT to using group (n= 29)

The neuroSPECT was conducted on a normal school day. In preparation for the test subjects did not consume, 24 hours before, tea, coffee, chocolate and cola drinks. 740 MBq of Tc99m HMPAO (Ceretec Amersham) was given intravenously at rest, in a low-light and low-noise environment. After an hour, tomographic imaging was taken in a dual-head Siemens ECAM with Low-Energy High-Resolution (LEHR) collimators.

In the NeuroSPECT processing the retro-projection three-dimensional reconstruction was used with a 4.25 Butterworth filter. Through volume normalization —using the Tallairach (a Segami Corp, Maryland, USA software) technique— each individual is compared with a normal database of the same age group. Results are expressed in standard deviations regarding the normal for each of the 14,000 volume units (*voxel*) in which the brain was divided. Also, a matrix is applied with the Brodmann's areas for the regional analysis of such data.[20]

Data Analysis

a) From the group evaluation the sample to be assessed is individually obtained.
b) The results of the neuropsychological tests of using and non-using subjects are compared applying classic statistical analysis models and statistical contrast non-parametric tests, by sample size.
c) NeuroSPECT information is analyzed for cortical and sub-cortical perfusion values expressed in a percentage of the maximum reference value, calculating maximum, minimum, average and standard deviation (SD) in each Brodmann's area. In order to identify altered perfusion subregions within the volume delimited by the different Brodmann's areas (ROI), we worked with the maximum or minimum values per area.

RESULTS

From the 565 assessed students, 368 (65.1%) declared not having use any drug in any form and 197 (34.9%) declared to only have "tried" it. The ages of the groups making up the sample ranged between 15 and 18 years of age, being 16 years of age the average of the using group (Table 1).

Results obtained in the neuropsychological tests, applied individually to selected users and non-users, show

significant differences in four out of five tests applied. In all tests the performance of the control group (non-user) is better as compared to the marijuana-using group.

Rey Word Memory: Performance of using students is diminished by 15% in tests that assess short-term verbal memory (p<0.05).

Benton Visual Retention Test: It shows considerably higher scores for non-using students as compared to using students in tasks involving attention skills, concentration, short-term retention, perception, visual memory and visuo-constructive abilities confirming an alteration of integration and structuring of spatial stimulus in users. Adolescent users make 3.8 errors in average per test against 1.7 errors by non-users. Thus, the amount of errors made by the using group is 21% higher. This difference is statistically significant (p<0.05), showing lower attention abilities, concentration and short-term spatial memory (Table 2).

Table 1. Results from neuropsychological tests for users (n=40) and non-using control group (n=40)

Tests	Control	Experimental	Student's t-Test for mean difference		
			T	Tc 0.05	p
Domino test	113.0	106.8	1.92	2.02	N.S.
Rey word memory test	7.4	6.3	2.90	1.99	<0.05
Benton retention test	8.9	7.9	3.94	1.99	<0.05
Benton error test	1.7	3.8	-5.37	1.99	<0.05
Rey Complex Figure Test	25.4	17.3	6.76	1.99	<0.05

N.S.: non-significant.

Rey Complex Figure Test: The scores obtained by both groups show significant differences in favor of non–users in tasks involving skills and execution strategies in the visuo-perceptive performance, visual memory, prioritizing abilities and organization of visual information (p<0.05). A
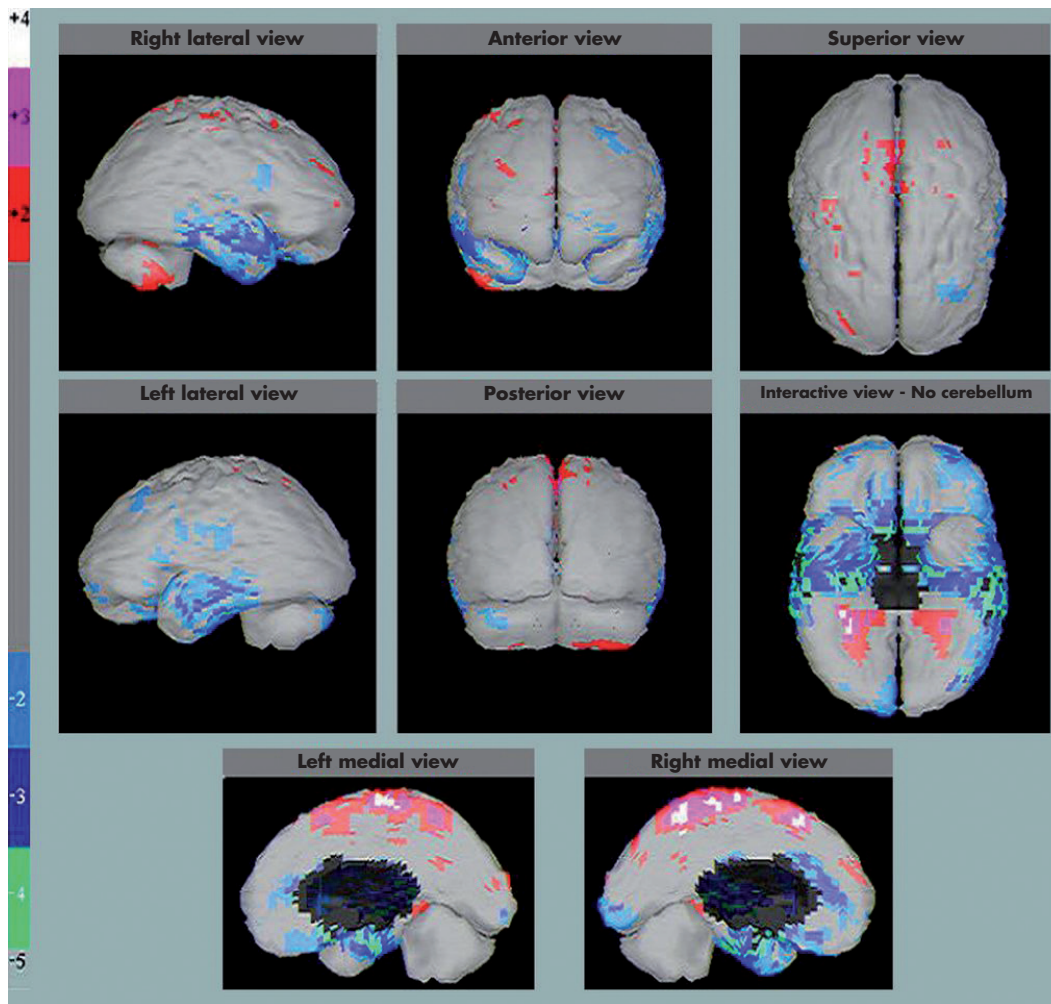

Figure 1. NeuroSPECT of marijuana-only-using student. There are function diminishment areas at 2, 3 and 4 standard deviations under the normal average (light blue, blue and green) concentrated especially in both temporal lobes in the mesial aspect and projecting both hippocampi. Also, subgenual bilateral hypoperfusion is observed in the Brodmann's area 25, which is an area that controls mood. There are bilateral lateral temporal hypoperfusion and multifocal areas in the frontal cortex, besides hypoperfusion in both anterior cingulates.

Table 2. Rey test. Error scores for control group (n=40) and experimental group (n=40)

Error Type	Strategy used	Control		Experimental	
		n	%	n	%
I	Construction on a rectangle (adults)	16	40.0	2	5.0
II	Details regarding the rectangle start	6	15.0	5	12.5
III	Integral contour without rectangle difference	2	5.0	3	7.5
IV	Recognizable details on a confused background	16	40.0	28	70.0
V	Juxtaposition of trial-error details (children)	0	0.0	2	5.0
VI	Association to a family scheme. Vague memories	0	0.0	0	0.0

difference close to 7 points was found in the average obtained by both groups, resulting in clear difficulties of evocation and limitations in the accuracy of visual memory of users. The test scores identify six types of execution strategies according to the age for visual memory, from the most detailed (Type I) to the most difficult ones (Type VI).

These broken down scores are delivered, by type of execution, in order to compare the development of both groups. From the control group, 16 students (40%) reached the type-I build strategy, that is, they achieve to apply prioritizing abilities, perceptive performance and planning. From the experimental group only two students (5%) access this style of execution. It is important to mention that 70% of the using group develops a type-IV execution style, peculiar to a more specific strategy and linked to cognitive immaturity.

Wisconsin Test showed that, in the total error category, 30% of the using group is located in the moderate-intermediate impaired level. In persevering errors, 26% is at intermediate impaired level or worse. Regarding the percentage of persevering answers, 17.2% of using students obtain scores of impairment higher than the average. These results disclose, in almost a third of the using group, limitations in the mental flexibility ability due to alterations in executive functions requiring planning strategies, organized inquiries and use of the environmental *feedback* to change the scheme.

Results of NeuroSPECT Evaluation

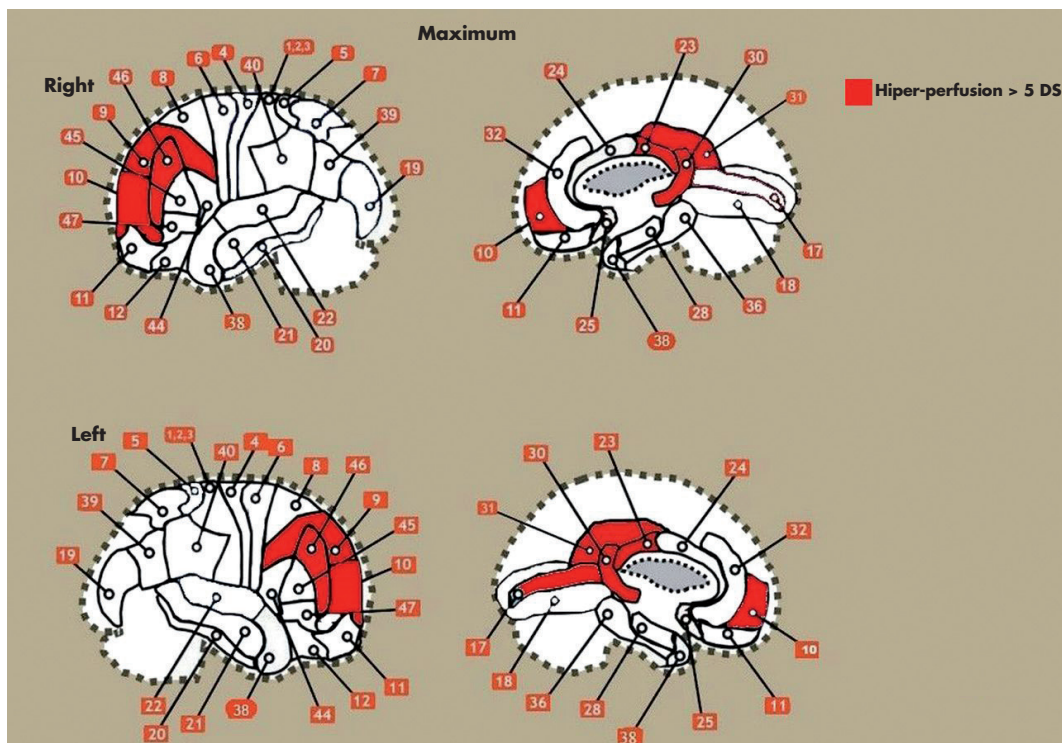The individual results obtained were compared with the normal population of the same age. Results were expressed in

Figure 2. In 29 volunteers exposed to marijuana, maximum levels were calculated within each of the Brodmann's areas pointed out. Abnormal areas that were more than 5 standard deviations over the normal average were considered. Brodmann's areas 9, 10 and 46 stand out bilaterally in the executive cortex of the frontal lobes. Likewise, there is an increase of perfusion in the posterior cingulate, Brodmann's area 30, and in Brodmann's area 31, besides the association visual cortex (area 17).
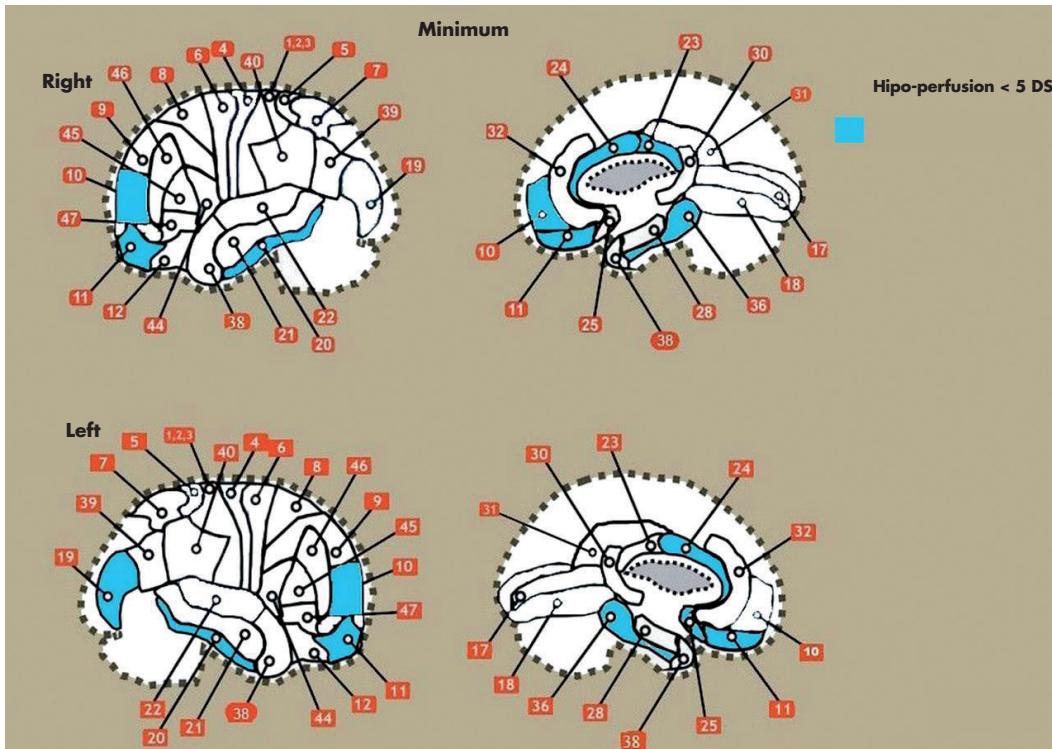
Figure 3. In 29 volunteers only exposed to marijuana, minimum levels were calculated within each of the Brodmann's areas pointed out, and the areas that were at less than 5 standard deviations under the normal average are emphasized. They are located in both frontal lobes, Brodmann's areas 10 and 11. Also, they are in the temporal lobe in the lower aspects, Brodmann's area 20, besides both anterior cingulates, Brodmann's area 24, and in left Brodmann's area 25 at a subgenual level. Finally, hypoperfusion is bilaterally observed in Brodmann's area 36 projected over the hippocampus.

Standard Deviations (DS) over and under the normal average (Figure 1). A Brodmann's areas matrix was projected on each hemisphere and the average and the SD was calculated in 47 cortical areas and in parasagittal sections. Initially, it was detected that the flaws partially took up each area, thus minimum and maximum values of the Brodmann's area were calculated (2.5% greater or lesser from the area, respectively). Those values that greater than 5 SD over or under the normal average were considered as abnormal values. Figures 2 and 3 show the heterogeneity of the areas affected with hyper or hypoperfusion. It is confirmed that there are sources within some Brodmann's areas that are hyperperfunded to 5 SD over the normal average: areas 9, 10, 46 (frontal lobe) of the right hemisphere; areas 23, 30 and 31 (posterior cingulate, cognitive circuit) bilaterally; and area 17 of left hemisphere, corresponding to the association visual area (Figure 2).

Hypoperfusion sources are observed lower than 5 SD under the normal average, bilaterally in the Brodmann's area 24, in the left hemisphere in the Brodmann's area 25, bilaterally in the projection of the hippocampus and Brodmann's area 36 as well as in the frontal lobes in the Brodmann's areas 10 and 11. Also, a deep hypoperfusion is observed in the 23-right and lower bilateral temporal *gyrus* (Figure 3).

CONCLUSIONS

There is an association between marijuana use in adolescents and harmful effects on brain functioning, especially in cognitive functions involved in learning: memory, attention, concentration and negative effects as for style of working, accuracy, material organization, execution strategies and ways of addressing the task. The importance of short-term verbal memory in students is evident: in the classroom most of the knowledge is provided orally. If there is no proper working memory, the processing of information thus received is hindered. In turn, the number of errors that young users make in tasks involving attention and concentration —combined with deficiencies in working strategies— constitutes an important factor linked to their poor academic performance problems.

Such association is evidenced through the differences observed in the results of the neuropsychological evaluation tests between marijuana using and non-using students. Using students obtain comparatively low results in all tests, with statistically significant differences. The foregoing allows establishing a clear association between the use and significant reduction of scores obtained in assessed cognitive functions; both regarding the expected and the results of the non-using group.

Through the Neuro-SPECT it is concluded that marijuana produces, in the cerebral cortex, multifocal functional alterations. Especially, *cognition* by hypoperfusion in the hippocampus projection (Brodmann's area 36) is affected, as well as *mood control* affected by Brodmann's area 25 in the left hemisphere and the *executive function* with frontal abnormality in the bilateral Brodmann's areas 10 and 11. It is worth mentioning that the frontal cortex takes part in the range of human behaviors related to the ethical dimension, a function that will also have an effect in the work and social behavior of marijuana-using students.[9]

It is remarkable that, in contrast to surveys conducted in cocaine users, in young marijuana users a focal increase occurred in the frontal function of Brodmann's areas 9, 10 and 46 and in the posterior cingulate, which are segments of the cognitive circuit, and in the Brodmann's area 23 that is an inter-hemispheric communication area. Furthermore, there are functional alterations, in form of multifocal hypofunction of disorganized distribution in marijuana smokers, although of minor statistical significance (less severity) than with cocaine users.

These findings allow us to put forward the presence of neurotoxicity in marijuana users since, when comparing their results with a normative database for persons of the same age group, none of the young users NeuroSPECT's surveys was normal. It is worth adding that the students reported to have used it even during the same week of the NeuroSPECT study.

The foregoing has an effect on the expectations for having a university education within the using group, which are significantly lower: 21% compared to 43% for non-users, according to Dörr et al.[3]

The results of the neuroimaging tests, which show effects in learning-related brain areas, are highly consistent with the scores obtained by the same subjects in the neuropsychological tests, which adds evidence to the negative effects of marijuana use in learning, a central theme of this survey. It is especially important the fact that such results correspond to adolescents who have neither been diagnosed nor labeled as addicts and who, thus, do not represent a public-health problem yet, nor are perceived as adolescents in social risk. However, these youngsters come from socially vulnerable populations associated with poverty, which worsens the consequences or effects that poor academic performance linked to the regular use of marijuana may have in them; considering that education should be the means allowing them greater social mobility.

The lack of risk perception in the consumption, the easy access to *cannabis*, the unquestionable harmful effect on the cognitive functions involved in the academic learning and performance, the increase of the number of using adolescent women, the evidence gathered on *cannabis* as instigator or facilitator of the use of other substances and the reduction of the onset age of use, constitute a problem for public health policies, which involves school, adolescents and their families. Regarding this challenge, the need of a commitment of the institutions is again confirmed, as well as family and school commitment, in the sense that using adolescents neither perceive any risk awareness from their parents or teachers, nor any social control on the use.

ACKNOWLEDGEMENTS

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Declaration of conflict interest: None