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Cognitive deterioration associated with the use of different psychoactive substances

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Introduction. The study of the neuropsychological deficits associated with substance abuse has become highly relevant in recent years due to the serious impact they have on the physical and mental health of users.

Methodology. The possible memory deficits and deterioration of executive functions were studied in a sample of 54 subjects undergoing drug detoxification and rehabilitation. Several neuropsychological tests were applied (Wechsler Memory Scale, Wisconsin Card Sorting Test, Stroop Test, Verbal Fluency Test and the Trail-Making Test).

Results. Subjects with a more prolonged history of alcohol and/or cannabis use had a greater deficit in working memory. Subjects with prolonged cannabis use also showed greater deficiencies in immediate, or short-term, memory and better conserved long-term memory, as well as less interference capacity, i.e., less inhibition of automatic responses. They also had impaired alternating attention and needed more time to execute activities that required logical and sequential thought. The study also reflected the importance of duration of use as a significant variable in the increase in memory deficits.

Conclusions. The duration and type of substance abuse are determinants in drug-induced cerebral deterioration.

Key words:
Memory, executive functions, substance dependence, cognitive deterioration, detoxification.

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Deterioro cognitivo asociado al consumo de diferentes sustancias psicoactivas

Introducción. El estudio de los déficits neuropsicológicos asociados al consumo de sustancias tóxicas ha cobrado gran relevancia en los últimos años debido a las graves repercusiones de salud física y psicológica de los consumidores.

Metodología. En el presente trabajo se evaluaron los posibles déficits de memoria y el deterioro de las funciones ejecutivas, en una muestra de 54 sujetos que se encuentran realizando un tratamiento de desintoxicación y deshabitación. Para ello se aplicaron diversos test neuro-psicológicos (la Escala de Memoria de Wechsler, Wisconsin Card Sorting Test, Test de Stroop, Test de fluidez verbal y el Test de Construcción de Senderos).

Resultados. Reflejaron la presencia de un mayor déficit en la memoria de trabajo en sujetos con una mayor duración de consumo de alcohol y/o cannabis. Los sujetos con un consumo prolongado de cannabis reflejaban también mayores carencias en la memoria inmediata mostrando más conservada la memoria demorada, así como una peor capacidad a la interferencia, es decir, muestran una menor inhibición a las respuestas automáticas. También se observa que poseen una atención alterante disminuida, necesitando más tiempo para realizar actividades que requieren un pensamiento lógico y secuencial. El estudio también reflejó la importancia de la duración del consumo como una variable significativa en el aumento de los déficits de memoria.

Conclusiones. el tiempo y tipo de consumo son determinantes en el deterioro cerebral producido por las drogas.

Palabras clave:
Memoria, funciones ejecutivas, drogodependencia, deterioro cognitivo, desintoxicación.

INTRODUCTION

Problems related to substance abuse generally affect society in one way or another. One million families in Spain have had first hand experience of the consequences of substance or alcohol abuse. Every year more than 20,000 people die prematurely as a result of excessive alcohol consumption. Every year more than 4,000 people are admitted to Spanish hospitals for psychoses produced by alcohol and other drugs.^{1,2} Although the number of people admitted for substance-induced psychosis is important, what is most worrisome is the trend; in the last 10 years the number of admissions for drug-induced psychoses has increased by 103% (Estrategia Nacional sobre Drogas. Plan de Acción 2005-2008 [National Drug Strategy: Action Plan 2005-2008]).

One of the first steps in the fight against substance abuse is to characterize and quantify the damage that substance abuse produces in the brain. Detection of the impact of substance abuse on executive function is fundamental, due to its influence on the prognosis of the outcome of dependence. In this sense, a large number of articles³⁻¹⁰ offer clear evidence of the profound deterioration that substance abuse produces in the brain. Substance abuse causes neuropsychological deterioration via diverse action mechanisms. In the first place, substances of abuse can cause morphologic alterations in brain structure, such as loss of brain volume, reduction in the percentage of gray matter, reduction in the volume of ventricular cerebrospinal fluid, widening of the pericortical space and both lateral ventricles, decreases in neuronal size and neuronal death or cerebral atrophy. Similarly, substances of abuse can exert harmful effects through the metabolic reorganization of synaptic connectivity circuits that occurs as a result of tolerance, abstinence and dishabituation processes, originating biochemical adaptations of the dopamine, serotonin and norepinephrine projection systems that interact with glutamate receptors and can block the mechanisms of long-term potentiation and long-term depression in the hippocampus and nucleus accumbens. Finally, alterations can be produced in cerebral vascularization, parenchymal and subarachnoid cerebral hemorrhage vasoconstriction, and cerebral ischemic infarction.

The primary objective of the present investigation was to study and corroborate some of the neuropsychological deficits known to be produced by prolonged substance abuse and to learn more about the functions most affected. Our working hypothesis, based on previous studies, was that the degree of neuropsychological affectation of subjects would be related to the type of substance(s) used and the duration of substance abuse.

In order to verify this hypothesis, various neuropsychological tests (Wechsler Memory Scale, Wisconsin

Card Sorting Test, Stroop Test, Verbal Fluency Test and the Trail-Making Test) were applied to a large sample (54 subjects) of subjects with alcohol and polysubstance abuse undergoing detoxification and dishabituation, all from the Municipal Therapeutic Community of Barajas. The subjects were men aged 21 to 61 years.

As we had hypothesized, the type and duration of substance abuse affected target functions in a determinant manner. Perhaps the most surprising conclusion of this study was related to the type of substance abuse. All the subjects had neuropsychological deficits, but alcohol and cannabis users showed more affectation of neuropsychological functions, particularly of the memory system and its interference capacity.

In conclusion, the fact that the two most socially "accepted" substances (cannabis and alcohol) had the greatest neuropsychological impact might suggest that our strategy in the "battle" against substance abuse should be reconsidered.

METHOD

Subjects

A sample of 54 subjects from the Barajas Municipal Therapeutic Community was obtained. The subjects were men aged 21 to 61 years.

In order to participate in the study, subjects had to satisfy the ICD-10 criterion for disorders due to psychoactive substance use:

- a) They must have presented three or more of the following manifestations simultaneously during at least one month or, if they persisted less than a month, the manifestations must have occurred repeatedly and simultaneously over a period of 12 months.
- b) An intense desire or compulsion to consume a substance.
- c) Diminished capacity to control substance use with regard to starting, ending or controlling the amount used, as shown by: frequent use of larger amounts or for more time than intended, or persistent desire or unsuccessful efforts to reduce or control substance use.
- d) A physiological picture of abstinence when substance use is reduced or stopped, as demonstrated by the abstinence syndrome characteristic of the substance, or by use of the substance itself (or similar substance) to relieve or prevent abstinence symptoms.
- e) Tests of tolerance of the effects of the substance, such as the need to significantly increase the amount of the

substance to achieve intoxication or the desired effect, or marked reduction of the effect after continued use of the same amount of substance.

- f) Concern about substance use manifested by loss of, or diminished, interest in other important activities that are pleasant or of interest as a result of substance abuse; or the dedication of a large amount of time to the activities necessary to obtain, use, or recover from the effects of the substance.
- g) Persistent substance use despite clear proof of its detrimental consequences, as evidenced by continued substance use when the individual is aware of, or can be assumed to have knowledge of, the nature and extent of damage.

In addition, the subjects had to have been abstinent from any type of substance abuse for more than one month, as confirmed by urine tests, to have normal or corrected to normal eyesight and to speak Castilian Spanish as the mother tongue or as a tongue in which the subject is fluent.

The demographic characteristics of the study subjects are summarized in the following table (Table 1).

Description of neuropsychological tests

Mini-Mental State Examination (MMSE)

This test is a neuropsychological screening instrument for assessing cognitive performance by evaluating the subject's orientation in space and time, memory, language and praxis. We used the MMSE to obtain a general idea of the subject's cognitive performance.

Wechsler Memory Scale III (WMS-III)

The WMS-III enables the evaluation of immediate, working and delayed memory. Each type of memory is evaluated using two stimuli (auditory and visual) and two types of tasks (recall and recognition). The WMS-III consists of 11 tests: 6 primary and 5 optional. The 6 main tests are applied twice at a time interval of approximately 30 minutes between applications. We also added the optional Digits test to evaluate attention span and working memory.

Wisconsin Card Sorting Test (WCST)

This test is a measurement of executive function that requires strategies of planning, organized queries and use of environmental "feedback" to change schemes. It measures the capacity to form new concepts, change cognitive strategy, tendency to perseveration, use of abstract

Table 1		Demographic characteristics of the sample	
Mean age	39.59	Marital status	
		Single	34 (62.96%)
		Married/ significant other	5 (9.58%)
Sex		Separated/ divorced	15 (27.77%)
Man	54 (100%)		
Woman	0		
		Occupational status	
Cultural level		Employed (on sick leave)	3 (5.55%)
No/primary studies	43 (79.63%)	Unemployed	44 (81.48%)
Secondary studies	9 (16.67%)	Permanent work disability	7 (12.96%)
University studies	2 (3.70%)		

reasoning, mental flexibility and capacity to adapt to possible environmental changes. Given its potential sensitivity to the effects of frontal lobe lesions, it is often cited as a measurement of frontal or prefrontal function. The test consists of organizing a set of cards in which each card contains 1 to 4 circles, crosses, stars and triangles of green, yellow, red or blue. The task consists of grouping the cards into 4 piles according to different criteria, without giving explicit instructions since the subject is who must guess the keys to organize the cards based on the examiner's answers ("correct" and "incorrect").

Stroop color and word test

This test is used to evaluate Executive Functions and is used broadly to evaluate the frontal lobe. It consists of three parts: The first part is to read words (names of colors) written in black ink. The second part is to name the color of the cards marked "x." The third part, called the interference task, is to read a list of words (names of colors) printed in different colors, in which the name of the color is printed in ink of another color. For instance, the word "red" is printed in ink that is never red, but green or blue. Comparison of the scores obtained on the three scales allows the effects of interference on the subject to be evaluated. This test measures sustained and selective attention, inhibition capacity and the capacity to classify information selectively in reaction to this information.

Verbal Fluency Test FAS

Verbal fluency is an attribute of the Broca area and an indirect measurement of executive functions. The Broca area is

evaluated with verbal fluency tests that consist of programmed phonemic and semantic type verbal production tasks. The phonological fluency task requires the subject to say as many words beginning with a certain letter (FAS) as possible in a one-minute period. The semantic fluency test consists of saying names of categories for one minute. The categories chosen were animals, fruits and kitchen utensils. The number of words in a category said in the established time period for the test is evaluated.

Trail-Making Test

The TMT has two parts, A and B. Part A is to consecutively join numbers distributed randomly on a paper with a line. Part B is more complex and consists of joining letters and numbers randomly distributed over a page in alternating order. TMT has an important spatial component that it is related to the right hemisphere and also evaluates visual-motor capacity and perceptive quickness. Aside from the spatial component, test execution requires logical and sequential thought, which is why it is more related to the left hemisphere. It also measures inhibition capacity, mental flexibility, anticipation capacity, alternating attention and working memory.

Procedure

The sample was obtained from the residents of the Municipal Therapeutic Community of Barajas (Madrid, Spain). After admission, a clinical history was opened to obtain all the biographical data and the patient's history of substance abuse. From the time of admission and for the duration of the subject's stay in the community, urine tests were made to detect the use of substances of abuse. A stay of one month and a half to two months in the community was planned, a period in which the elimination of toxins from the body was confirmed and any bias derived from recent substance use was eliminated. On this date, we started to apply the battery of neuropsychological tests. The MMSE was the first test administered, as a preliminary examination of the subject's cognitive status and spatial and temporal orientation.

The entire neuropsychological battery took about 2.5 hours to complete, divided into two mornings. The time differences depended on the subject's characteristics. Some subjects needed more time to carry out the different tests than others. The evaluation was corrected after it was completed. All the scores obtained were entered in a computer for statistical analysis.

Statistical analysis

Once the evaluation was completed and tests were corrected, the statistical analysis was made. Of the 54

original patients, 12 were eliminated from the analysis because a large part of their data was incomplete, leaving 38 patients. Of these 38 patients, some of them had incomplete observations or missing data. Consequently, missing data were imputed using the SAS "proc mi" procedure. The statistical analysis was conducted according to the following steps:

Data were imputed by means of the MI (Multiple Imputation) method of SAS. This multiple imputation technique replaces each missing value with a set of possible values that represents the uncertainty of the true value imputed. The chosen standard statistical analysis can be applied to the various "complete" sets and the results are combined to estimate the proposed parameters. MI has three phases:

- Imputation: lost values are imputed m times, generating m "complete" data sets.
- Analysis: each of the m "complete" data sets is analyzed using standard statistical methods.
- Combination: the results obtained from each one of the m data sets are combined to make the inference.

Imputation is the most critical step because it depends on assumptions about the characteristics of the loss mechanism for the imputation model applied. The multiple imputation technique can be applied to all sorts of data prior to any statistical analysis and it allows ancillary information to be added to the imputation model. It works under the assumption that data are lost randomly (MAR), i.e., that the probability that an observation is lost depends on the observed values but not on the lost values of the corresponding unit.

The basic assumptions for a canonical correlation were reviewed (normality, non-redundancy, homoscedasticity).

Redundancy was corrected with principal components analysis.

Canonical correlation was performed.

RESULTS

With regard to the memory system, individuals with more alcohol use, more cannabis use, and less cocaine use had a greater deficit in working memory than in short-term memory. In addition, subjects who used cannabis had more short-term memory impairment and better conserved long-term memory than the subjects with alcohol abuse. With regard to the duration of substance abuse, the results of the study showed that the duration of use was significant for the appearance of memory deficits, indicating that the

longer the duration of alcohol abuse (mainly), as well as cannabis use, the greater the problems in working memory.

As regards the executive functions, patients with a greater duration of cannabis use and alcohol use had worse interference capacity, i.e., less inhibition of automatic responses. It was also observed that they had diminished alternating attention, needing more time to carry out activities that require logical, sequential thought. However, the phonological aspect of verbal fluency was better conserved in patients with cannabis or alcohol abuse compared to other types of substance abuse.

DISCUSSION

The anatomo-functional localization of the executive functions (EF) is the frontal lobes and their connections. The executive system coordinates multiple complex processes necessary to start and stop mental operations, and to maintain motivation and persistence.

The results obtained with regard to EF were consistent with the findings of previous studies in subjects with alcohol abuse that demonstrate deficits in executive functions, such as impaired inhibition of automatic response, mental flexibility, generalization of concepts and execution of visuo-spatial areas.¹¹⁻¹³ Previous studies of subjects with cannabis abuse show significantly deteriorated performance with regard to attention, information processing and memory tasks.¹⁴ In the prospective study by Fletcher,¹⁵ memory deficits were also detected in free recall and selective and divided attention tasks.

With regard to memory, the results of the study presented significant evidence that individuals with more alcohol abuse (mainly), more cannabis abuse, and less cocaine abuse presented a greater deficit in working memory than in short-term memory, without showing any relation to long-term memory. This alteration in working memory also indicated a disturbance in the three subsystems that compose working memory, as envisioned by Baddeley-Hitch (1974): the phonological loop (which allows the active storage of verbal information), the visuo-spatial sketch pad (for the creation, storage and manipulation of visual images) and the central executive system (which guides attention by coordinating cognitive processes, including working memory, and regulating the selection strategies and control functions). This type of memory is a key to learning new things. When these results were compared to the existing bibliography, they coincided with a recent review by Landa⁸ that concludes that most investigations indicate the existence of deterioration in the working memory and executive functions in subjects with alcohol abuse. In the investigation by Ambrose,¹⁶ in which a test designed to determine the

functionality of the working memory (delayed alternation task) was used, the same conclusion was reached. These authors claim that this temporary memory store is affected in subjects with alcohol abuse, even in the absence of other severe cognitive deficits. However, there is less coincidence with regard to the rest of the mnemonic alterations in persons with alcohol abuse. In some studies, general memory capacity has been found to be affected, whereas verbal memory remains unaltered.^{7, 17, 18} In others, better conservation of the visual memory¹⁹ is observed, although discrepant results have been reported.^{17, 18} The results also indicate that subjects who use cannabis have more impaired short-term memory, showing better conserved long-term memory compared to short-term memory. Studies of the impact of cannabis also suggest the presence of memory deficits in cannabis users.^{4, 20}

With respect to the duration of cannabis use, the results of this study coincided with other studies²⁰⁻²² that show that neuropsychological deficits are associated with the frequency, intensity and duration of cannabis use.

In any case, it must be emphasized that it is extremely difficult to obtain an exhaustive history of cannabis use due to the combination of multiple substances at different periods of time and the problems that subjects have in remembering details about use in the context of a totally destructured life. In addition, we wish to remark that since there was no control group in the study, these results give only a partial view of the impact of substance abuse on memory and EF, since they only indicate the functions that were more affected compared to other functions. These results would have to be compared to a control group to more clearly identify the functions that may be affected by prolonged substance abuse.

Despite these difficulties, the hypotheses established in the present study were corroborated: the duration and type of substance abuse were determinant in the cerebral deterioration produced by drugs.

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