Originales

Addictiveness as a risk factor for verbal memory deficit in schizophrenia: a case-control study

La adictividad como factor de riesgo del déficit de memoria verbal en la esquizofrenia: estudio de casos y controles

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Received: 14/07/2021 · Accepted: 07/09/2021

Cómo citar este artículo/citation: López Lorenzo, S., Jimeno Bulnes, N. and Vargas Aragón, M. L. (2021). Addictiveness as a risk factor for verbal memory deficit in schizophrenia: a case-control study. *Revista Española de Drogodependencias*, *46*(3), 48-59. https://doi.org/10.54108/red.2021.46.03.004

Abstract

Cognitive deficit is one of the main prognostic predictors in schizophrenia, mainly the deficit in verbal memory. The causal relationship between substances use, substance use disorders and psychotic syndrome is probably multidirectional and still is under the possible effect of confusion factors. The Addictiveness in the Psychotic Syndrome Assessment Scale (APSAS) evaluates in a global mode the dimension of adictivity taking in account all these factors: beginning, frequency, length, and intensity. The objective of the study is to know if the dimension of adictivity is associated to memory disorders. A group of psychotic subjects with memory deficits (n = 47) and a control group of psychotic subjects without memory deficits (n = 58) are compared obtaining a major adictivity in the first group. According to our results, the score of APSAS > 55 indicates possible memory deficits. This measuring can provide relevant information on the actual state, evolution and prognose of patients with comorbidity of psychosis and addiction.

Keywords

Adiction; schizophrenia; comorbidity; cognition; verbal memory; substance use; psychosis.

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Resumen

El déficit cognitivo es uno de los principales predictores pronósticos de la esquizofrenia, especialmente el déficit de la memoria verbal. La relación de causalidad entre el uso de sustancias, los trastornos por uso de sustancias y el síndrome psicótico es probablemente multidireccional y aún está sujeto a diversos posibles factores de confusión. La Escala de Evaluación de la Adictividad en el Síndrome Psicótico (EASP) evalúa de manera global la dimensión de adictividad atendiendo a todos estos factores: inicio, frecuencia, duración e intensidad. El objetivo del estudio es conocer si la dimensión de adictividad se asocia al déficit de memoria verbal. Para ello se compara un grupo de sujetos psicóticos que presentaban déficit de memoria (n= 47) y un grupo control de sujetos psicóticos sin déficit de memoria (n= 58) y se comprueba una mayor adictividad en el primer grupo. Según nuestros resultados, una puntuación en EASP > 55 es indicador de posible déficit de memoria. Esta medición puede aportar información relevante sobre el estado actual, evolución y pronóstico de los pacientes con comorbilidad de psicosis y adicción.

Palabras Clave

Adicción; esquizofrenia; comorbilidad; cognición; memoria verbal; uso de sustancias; psicosis.

INTRODUCTION

From the first descriptions of schizophrenia, the cognitive deficit was already considered a cardinal symptom. This cognitive deficit has not only been described in subjects with long-lasting schizophrenia, but also in patients with a first psychotic episode, patients in remission, and even in studies in high-risk subjects and in healthy first-degree relatives of patients with psychosis. Thus, today there is consensus to consider that neurocognitive deficit plays a key role in schizophrenia (Cella et al., 2020; Falkai et al., 2015; Krug et al., 2020).

In addition, several studies have shown the existence of significant differences in cognitive performance between healthy people and subjects with schizophrenia. Patients with schizophrenia perform 1.5-2 standard deviations lower than healthy individuals on different cognitive tests (Heinrichs & Zakzanis, 1998; Solís-Vivanco et al., 2020).

Likewise, in relation to functional response, cognitive functions are considered better prognostic predictors than symptomatology, especially verbal memory deficit. Moreover, verbal memory has been proposed as a marker of genetic vulnerability for schizophrenia. Furthermore, the impairment of verbal memory in these patients corresponds to the structural alterations found in the temporal lobe and hippocampus (Antoniades et al., 2018). These studies are reinforced both by post-mortem neuropathological investigations and in vivo studies using structural Magnetic Resonance Imaging (MRI) in schizophrenia (Fernandez et al., 2018; Pirnia et al., 2015). The verbal memory deficit in psychotic disorders has a direct impact on occupational, family, and social functioning, as well as on health and lifestyle. This process also has a strong prognostic impact and on the clinical evolution of the illness. For all these reasons, it is widely accepted

that the study of cognition in schizophrenia is important for a correct etiopathogenic, pathophysiological, and clinical understanding of the illness.

Another highly prevalent and clinically relevant problem associated with schizophrenia is the use of psychoactive substances. Epidemiological studies in the general population and those based on the clinical evaluation of schizophrenic populations have revealed that substance use is more frequent in people with schizophrenia than in the general population. The systematic review and meta-analysis carried out by Hunt et al. (Hunt et al., 2018), where the prevalence of comorbidity of substance use and their comorbidity with schizophrenia spectrum disorders are studied in community and clinical settings of different countries, from 1990 to 2017, concludes that the prevalence of comorbidity between psychotic pathology and drug use disorders is 42%, that substance use was higher in men (48%) than in women (22%), that people with addictiveness showed an earlier age of onset of schizophrenia, and that these prevalence rates of comorbidities have not changed over time.

In relation to this, a series of theories have been proposed with the intention of explaining the high incidence of comorbidity between psychosis and addiction (Khokhar et al., 2018).

1. Addiction and psychosis may have common factors: a shared biological vulnerability characterized by a dysfunction of mesocorticolimbic dopaminergic circuits is proposed. This means that they would have different symptomatic expressions of the same neurobiological abnormalities (Brady & Sinha, 2005).
2. Psychosis is a risk factor for the development of a comorbid substance use disorder. Patients would use substances in an attempt to minimize and stop the symptoms resulting from their illness and from their drug treatment (self-medication). Today this hypothesis is practically rejected.
3. Addiction as a risk factor for the development of psychosis. This hypothesis relates to research that proposes a relationship between previous cannabis use and the development of subsequent psychosis (Lowe et al., 2019).
4. Bidirectional relationship between addiction and psychosis: there would be a continuous interaction between both, by which each of them could contribute to triggering, maintaining, or worsening the other.

Ultimately, these data indicate that the causal relationship between substance use, substance use disorders and psychotic syndrome is probably multidirectional and subject to various possible confounding factors.

Research on comorbidity between addictive disorders and psychotic syndrome presents, among others (Jimeno et al., 1997), two methodological difficulties. The first is that the evaluation or measurement of substance use as a risk factor in psychiatry is complex, since it is common to use various substances with highly variable patterns of onset, frequency, duration, and intensity. As a potential way to address this first difficulty was constructing the Addictiveness in the Psychotic Syndrome Assessment Scale (APSAS) which is presented in another article of this monographic issue (Vargas et al., 2021).

Although in previous studies of our group two dimensions seemed to differentiate - legal addiction and illegal addiction- (Vargas & Lopez, 2010), the subsequent analysis with a larger sample suggests that addictiveness is a one-dimensional construct as shown in the accompanying article to this monograph (Vargas et al., 2021). Furthermore, its independence with respect to the remaining clinical dimensions of the psychotic syndrome seems to be confirmed. The second difficulty is that of differentiating psychiatric comorbidity in substance-using patients, since the acute or chronic effects of substance use may coincide with the symptoms of various mental disorders. Faced with this problem, we have chosen to consider addictiveness, not as a comorbid disorder, but as one more symptomatic dimension of psychosis. It would be caused by a frontal subcortical alteration, largely coinciding with the one responsible for the positive and negative schizophrenic symptomatology.

Since verbal memory alterations are one of the main prognostic predictors of schizophrenia and considering that these alterations share common pathophysiological mechanisms with addiction and psychosis, memory alterations could be considered as a common marker, both of the classical dimensions of the psychotic syndrome and the addictiveness dimension. The objective of this study is to find out if there is an association between the addictiveness dimension and memory deficits in the clinical spectrum of schizophrenia. The finding of such an association would allow, on the one hand, to support the proposed model according to which addictiveness would be another manifestation of a common neurocognitive disorder which underlies psychotic disorders and, on the other, to provide useful knowledge for the use of neuropsychological examination in the study of dual pathology.

MATERIAL AND METHODS

A case-control study has been carried out on 105 outpatients with some type of psychotic disorder. The sample, which is described in detail in the accompanying article to this monograph (Vargas et al., 2021), was divided into a group of cases with memory deficit (n = 47) and a group of controls without memory deficit (n = 58). Those subjects who scored Z <-1 in any of the following four memory tests were assigned to the group of cases: immediate memory index of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Sanz et al., 2009; Vargas et al., 2009), delayed memory index of RBANS, short-term free recall of the Spanish version of the California Verbal Learning Test (*Test de Aprendizaje Verbal España-Complutense* -TAVEC-) (Benedet & Alejandre, 2014), long-term free recollection of TAVEC. Subjects who scored Z > -1 in each of the four tests were assigned to the group of controls with normal functioning in verbal memory. Both groups were compared in the addictiveness dimension, which was evaluated using the APSAS scale. A contrast of the mean difference was performed using the Student's t statistic and comparison of proportions was performed using Fisher's exact test. For type I error, p <0.05 was taken as the level of statistical significance. Table 1 shows the sociodemographic and clinical characteristics of both groups. Significant differences are observed in the clinical characteristics, so that the group with cognitive deficits presents more symptoms

and worse functional performance. Using logistic regression, the potential confounding effect of age, and symptom intensity according to the PANSS (Kay et al., 1987) and the ICG (Rabinowitz et al., 2006) scales, and general cognitive functioning evaluated with the Trail Making test, part B (Llinàs-Reglà et al., 2017), were successively controlled. Using a ROC curve, it was studied the utility of the APSAS as an indirect estimator of the risk for cognitive deficit associated with substance use.

RESULTS

Table 2 shows the scores obtained in the different items, dimensions, and total score of the EASP in both groups. The effect size by Cohen's d indicator is also indicated. The difference in addictiveness is significant between both groups, such that memory deficit is associated with greater general addictiveness with a moderate effect size (d> 0.5). The most important effect is associated with the use of opioids and cocaine. The differences remain statistically significant after controlling for the potential confounding effect of age, symptom intensity, and general cognitive functioning. Table 3 shows the correlations between the symptom dimensions and the general neurocognitive performance evaluated with TMB. Here it can be observed that, contrary to what happens with the remaining symptom dimensions, addictiveness (EASP) is not associated with general cognitive

Table 1. Sociodemographic and clinical characteristics of the sample (n = 105)

	With memory deficit (n=47)	Without memory deficit (n=58)	
			Fischer (d.f.); p (bilateral)
Sex: n (%)			
Men	38 (80,85 %)	31 (53,45 %)	8,570 (1); *p = 0,004*
Women	9 (19,15 %)	27 (46,55 %)	
			t (g.l.); p (bilateral)
Age (years): mean (SD)	38,59 (10,42)	40,97 (8,95)	1,257 (103); *p = 0,212*
Years of education	8,62 (2,97)	10,90 (3,49)	3,553 (103); *p= 0,001*
PANSS[1]			
PANSS- positivo	13,40 (4,43)	9,84 (2,91)	-4,743 (76,358); *p < 0,001*
PANSS- negativo	17,60 (7,32)	14,64 (6,68)	-2,161 (103); *p = 0,033*
PANSS-general	28,98 (8,93)	23,95 (7,68)	-3,054 (91,189); *p = 0,003*
PANSS-total	59,98 (18,71)	48,43 (15,41)	-3,468 (103); *p = 0,001*
FCQ-3[2] (n = 78)	41,64 (27,99)	21,53 (20,57)	-3,492 (55,975); *p = 0,001*
ICG[3]	3,51 (1,33)	2,33 (1,36)	-4,487 (99,192); *p < 0,001*
GAF[4]	62,79 (13,73)	71,31 (12,43)	3,333 (103); *p= 0,001*

[1] Positive and Negative Syndrome Scale. [2] Frankfurt Complaint Questionnaire, third version. [3] Clinical Global Impression.
[4] Global Assessment of Functioning scale.

performance. It appears, therefore, that addictiveness is selectively associated with memory deficits. Figure 1 shows the ROC curve (area under the curve 0.664; SD 0.054; p = 0.004). According to this analysis, the cut-off point of EASP ≥ 55 (habitual-high addictiveness) can be proposed as an indicator of possible memory deficit (sensitivity 62%, specificity 63%).

DISCUSSION

The objective of our work has been to study the association between the addictive dimension and the memory deficit in a clinical sample of outpatients diagnosed with some type of psychotic disorder. The results of our study determine that addictiveness is associated with memory deficit in psychotic

Table 2. Addictiveness (APSAS) in the groups with memory deficit and without memory deficit

Substance	With memory deficit (n=47)	Without memory deficit (n=58)	t (g.l.); *p* (bilateral)	*d*
1. Tobacco	15,64 (5,49)	12,47 (7,13)	-2,576 (102,766); *p= 0,011*	0,48
2. Coffee and other drinks and foods	12,77 (5,99)	11,95 (6,31)	-0,675 (103); *p= 0,501*	0,13
3. Alcohol	11,94 (5,69)	8,98 (6,02)	-2,562 (103); *p= 0,012*	0,49
4. Cannabis	8,32 (6,97)	5,33 (6,18)	-2,329 (103); *p= 0,022*	0,45
5. Amphetamines and psychostimulant 'pills'	3,23 (4,88)	1,76 (3,70)	-1,713 (84,074); *p= 0,090*	0,34
6. Hallucinogens	1,94 (3,45)	1,02 (2,49)	-1,530 (81,236); *p= 0,130*	0,31
7. Cocaine	5,87 (6,91)	2,29 (4,26)	-3,104 (73,016); *p= 0,003*	0,61
8. Opiates	4,26 (6,13)	0,93 (3,06)	-3,392 (64,352); *p= 0,001*	0,67
9. Psychopharmacological drugs	2,13 (4,70)	0,36 (1,95)	-2,413 (58,854); *p= 0,019*	0,50
10. Volatile substances	0,28 (1,90)	0,00 (0,00)	-1,000 (46,000); *p= 0,323*	0,22
11. Gambling	4,66 (6,66)	2,72 (5,40)	-1,608 (88,125); *p= 0,111*	0,32
12. Other behavioural addictions	2,87 (4,72)	2,64 (4,31)	-0,266 (103); *p= 0,791*	0,05
Total APSAS	73,89 (42,57)	49,75 (31,65)	-3,222 (83,281); *p= 0,002*	0,64

Table 3. Correlations between symptom dimensions and general neurocognitive performance assessed with the Trail Making Test part B

			EASP	PABNSS pos	PANSS neg	PANSS gen	PANSS tot	FCQ-3	ICG	GAF	TMB
Spearman's rho	EASP	Correlation Coefficient	1,000	,049	-,193*	-,041	-,093	,289*	,026	-,042	,021
		Sig. (2-tailed)	.	,624	,050	,676	,345	,011	,792	,674	,833
		N	104	104	104	104	104	77	104	104	103
	PABNSS pos	Correlation Coefficient	,049	1,000	,649**	,791**	,849**	,542**	,800**	-,735**	,370**
		Sig. (2-tailed)	,624	.	,000	,000	,000	,000	,000	,000	,000
		N	104	105	105	105	105	78	105	105	104
	PANSS neg	Correlation Coefficient	-,193*	,649**	1,000	,762**	,900**	,255*	,763**	-,798**	,372**
		Sig. (2-tailed)	,050	,000	.	,000	,000	,024	,000	,000	,000
		N	104	105	105	105	105	78	105	105	104
	PANSS gen	Correlation Coefficient	-,041	,791**	,762**	1,000	,950**	,412**	,852**	-,820**	,337**
		Sig. (2-tailed)	,676	,000	,000	.	,000	,000	,000	,000	,000
		N	104	105	105	105	105	78	105	105	104
	PANSS tot	Correlation Coefficient	-,093	,849**	,900**	,950**	1,000	,416**	,889**	-,869**	,390**
		Sig. (2-tailed)	,345	,000	,000	,000	.	,000	,000	,000	,000
		N	104	105	105	105	105	78	105	105	104
	FCQ-3	Correlation Coefficient	,289*	,542**	,255*	,412**	,416**	1,000	,572**	-,452**	,348**
		Sig. (2-tailed)	,011	,000	,024	,000	,000	.	,000	,000	,002
		N	77	78	78	78	78	78	78	78	77
	ICG	Correlation Coefficient	,026	,800**	,763**	,852**	,889**	,572**	1,000	-,896**	,427**
		Sig. (2-tailed)	,792	,000	,000	,000	,000	,000	.	,000	,000
		N	104	105	105	105	105	78	105	105	104
	GAF	Correlation Coefficient	-,042	-,735**	-,798**	-,820**	-,869**	-,452**	-,896**	1,000	-,467**
		Sig. (2-tailed)	,674	,000	,000	,000	,000	,000	,000	.	,000
		N	104	105	105	105	105	78	105	105	104
	TMB	Correlation Coefficient	,021	,370**	,372**	,337**	,390**	,348**	,427**	-,467**	1,000
		Sig. (2-tailed)	,833	,000	,000	,000	,000	,002	,000	,000	.
		N	103	104	104	104	104	77	104	104	104

*. Correlation is significant at the 0.05 level (2-tailed).

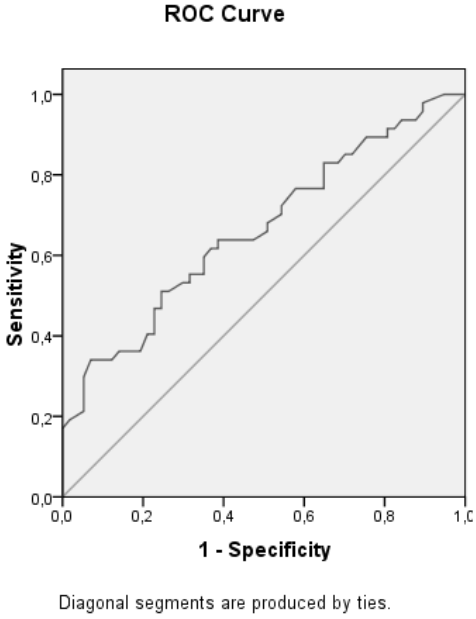
**. Correlation is significant at the 0.01 level (2-tailed).

disorders in a way that is independent of clinical status, general cognitive deficit, and age. Our results also support the hypothesis that addictiveness is an independent dimension in the spectrum of schizophrenia, which differs from the positive, negative, disorganized and hostility dimensions (Vargas & Lopez, 2010).

The prevalence of the diagnosis of dual pathology in schizophrenia is high, and in addition these patients have a greater tendency to obtain negative results in different spheres of life, and a worse prognosis of the illness. In this sense, it has been shown that patients with dual pathology have higher rates of relapses and hospitalizations, more severe symptoms of the illness, less adherence to treatment, more mood swings and aggressiveness, more suicidal ideation, as well as alterations in global functioning with a higher risk for social and legal problems (Hunt et al., 2018).

In recent years, different theories have been developed to explain the association between substance use and psychosis. Thus, it has been suggested that addiction in psychosis can be a causal or precipitating factor in the development of a psychotic episode in vulnerable subjects, or that it could be a consequence of the disease. Another option could simply be the existence of high comorbidity. These hypotheses are not mutually exclusive, and may be related to each other (Green, 2007; Green et al., 2008). In this sense, scientific literature explains these results under the hypothesis that there is a genetic susceptibility in schizophrenia in which brain circuits involved in reward and motivation are affected, specifically in the dopaminergic mesocorticolimbic system. Thus, these circuits can drive in these persons both initiation as the continuous use of

Figure 1. ROC curve of APSAS scoring for the diagnose of verbal memory deficit



addictive substances (Deserno et al., 2015; Thompson et al., 2013). Magnetic resonance imaging studies support this hypothesis (Heckers, 2001), as do the results found in research with animal models (Winship et al., 2019). Dysfunction of the hippocampus and the frontal cortex have been proposed as responsible for the dysfunction of the brain reward circuit in these patients. The hippocampus plays a key role in modulating dopaminergic activity within the nucleus accumbens. Development of these abnormalities in the interaction between the hippocampus, prefrontal cortex, and nucleus accumbens may produce motivational disorders consisting in long-term substance abuse (without prior drug exposure), and simultaneously they may facilitate the reinforcing effects of substances, consistent with

the dopaminergic hypersensitivity observed in patients with dual diagnosis (Hunt et al., 2018; Thompson et al., 2013).

The results of our study, which show an association of addictiveness with deficits in a function closely related to the hippocampus, such as memory, support this model. The addictiveness construct, like memory deficits, could be interpreted as related to alterations in the hippocampus, the structure responsible for the regulation of emotion, learning, and memory (Antoniades et al., 2018).

The assessment of addictiveness in psychotic syndrome can be considered important not only from the point of view of early detection and intervention, but also for the development of eventual more personalized treatments in clinical practice. It also supports the convenience of performing cognitive rehabilitation therapies, with the aim of improving memory to achieve greater social integration. However, we must point out that memory impairment, in turn, can crucially disrupt the therapeutic benefit, since the retention of complex instructions, the selection of relevant information in sessions or the generalization of what has been learned to other situations might be diminished if there were a strong memory impairment.

Various investigations link memory deficits with cannabis use more than with other substances (Urits et al., 2020). However, in our study, memory deficit was associated with greater addictiveness for the consumption of opioids and cocaine. This suggests that cognitive verbal memory deficits in schizophrenia may be due to various types of factors, those of schizophrenia and those derived from drug use. The memory deficit associated with schizophrenia could produce a ground effect whereby the memory deficit associated with the use of cannabis would go unnoticed. This is not the case in opioid and cocaine users, who could associate less primary schizophrenic deficit, which would reveal the detrimental effect of the substance on memory. More work is needed in this line to analyse this argument in depth, although our study points out that the neuropsychological evaluation could be very useful in the differential diagnosis of schizophrenia with dual pathology as we are proposed in previous research (Vargas et al., 2009).

The results obtained in this study should be interpreted with caution, fundamentally given two limitations: i) the sample of psychotic disorders used is heterogeneous, therefore, the results should be confirmed in other studies with independent samples, ii) the cross-sectional nature of this research, that does not allow comparing the evolution in both groups of patients. Therefore, the validity of these results should be confirmed in other investigations that use independent samples of greater homogeneity and size, and carry out longitudinal studies. However, among its strengths is firstly the consistency of the results obtained suggesting the interest of the association found between memory deficit and the clinical dimension of addictiveness in patients with comorbidity of psychosis and substance use, and secondly, the need, in the clinical practice, of the evaluation of this deficit to improve the prognosis and treatment of these patients.

For future work in this line, it should be noted the importance of continuing to examine the role of addiction in the development of psychotic disorders, both in clinical samples and in subjects at high risk of developing psychosis. It is also important to evaluate and analyse the effects of reducing consumption in these patients, to continue researching in the development of new

pharmacological treatments that improve the cognitive functioning of memory, in addition to perfecting comprehensive rehabilitation and treatment programs that help both to " clinic recovery", understood as the remission of symptoms, and to the "personal recovery", conceived as social integration and satisfaction with life in a complementary and bidirectional way (Slade et al., 2008).

CONCLUSIONS

The present study supports that the addiction dimension in psychosis may be the result of brain alterations common to the mechanisms of psychosis and addiction. In relation to the clinical applications of our work, the present findings support the use of the APSAS as a valid and useful tool to measure the dimension of addiction in psychosis. Addictiveness is an independent dimension and is associated with a memory deficit, so it could be a useful prognostic indicator if we consider that verbal memory is a good prognostic predictor of psychosocial functioning in schizophrenia. According to our results, an APSAS score $\geq$ 55 may be an indicator of poor prognosis associated with memory deficit. This measurement can provide relevant information on the current status, evolution and prognosis of patients with comorbidity of psychosis and addiction.

ACKNOWLEDGES

This work is part of the research line of the doctoral program in Clinical and Health Psychology. Autonomous University of Madrid UAM. Research project: Analysis of the clinical utility of the Verbal-Complutense Learning Test (TAVEC) and its predictive capacity in long-term recovery from schizophrenic syndrome.

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