Impact of neuropsychological disorders on clinical aspects of smoking

Impacto de las alteraciones neuropsicológicas sobre aspectos clínicos en tabaquismo

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Abstract

Studies examining associations between cognitive measures and clinical aspects of smoking are scarce and generally limited to predicting risk profiles or relapses. However, it is essential to understand the influence of several measures of executive function in nicotine addiction in order to investigate factors associated with smoking maintenance. This study examined the ability of working memory and delay discount to predict years of smoking. The sample consisted of 180 smokers who were assessed at baseline with measures of cognitive impulsivity (Delay Discounting Task) and working memory [Visual Search and Attention Test (VSAT) and Letter-Number Sequencing (WAIS III)] while the outcome measure was years of smoking. Consistent with predictions, working memory evaluated with Visual Search and Attention Test was a statistically significant factor in predicting years of nicotine addiction. These findings suggest that working memory is clinically relevant in nicotine dependence and proposes a pattern of executive functioning associated with smoking.

Keywords: Smoking; addictive behavior; working memory; delay discount.

Resumen

Los estudios que examinan las asociaciones entre las medidas cognitivas y los aspectos clínicos del tabaquismo son limitados y, en general, se limitan a predecir perfiles de riesgo o recaídas. Sin embargo, es esencial comprender la influencia de varias medidas de la función ejecutiva en la adicción a la nicotina a fin indagar factores asociados al mantenimiento del tabaquismo. En el presente estudio se examinó la capacidad de la memoria de trabajo y el descuento por retraso para predecir los años de tabaquismo. La muestra consistió en 180 fumadores que fueron evaluados en la línea de base con medidas de impulsividad cognitiva (Tarea de Descuento de Retraso) y memoria de trabajo [Prueba de Búsqueda y Atención Visual (VSAT) y Secuenciación de Números de Letras (WAIS III)] mientras que la medida de resultado fue los años de adicción. De acuerdo con las predicciones, la memoria de trabajo evaluada con la Prueba de Búsqueda y Atención Visual fue un factor estadísticamente significativo para predecir los años de adicción a la nicotina. Estos hallazgos sugieren que la memoria de trabajo es clínicamente relevante en la dependencia de la nicotina y plantea un patrón de funcionamiento ejecutivo asociado al tabaquismo.

Palabras clave: Fumar; comportamiento adictivo; memoria de trabajo; descuento por retraso.

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The tobacco epidemic is one of the most persistent international threats to public health (WHO, 2019). Given that a sizeable percentage of smokers become dependent, nicotine has been shown to be one of the most addictive psychoactive substances (Detandt, Bazan, Quertemont & Verbanck, 2017). Specifically, the reinforcing effects of nicotine trigger the activation of the brain reward system that drives the probability of repeat consumption (Carlson, Birkett & Redolar Ripoll, 2018). Nicotine addiction therefore represents a disorder semiologically characterised by compulsive use, a gradual loss of control over use and the appearance of a characteristic clinical picture of syndromes associated with withdrawal (Zarrindast & Khakpai, 2019). The consolidation of dependence is the result of the confluence between earlier vulnerability factors and a specific configuration of neurological mechanisms driving the predominant neuroadaptive changes in addictive processes (Corominas, Roncero, Bruguera & Casas, 2007). The high addictiveness and toxicity resulting from chronic nicotine abuse modulate neural mechanisms involved in vital cognitive functions such as working memory, attention and inhibitory control (Zlomuzica et al., 2018). The controlled administration of nicotine has been shown to weaken certain attentional, cognitive and mood deficits associated with schizophrenia, attention-deficit/hyperactivity disorder, Alzheimer's, Parkinson's, late-life depression and mild cognitive impairment (Gandelman et al., 2018; Heishman, Kleykamp & Singleton, 2010; Newhouse et al., 2012). Chronic use, however, affects the functionality of connectivity and brain coordination, compromising cognitive processes subordinate to these structures (Durazzo, Meyerhoff & Nixon, 2010). Specifically, the impairment of working memory, understood as the ability to temporarily retain information while operating with it, (Wechsler, 1999), could favour smoking maintenance by predisposing to ruminative thoughts about the drug (Kübler, Murphy & Garavan, 2005). Wagner et al. (2013) examined the cognitive profile of smokers and non-smokers to investigate whether smokers showed cognitive deficits associated with chronic use. They assessed six domains: 1) episodic memory [Auditory Verbal Learning Test (AVLT; Helmstaedter, Lendt & Lux, 2001)], 2) visual attention [Trail Making Tests (TMT; Reitan, 1958)] and digit symbol [Wechsler Adult Intelligence Scale (WAIS; Wechsler, 1999)], 3) verbal fluency (letter fluency task S, A, B and N), 4) working memory measured with digit-span [Wechsler Adult Intelligence Scale (WAIS; Wechsler, 1999)] and sequence of numbers (Gold, Carpenter, Randolph, Goldberg & Weinberger, 1997) 5) impulsivity [The Continuous Performance Test (CPT-IP; Cornblatt, Risch, Faris, Friedman & Erlenmeyer-Kimling, 1988)] and 6) interference using a Stroop task (Stroop, 1935). The results showed smokers to have significant deficits in visual attention (TMT and WAIS digits) and impulsivity (CPT-IP) (Wagner et al., 2013). More recently, Hu et al. (2017) explored the link between smoking and cognitive performance in working memory between smokers and non-smokers, measured with the information, arithmetic and digit subtests [Wechsler Adult Intelligence Scale (WAIS; Wechsler, 1999)], and in dysexecutive symptomatology [Dysexecutive Questionnaire (DEX; Bodenburg & Dopslaff, 2008)]. Smokers scored higher in dysexecutive symptoms and lower on the arithmetic and digit subtests (WAIS) compared to non-smokers. Similarly, a direct correlation was revealed between working memory (Digits) and the age of smoking onset (Hu et al., 2018).

Impulsive behaviour is a well-known etiological factor in the field of nicotine addiction (Billieux et al., 2010). One of the commonly explored impulsive dimensions is delayed discounting (De Wit, 2009), assessed in tasks with a choice between a smaller immediate reward or a greater but delayed reward (Verdejo-García, Alcázar-Córcoles & Albein-Urios, 2019). A recent meta-analysis examining performance in different neuropsychological domains between smokers and non-smokers concluded that smokers had higher rates of cognitive impulsivity. This was linked to a preference on the part of smokers for devaluing long-term in favour of immediate rewards on delayed-discounting tasks (Conti, McLean, Tolomeo, Steele & Baldacchino, 2019). Furthermore, delayed discounting tasks have emerged as powerful predictors of relapse in both adult (González-Roz, Secades-Villa, Pericot-Valverde, Weidberg & Alonso-Pérez, 2019; López-Torrecillas, Perales, Nieto-Ruiz & Verdejo-García, 2014; Reynolds, Richards, Horn & Karraker, 2004) and adolescent samples (Krishnan-Sarin et al., 2007; Sheffer et al., 2014). However, to our knowledge, research on its predictive powers in other clinical aspects of smoking is limited. Similarly, although smoking has been a focus of study in recent decades, most authors have concentrated on detecting the early factors that trigger onset (Gustavson et al., 2017; Harakeh et al., 2012; Lydon, Wilson, Child & Geier, 2014), on the adverse consequences of chronic smoking (Billieux et al., 2010; Detandt et al., 2017; Lyvers, Carlopio, Bothma & Edwards, 2014; Sheffer et al., 2014; Valentine & Sofuoglu, 2018), as well as on exploring variables that jeopardise abstinence (González-Roz et al., 2019; Harvanko, Strickland, Slone, Shelton & Reynolds, 2019; Krishnan-Sarin et al., 2007; Luijten, Kleinjan & Franken, 2016). Therefore, in comparison with the interest aroused by other stages of nicotine addiction such as onset or withdrawal, there is still a paucity of studies exploring factors linked to repeated tobacco use, in particular, research reporting on the influence of neuropsychological variables that perpetuate nicotine addiction. Moreover, it has been found that the therapeutic response is not homogeneous among smokers (Villalbi et al., 2019), in part because the factors that motivate smoking in different groups are unknown (O'Dell & Torres, 2014). Therefore, from a clinical and public health point of

view, it is essential to investigate the factors associated with smoking maintenance which could favour the development of new therapeutic approaches. The aim of this study is therefore to provide empirical evidence on the association between performance on neuropsychological tasks assessing working memory and impulsivity and years of addiction in a sample of smokers seeking to begin smoking cessation treatment. Based on the reviewed evidence highlighting the potential role of working memory in prompting ruminative thoughts about the drug, we hypothesise that the variables involved in working memory will be good predictors of years of addiction.

Method

Participants

The sample comprised 180 smokers who had requested treatment in the smoking cessation program of the Occupational Risk Prevention Service of the University of Granada. Mean participant age was 47.3 (SD = 8.31) within a range from 27 to 69 years, and 59% were women. The mean score of the sample on the Fagerström test was 4.49 (SD = 2.32) and mean smoking intensity was 17.9 (SD = 8.94) cigarettes per day. Inclusion criteria were: 1) being a smoker (Fagerström > 3), 2) aged over 18 years, 3) having a work relationship with the University of Granada, 4) voluntary participation in the treatment offered by the Occupational Risk Prevention Service and 5) completion of all questionnaires, inventories and tasks in the pre-treatment and monitoring assessment. Exclusion criteria were: being diagnosed with a serious mental disorder (bipolar and/or psychotic disorder, etc.) or one requiring medication on a regular basis (anxiolytics, antidepressants, etc.), as well as concurrent addiction to other substances (cocaine, heroin, alcohol, etc.). All participants were informed about the aims of the study and consented to take part. Prior to the assessment, participants were informed of the voluntary nature of the program, as well as of the confidential nature of data processing (article 7 of Law 41/2002); informed consent was thus obtained, ensuring that our research process was backed by the legislative framework established by the Code of Ethics (subject to the latest adaptation of Law 25/2009). In addition, the study was approved by the Ethics Committee in Human Research of Granada University.

Instruments

All neuropsychological assessments were carried out by duly trained psychologists.

- **Letter-Number sequencing** *(Wechsler Adult Intelligence Scale, WAIS III;* Wechsler, 1999, *Spanish adaptation, TEA Ediciones*). In this test a combined sequence of

Table 1. *Demographic characteristics of the sample.*

Category	Measurement	Percentage	Mean	SD	Range
Sociodemographic variables	Age		47.3	8.31	27-69
	Years of schooling		17.13	5.40	8-25
Professional career	Office worker	62.5%			
	Lecturer	19.5%			
	Researcher	4%			
	Service personnel	14%			
Smoking variables	Fagerström Nicotine Addiction Test		4.49	2.32	0-10
	Severe (TFDN >7)	22%			
	Moderate (TFDN<7)	78%			
Cigarette brands	Blond	83.5%			
	Dark	8.5%			
	Rolling	8%			
	Years of addiction		28.43	9.84	4-57
	Number of cigarettes a day		17.9	8.94	2-60
	Level of nicotine in mg per cigarette		.99	.13	,60-1.8
	Earlier attempts to quit		1.27	1.35	0-12
Working memory					
	Letter-Number Sequencing (WAIS III)		8.70	2.90	0-15
	Visual Search and Attention Test (VSAT) (Cues)		227.17	59.01	18-383
	Visual Search and Attention Test (Errors)		7.34	11.31	0-95
Delay discount	Now or later? task		.57	.22	0-1

Note. N = 180.

letters and numbers is read to the participant. The participant then has to reproduce this sequence by first repeating the numbers, from smallest to largest, and then the letters, in alphabetical order. The task involves maintenance and manipulation of information from working memory. The test contains six elements, each one consisting of three sequences of equal length. Administration is interrupted when the subject fails all three sequences of the same element. The total number of correct responses constitutes the variable score.

- ***Visual-search attention test*** (VSAT; Trenerry, Crosson, Deboe & Leber, 1990). In this visual search test, a target (a letter or coloured symbol) is identified in a matrix designed to explore sustained attention, understood as the ability to rapidly activate and inhibit motor responses. In this case, the total score of stimuli detected was used as an independent variable.
- ***Delay Discounting Task Questionnaire*** **Now or later?** (Delay Discounting Task, DDT; Kirby, Petry & Bickel, 1999). This is a 27-question monetary choice questionnaire that asks for preferences between smaller and immediate or larger but delayed rewards varying according to their value and time to be obtained. The area under the curve (AUC) was calculated using the Myerson, Green and Warusawitharana (2001) proposal. The AUC was estimated for the range of reward sizes covered in the questionnaire (small €5-35; medium €50-60; and large €75-85), according to the formula (x2-x1) [(y1-y2)/2], where x1 and x2 are successive delays, y1 and y2 are the subjective values associated with these delays (Myerson, Green & Warusawitharana, 2001). The predictive variable was AUC, with lower AUC values indicating greater impulsivity.

Tobacco use pattern

Semi-structured interview for smokers (López-Torrecillas, 1996) This is used to gather sociodemographic information, family history, years of addiction, number of cigarettes per day and smoking history in the first treatment session. The coding of the criterion variable "Years of addiction" was defined as the number of years from the date of onset to the beginning of smoking cessation treatment.

Fagerström Nicotine Dependence Test (FNDT) (Fagerstrom & Schneider, 1989) This consists of 6 items assessing the degree of physiological dependence. The maximum score is 10 points and is categorised into mild (0-3 points), moderate (4-7 points) and severe dependence (8-10 points).

Procedure

This quasi-experimental, observational and cross-sectional study employed non-random and incidental sampling since participants voluntarily requested to join the program. They were assessed individually before starting smoking cessation treatment (the measures of this study thus correspond to the baseline assessment), and the study instruments were part of a larger protocol aimed at neuropsychological assessment within a smoking cessation intervention. This subsequent intervention consisted of three phases: (1) psychoeducational phase (activity planning and target setting) to reduce smoking and to conduct neuropsychological tests and apply psychological instruments; (2) prescription and controlled administration of varenicline, a partial agonist/antagonist drug at the neuronal receptors for nicotinic-type acetylcholine α4β2 in the presence of nicotine and (3) clinical follow-ups with relapse prevention strategies, promotion of healthy lifestyle habits and strategies aimed at increasing motivation.

The program's initial session consisted of a semi-structured interview for smokers (López-Torrecillas, 1996) as well as a neuropsychological assessment with the measures described above. This initial evaluation was carried out in a single session, with appropriate breaks to avoid fatigue. Each participant was assigned a unique code to ensure individual monitoring while safeguarding anonymity, with the project leader as the person in charge of safeguarding the records.

Statistical analysis

Statistical analysis was performed using version 20.0 of the IBM SPSS program. Participants were characterised with descriptive statistics, and relationships between variables were assessed with Pearson's correlations, with statistical significance at $p<.05$. To analyse the specific contribution of the independent variables to years of addiction, a hierarchical regression analysis was performed. In all, the appropriate statistical procedures were performed to ensure that the assumptions required by the regression model were met.

Results

The Pearson test was applied to check for the existence of associations between the variables; this yielded inverse correlations in our study between the variables measuring working memory (WAIS and VSAT) and the criterion variable, with the relationship for WAIS (r = -.020; p = .05) being slight, but moderate for VSAT (r = -,415; p = .05). In this regard, smokers with low scores on working memory tests tend to be addicted for more years. In relation to the variable measuring delayed discount (Delay Discounting Task, DDT), a slight direct relationship is observed with the criterion variable (r = -.084; p = .05). In this test, therefore, the more smokers discount, that is, behave impulsively, the greater the number of years of addiction (Table 2).

Table 2. *Matrix of correlations between criterion and independent variables.*

Variables	Years	WAIS	VSAT	AUC
Year	1			
WAIS	-.020	1		
VSAT	-.415*	.162*	1	
DDT	.084	-.022	-.043	1

Note. N = 180. Years = Years of addiction; WAIS: Total score in the Letter-Number Sequencing subtest of the Wechsler Adult Intelligence Scale, WAIS III; VSAT = Total Stimuli in the Visual Search and Attention Test; DDT = Total score on the Now or Later Test.
*P<.05.

Regarding the hierarchical regression analysis (Table 3), it was observed that the variables measuring working memory (WAIS and VSAT) explained 17.5% of the variance. Finally, in the third step, when incorporating the AUC variable measuring delay discount, the model explained 17.9% of the criterion variance, leaving a statistically significant final model, $F_{(3,176)} = 12.80$; $p < .000$. In the final model, only the VSAT working memory variable was statistically significant ($\beta = -.070$, $p < .000$). In the regression equation it can thus be observed that the variable score in VSAT is the independent variable with the greatest weight in the regression equation. An increase of one standard deviation in VSAT means an increase in addicted years of .420. Finally, when observing the width of the confidence intervals of the partial regression coefficients, we find better adjusted estimates in the working memory tests (VSAT and WAIS), but greater interval width in the impulsivity test (Delay Discounting Task, DDT), which signals less precision when estimating the population value of this regression coefficient.

Table 3. *Hierarchical regression analysis.*

Variable	R	R^2	gl	β	t	p	95% IC of β
Step 1							
WAIS	.020	.000	1	-.069	-.273	.786	-.570-.432
Step 2							
WAIS				.163	.697	.487	-.299-.626
VSAT	.418	.175	1	-.071	-6.113	.000	-.093- -.048
Step 3							
WAIS				.167	.049	.478	-.296-.630
VSAT				-.070	-.420	.000	-.093--.047
TDD	.423	.179	1	2.871	.067	.329	-2.919-8.66

Note. N = 180. WAIS: Total score in the Letter-Number Sequencing subtest of the Wechsler Adult Intelligence Scale. WAIS III; VSAT = Total Stimuli in the Visual Search and Attention Test; DDT = Total score on the Now or Later Test.
*P<.05.

Discussion

The aim of this study was to explore the relationship between years of nicotine addiction and performance in neuropsychological tasks in smokers seeking to initiate smoking cessation treatment. The results indicate that working memory tasks (WAIS and VSAT), together with a delayed discount task, make up a significant regression model explaining 17.9% of the criterion variance. However, in our sample only the VSAT variable serves as the main predictor of years of addiction, with an inverse correlation indicating that the lower the VSAT performance, the more years of addiction. These findings are similar to those reported by Wagner et al. (2013) showing significant deficits in visual attention in smokers compared to non-smokers (Wagner et al., 2013). They are also congruent with the functional-structural hypothesis, which posits a superposition of the chronic structural effects of smoking on the functional effects of acute administration of nicotine (Sutherland et al., 2016). Consequently, research attributing beneficial properties to nicotine cite groups distinguished by an altered cholinergic system or underlying nAChR dysfunction (Gandelman, Newhouse & Taylor, 2018). Specifically, controlled nicotine administration promotes improvements in functional performance in the lateral prefrontal cortex (LPF), anterior cingulate cortex (ACC), thalamus and cuneus, that is, regions traditionally associated with attention, working memory, and task execution, which require external-oriented processing (executive control network) (Gandelman et al., 2018; Sutherland et al., 2015). However, chronic nicotine use involves cognitive performance impairment (Durazzo et al., 2010) as well as neuroadaptations that lead to decreases in the grey matter of regions commonly identified in processes associated with addiction such as ventromedial PFC, insula, thalamus and cerebellum (Sutherland et al., 2016). Specifically, the insula as a substrate assigned to cognitive and attentional control (Bi et al., 2017) and involved in the need to smoke (Paulus & Stewart, 2014) seems to play a critical role in smoking maintenance (Sutherland & Stein, 2018). Furthermore, structural differences in the insula between smokers and controls are more easily seen in smokers with longer histories of smoking exposure (Li et al., 2015). As our results aim to contribute behavioural data to the discussion on structural alterations resulting from the harmful impact of smoking, our inferential hypothesis is that smokers with a greater history of addiction show poorer performance in the demanding tasks of working memory and attentional control which predispose towards ruminative thoughts of craving traditionally linked to addiction (Hester & Garavan, 2009; Kübler et al., 2005).

The Delay Discounting Task (DDT), on the other hand, did not yield statistical significance, which may indicate that this variable plays a significant role in other stages of addiction, an assumption which is consistent with the hypothesis held by Reynolds and Fields (2012) stating that the different dimensions of impulsivity can have various effects at the onset of use or in later stages (Reynolds & Fields, 2012). In this case, delayed discount has been widely

linked to treatment response (González-Roz et al., 2019; Krishnan-Sarin et al., 2007; López-Torrecillas et al., 2014; Reynolds et al., 2004; Sheffer et al., 2014). In summary, research indicates that, despite the coexistence of individual differences facilitating onset or risk of relapse, the effects of nicotine on cognitive aspects suggest that the causes of smoking maintenance are heterogeneous (Bedi et al., 2011; García-Rivas & Deroche-Gamonet, 2019; Hall et al., 2015).

Our results show that cognitive processes which need working memory, such as sustained attention and visual search, seem to have an influence on smoking maintenance. However, there are some limitations which need to be pointed out, such as the nature of the sample since, being non-random and incidental, it limits the generalisability of results. In addition, the cross-sectional nature of the study makes it difficult to obtain data showing development over time and the inferred causal relationship between the variables. Therefore, the importance is stressed of implementing longitudinal designs allowing the development of dependency to be considered. Finally, this study may stimulate interest in trying to clarify the implications of neuropsychological variables in clinical aspects of smoking behaviour as relevant and hermetic as habit maintenance. Therefore, identifying mediating variables that motivate nicotine use is crucial in developing more effective therapeutic strategies (O'Dell & Torres, 2014) which include these neuropsychological variables. Our results should thus be interpreted as a starting point for new research investigating the implication of cognitive variables both in the maintenance of chronic smoking and their possible role in obstructing of the path to abstinence; since the predictive capacity of neurocognitive factors has been occasionally explored in smoking cessation (Luijten et al., 2016) despite representing a priority objective in preventive policies (Villalbi et al., 2019).

Conflict of interests

The authors declare that no conflict of interest.

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