Cognitive functioning in patients with alcohol use disorder who start outpatient treatment

Funcionamiento cognitivo en pacientes con trastorno por uso de alcohol que inician tratamiento ambulatorio de deshabituación alcohólica

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Abstract

The main objective of the present study is to analyze the presence of cognitive impairment associated with alcohol consumption in patients with moderate or severe alcohol use disorder seeking outpatient treatment for their dependence. To do this, we compared a sample of 111 patients with active alcohol use disorder who initiated ambulatory treatment with 100 healthy controls. We compared sociodemographic and clinical variables associated with alcohol consumption, such as alcohol craving and impulsivity. A systematized battery of cognitive tests was also used in the comparison, which allowed the evaluation of the following functions: Attention, anterograde memory, processing speed, verbal fluency, executive function and implicit attitude towards alcoholic beverages. Compared with healthy controls, patients with moderate or severe alcohol use disorder performed significantly worse in all tests used, and therefore in all cognitive functions evaluated, but for two tests, the *Iowa Gambling Test* and the *Implicit Association Test*. The analysis through a correlation matrix of the patient group indicates that patients who report more impulsivity and more chronic alcohol abuse and with more addiction are those who suffer greater deterioration in their cognitive function. Cognitive damage associated with alcohol consumption was distributed heterogeneously among patients. The present study confirms the presence of cognitive deterioration associated with alcohol consumption in patients seeking outpatient treatment.

Key Words: Alcoholism, alcohol use disorder, impulsivity, alcohol related brain damage, executive function.

Resumen

El objetivo principal del presente estudio es analizar la presencia del deterioro cognitivo asociado al consumo de alcohol en los pacientes con trastorno por uso de alcohol moderado o grave que demandan tratamiento de deshabituación alcohólica ambulatorio. Para ello, se comparó una muestra de 111 pacientes con trastorno por uso de alcohol activo que iniciaban tratamiento ambulatorio versus 100 controles sanos. Se compararon variables sociodemográficas y clínicas asociadas al consumo de alcohol, como el *craving* de alcohol y la impulsividad. También se empleó en la comparación una batería sistematizada de pruebas cognitivas que permitía valorar las siguientes funciones: atención, memoria anterógrada, velocidad de procesamiento, fluidez verbal, función ejecutiva y actitud implícita ante las bebidas alcohólicas. En comparación con los controles sanos, los pacientes con trastorno por uso de alcohol moderado o grave presentaban un rendimiento significativamente inferior en todas las pruebas utilizadas, y por ello en todas las funciones cognitivas evaluadas, con la excepción de dos pruebas, el *Iowa Gambling Test* y el *Implicit Association Test*. El análisis a través de una matriz de correlaciones del grupo de pacientes indica que los pacientes que refieren más impulsividad y un consumo abusivo de alcohol más cronificado y con más adicción son los que presentan un mayor deterioro en su función cognitiva. El daño cognitivo asociado al consumo de alcohol se distribuyó de forma heterogénea entre los pacientes. El presente estudio confirma la presencia del deterioro cognitivo asociado al consumo de alcohol en los pacientes que demandan tratamiento ambulatorio.

Palabras clave: Alcoholismo, trastorno por uso de alcohol, impulsividad, daño cerebral asociado al consumo de alcohol, función ejecutiva.

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It is beyond doubt that chronic abusive alcohol consumption damages brain tissue and thereby impairs cognitive function (Draper, Karmel, Gibson, Peut, & Anderson, 2011; Erdozain et al., 2014; Florez, Espandian, Villa, & Saiz, 2019; Hayes, Demirkol, Ridley, Withall, & Draper, 2016; Laramee et al., 2015; Ridley, Draper, & Withall, 2013; Sachdeva, Chandra, Choudhary, Dayal, & Anand, 2016; Stavro, Pelletier, & Potvin, 2013; Wollenweber et al., 2014). Such alcohol-related brain damage (ARBD) originates from two toxic mechanisms acting in combination (Moretti, Caruso, Dal Ben, Gazzin, & Tiribelli, 2017): on the one hand, the direct neurotoxic effect of ethanol, mainly mediated by a glutamatergic excitotoxicity (Stavro et al., 2013; Wollenweber et al., 2014); and, on the other hand, the damage associated with thiamin deficiency, which gives rise to Wernicke-Korsakoff syndrome (Galvin et al., 2010; Maharasingam, Macniven, & Mason, 2013; Stavro et al., 2013). These two mechanisms combine in patients with ARBD in a dimensional way, that is, the brain damage, and with it the cognitive deterioration, that they produce, can range from mild to entering the dementia spectrum (Moretti et al., 2017; Ridley et al., 2013; Zahr & Pfefferbaum, 2017). Among patients with alcohol use disorder, ARBD is very widespread, with detection rates of up to 78% in the autopsies performed on such patients (Ridley et al., 2013). ARBD is characterized by marked, generalized brain atrophy caused by neuronal destruction and damage to the white matter (Ridley et al., 2013; Stavro et al., 2013). The following brain areas seem to be particularly affected by ARBD (Zahr & Pfefferbaum, 2017): the white matter of the prefrontal cortex, the corpus callosum and the cerebellum, as well as the gray matter in the prefrontal cortex, the hypothalamus and the cerebellum.

This brain damage is accompanied by the presence of especially intense impairment in the following cognitive functions (Aharonovich et al., 2018; Hagen et al., 2016; Hayes et al., 2016; Horton, Duffy, Hollins Martin, & Martin, 2015; Maharasingam et al., 2013): anterograde memory, executive function (decision making, temporal orientation, emotional judgments and verbal fluency) and visuospatial tasks. Working memory and response time are generally impaired. The cognitive deterioration profile of ARBD will differ in each patient in extent and intensity depending on different variables. The key element is the duration and intensity of alcohol use, especially binge drinking episodes, which will result in a specific combination of direct damage and thiamine deficiency (Golpe, Isorna, Barreiro, Brana, & Rial, 2017; Hagen et al., 2016; Hayes et al., 2016; Horton et al., 2015). But the way in which this cognitive deterioration manifests itself will also be modulated by other variables (Hayes et al., 2016; Ridley et al., 2013; Sachdeva et al., 2016): women are more vulnerable to the neurotoxic effects of ethanol, while deterioration is counteracted by the level of education attained; and the presence of other psychiatric disorders (some, such as depression, involving high comorbidity with alcohol use disorder (Briere, Rohde, Seeley, Klein, & Lewinsohn, 2014; Shoval et al., 2014)), with consumption of other toxins and vascular or trauma damage exacerbating deterioration.

It is important to emphasize that the effects of ARBD on the brain areas which control impulses, attention and memory will mean that affected patients are more vulnerable to alcohol addiction because they are less able to control the urge to drink alcohol despite its negative consequences. (Carmona-Perera, Sumarroca-Hernandez, Santolaria-Rossell, Perez-Garcia, & Reyes Del Paso, 2018; Koob, 2003; Koob & Volkow, 2010; Mujica-Parodi, Carlson, Cha, & Rubin, 2014; Volkow, Koob, & McLellan, 2016)

Overall, the cognitive deterioration produced by ARBD and its implications for the daily activities of affected patients is less than that produced by degenerative processes or vascular damage in the brain, especially at the language level (Horton et al., 2015). Moreover, deterioration stops with abstinence, and is even partially reversed, again in a variable manner for each patient, if such abstinence is consolidated. It is estimated that at least one year of abstinence is required to consolidate improvement, with the impairment in anterograde memory being the most resistant to improvement (Sachdeva et al., 2016).

Despite the high prevalence of ARBD, studies carried out to date indicate that neither primary care services nor specific care units for patients with alcohol use disorder routinely assess cognitive impairment associated with alcohol use. (Aharonovich et al., 2018; Draper et al., 2011; Hagen et al., 2016; Rehm, Allamani, Aubin, et al., 2015; Rehm, Allamani, Della Vedova, et al., 2015; Rehm, Rehm, Shield, Gmel, & Gual, 2013; Rehm, Shield, Gmel, Rehm, & Frick, 2013). This clinical scenario is especially troubling since the affected cognitive functions are of vital importance if patients wish to complete alcohol detoxification/cessation successfully (Litten et al., 2015). If attention, memory, and planning capacity are affected, patients will find it difficult to follow the medical and therapeutic guidelines in outpatient treatment without support. In addition, significant improvements in these cognitive functions take time and will not be present during the critical initial moments to consolidate abstinence. (Sachdeva et al., 2016).

The aim of the present study is to improve current knowledge regarding the cognitive impairments which patients with alcohol use disorder present when they seek treatment to stop drinking. For this purpose, a group of such patients will be compared with another group from the normative population without alcohol problems. Our main hypothesis is that, when compared with the control group, the group of patients will manifest severe cognitive dysfunctions which diminish the possibilities of success in outpatient alcohol withdrawal programs.

Material and methods

Participants

The final sample consisted of 100 healthy controls and 111 patients with active alcohol use disorder at the time of recruitment. Participants were recruited in three health care units: the La Calzada Mental Health Centre in Gijón (health area 5 of Asturias), the Addictive Behavior Unit at the psychiatry department of the Ourense Hospital Complex, and the Institute of Neuropsychiatry and Addictions at the Parc de Salut Mar, in Barcelona

The inclusion criteria for the patients were: being over 18 years of age, meeting DSM-5 criteria for moderate or severe alcohol use disorder, having an alcohol consumption over the past month of more than 60 grams of ethanol per day in men and 40 grams of ethanol per day in women, expressing a clear desire to control drinking, having no history of suicide attempts and no history of depressive episodes (uni or bipolar), scoring below 5 on the Hamilton Depression Rating Scale (HMDRS) at the time of assessment, agreeing to participate in the study and signing the corresponding informed consent.

The inclusion criteria for the control group were: aged over 18, no personal history of any mental disorder, no family history of alcohol use disorder, major depression and/or attempted suicide/completed suicide, alcohol consumption over the last month not exceeding 30 grams of ethanol per day, agreeing to participate in the study and signing the corresponding informed consent.

The exclusion criteria for both groups were being under 18, presenting organic or psychiatric pathology (according to the DSM 5) which, in the opinion of the researchers, would impede participation in the present study (including substance use disorders with the exception of alcohol in the patient group and smoking for both groups), refusing to participate in the study or sign the corresponding informed consent. Qualified researchers interviewed all candidates for participation in the study to verify that inclusion and exclusion criteria were met.

The controls were obtained through the staff at the centers and the people accompanying the patients. They were matched to patients by sociodemographic criteria.

All participants were thoroughly informed about the nature and characteristics of the study and gave their consent to participate in writing. All were presented with a 50 euro gift card for their participation in the study. The study was carried out following the ethical and legal guidelines regarding the protection of personal data and studies with humans, and fulfilling the Helsinki Declaration guidelines (Rickham, 1964). The study was approved by the following Research Ethics Committees: Pontevedra – Vigo – Ourense (2016-313), Principado de Asturias (2017-06), and Parc de Salut Mar (2017/7221/I).

Process

The design is transversal with a case-control comparison. The first step was to assess all participants to verify that they met the inclusion and exclusion criteria. Next, sociodemographic and clinical variables were collected. Finally, the battery of cognitive tests was completed. To complete the entire protocol, an average of 3 sessions not separated by more than 72 hours was necessary.

Variables

Using an ad-hoc questionnaire, the following sociodemographic and substance use variables were collected: sex, age, marital status, living arrangements, educational level, employment status, age of onset of drinking and smoking, alcohol and tobacco consumption during the previous month, age of onset of alcohol dependence (cases), family history of alcoholism.

The following questionnaires were used to collect clinical variables: to assess the presence of depression as an exclusion criterion, the Hamilton Depression Rating Scale-17 items (HDRS-17) (Bech, 1990); to assess impulsivity, the Barratt Impulsiveness Scale – 11 (BIS-11) (Patton, Stanford, & Barratt, 1995); and to assess alcohol use disorder, the Obsessive Compulsive Drinking Scale (OCDS) (Anton, 2000).

The cognitive battery used to obtain neuropsychological variables is shown in Table 1. The tests used were: to measure overall IQ, the WAIS-III Symbol Search and Arithmetic subtests (Hagen et al., 2016); to measure attention, the D2 Attention Test (Steinborn, Langner, Flehmig, & Huestegge, 2018); to measure memory, the California Verbal Learning Test (CVLT) (Elwood, 1995) and WAIS Digit Symbol and Digit Span tests (Hagen et al., 2016); to measure executive function, the FAS and semantic category of animals (del Ser Quijano et al., 2004), the Stroop Color Word Test (SCWT) (Scarpina & Tagini, 2017), Wisconsin Card Sorting Test (WCST) (Nyhus & Barcelo, 2009), and the Iowa Gambling Test (IGT) (Steingroever, Wetzels, Horstmann, Neumann, & Wagenmakers, 2013); and to measure automatic processing, the Implicit Association Test (IAT) adapted for alcohol use (Ostafin, Marlatt, & Greenwald, 2008).

Data analysis

Comparing the continuous variables of the two groups under study was done by means of Student's t-test, while the analysis of differences between both groups in the distribution of categorical variables was carried out with the chi-square test. Clinical and cognitive variables were also compared using a correlation matrix. The level of significance was set at $p < 0.05$.

Results

Table 2 shows the distribution of the sociodemographic and clinical variables of the sample, indicating the varia-

Table 1. *Battery of neuropsychological tests.*

Neuropsychological test	Main function evaluated	Characteristics
Symbol search (from WAIS-III)	Processing speed (**IQ**)	Measures the ability to quickly identify the presence of figures in a series. Non verbal.
Arithmetic (from WAIS-III)	Abstract reasoning (**IQ**)	Measures the mental solving of arithmetic problems given a time limit. Verbal.
Attention Test D2	Sustained attention / inhibition of response (**Attention**)	Measures the ability to focus on relevant visual stimuli and ignore irrelevant ones. Non verbal.
California Verbal Learning Test (CVLT)	Immediate recall, deferred and identification (**Memory**)	Measures the ability to remember lists of words over several attempts, with and without interference. Verbal.
Digit Symbol (from WAIS-III)	Working memory (**Memory**)	Measures speed in converting numbers into symbols according to an established sequence. Non verbal.
Digit Span (from WAIS-III)	Short-term memory (**Memory**)	Measures the ability to remember and follow a sequence of numbers. Verbal.
FAS and semantic category of animals	Verbal fluency (**executive function**)	Measures the ability to generate word lists by categories. Verbal.
Stroop Test (SCWT)	Divided attention and interference resistance (**Executive function**)	Measures the ability for color recognition. Non verbal.
Wisconsin Card Sorting Test (WCST)	Abstract Reasoning and Cognitive Flexibility (**Executive Function**)	Measures the ability to select cards based on categories. Non verbal.
Iowa Gambling Test (IGT)	Decision making and cognitive flexibility (**executive function**)	Measures the ability to select stimuli based on short and long term rewards. Non verbal.
Implicit Association Test (IAT)	Implicit attitude to a stimulus (**Automatic processing**)	Measures speed of matching words based on implicit attitudes related to alcohol. Non verbal.

bles in which there are significant differences between patients and healthy controls.

Sociodemographic variables (Table 2)

There are no significant differences with respect to the variables which may exert a bias in terms of cognitive assessment and cognitive impairment associated with alcohol consumption: age, sex and completed years of schooling. Nevertheless, alcohol use disorder does imply the presence of significant differences with respect to the following clinical and sociodemographic variables: controls are more frequently found to have a partner ($X^2 = 4.48$, $p = 0.035$), to live with a relative ($X^2 = 12.385$, $p = 0.002$) and to be in active employment ($X^2 = 36.828$, $p < 0.001$).

Variables related to drinking, smoking and impulsivity (Table 2)

Alcohol use disorder was involved in the significant differences found in the following variables: greater impulsivity measured through the BIS (BIS-11 cognitive) ($t = -3.60$, $p < 0.001$), BIS-11 motor ($t = -3.02$, $p = 0.003$), BIS-11 non-planning ($t = -3.35$, $p = 0.001$), BIS-11 total ($t = -4.04$, $p < 0.001$)); higher scores for pathological alcohol use as measured by OCDS - Obsessive ($t = -14.18$, $p < 0.001$), OCDS – Impulsive ($t = -22.95$, $p < 0.001$), OCDS – Total ($t = -21.23$, $p < 0.001$); earlier smoking onset age ($t = 3.96$, $p < 0.001$) and greater daily consumption of cigarettes ($t = -5.10$, $p < 0.001$); greater daily alcohol consumption (SDUs) ($t = -14.8$, $p < 0.001$); higher number of family members affected by alcohol use ($t = -4.73$, $p < 0.001$).

Cognitive variables (Table 3)

Table 3 shows the results yielded by the different cognitive tests in each group with respect to neuropsychological variables. In all tests, significant results were obtained which indicated better cognitive function in the control group, with the exception of IGT and IAT, in which no significant differences between the groups were found.

A correlation study was also carried out to study how variables related to alcohol use and impulsivity influence cognitive tests in the patient group. Table 4 shows the significant correlations. It was found that variables linked to chronic alcohol use (years of alcohol dependence, percentage of lifespan with alcohol dependence, OCDS and BIS) correlated more closely with worse cognitive function compared to the variables linked to severe alcohol use (SDUs, GOT, GPT, GGT and MCV).

Table 5 presents a matrix of correlations between variables related to alcohol use and impulsivity in the baseline assessment. A significant positive correlation was observed between BIS and OCDS, and between the analytical variables linked to alcohol use (GOT, GPT, GGT and MCV) and with SDUs.

Table 2. *Sociodemographic variables and related to alcohol consumption.*

	Controls (100)		Cases (111)		Total (211)		
	mean	DS	mean	DS	mean	DS	p
Age	48.66	9.569	49.07	8.405	48.88	8.956	0.741
Onset age, alcohol use	18.21	6.414	17.21	4.226	17.56	5.114	0.274
SDUs per day, previous month	0.53	0.688	9.613	6.426	5.308	6.521	‹0.001
Onset age, smoking	18.1	4.687	14.16	7.541	15.42	6.996	‹0.001
Cigarettes per day, previous month	3.75	6.722	9.811	10.338	6.938	9.3	‹0.001
Education, completed years	12.76	2.417	13.3	2.881	13.04	2.679	0.142
Family members affected by alcohol	0.27	0.566	0.973	1.449	0.6398	1.172	‹0.001
BIS11- Cognitive	14.85	5.809	18.58	9.038	16.81	7.885	‹0.001
BIS11- Motor	13.82	6.327	16.59	7.03	15.28	6.833	0.003
BIS11- Non-planning	16.28	6.482	19.72	8.379	18.09	7.717	0.001
BIS-Total	44.99	15.54	55.09	20.67	50.3	19.06	‹0.001
OCDS- Obsessive	0.06	0.371	6.5135	4.78	3.455	4.74	‹0.001
OCDS-Impulsive	0.72	1.349	10.703	4.356	5.972	5.98	‹0.001
OCDS-Total	0.79	1.559	17.207	7.981	9.427	10.101	‹0.001
Onset age, alcohol dependence			33.362	9.148			
GOT			38.53	25.44			
GPT			37.02	20.37			
GGT			130.4	167.5			
VCM			95	6.363			
Sex (% males)		74%		78.37%		76.30%	0.4551
Marital status (% married - de facto couple)		56%		41.44%		48.34%	0.035
Living arrangements (% single)		20%		24.32%		22.27%	0.002
Employment situation (% active)		80%		39.63%		58.76%	‹0.001

Note. SD: standard deviation; SDU: standard drink unit; BIS: Barratt Impulsiveness Scale; OCDS: Obsessive Compulsive Drinking Scale; GOT: glutamate oxalacetate transaminase; GPT: glutamate pyruvate transaminase; GGT: gamma glutamyl transferase; MCV: mean corpuscular volume.

Discussion

The present study uses a systematized battery of verbal and non-verbal tests to compare the cognitive performance of a group of patients with alcohol use disorder seeking cessation treatment to that of a group of healthy volunteers, matched by the main sociodemographic variables influencing cognitive capacity (age, sex and completed years of schooling). As expected, and confirming the main hypothesis, the patient group displayed significant deficits compared to healthy volunteers in almost all tests. Both attention and processing speed, anterograde and working memory, as well as executive function (verbal fluency, resistance to interference, abstract reasoning and cognitive flexibility) were significantly affected in patients. Indeed, only two tests, IGT and IAT, revealed no significant differences. These findings confirm the results previously obtained in neuroimaging and neuropathology studies indicating the presence of diffuse damage throughout the brain, but with more severe involvement of the prefrontal cortex, the hypothalamus and the cerebellum (Erdozain et al., 2014; Hayes et al., 2016; Zahr & Pfefferbaum, 2017), and are similar to those obtained by other studies in which cognitive function was analyzed in patients with alcohol use disorder compared to a control population (Aharonovich et al., 2018; Romero-Martinez, Vitoria-Estruch, & Moya-Albiol, 2018).

As a group, patients were aware of their greater impulsiveness and inability to plan, as reflected in the results obtained with BIS-11. In addition, these cognitive disorders, together with the negative consequences of alcohol intoxication, affect the patient's capacity for socio-familial integration. Results indicate that patients more often tend to lack a stable partner, to live alone and be unemployed. As if this were not enough, their physical health is more

Table 3. *Comparison of neuropsychological tests between controls and patients at baseline assessment.*

	Controls (SD) N = 100	Cases (SD) N= 111	P
IQ			
SYMBOL SEARCH Correct	30.78 (8.33)	23.95 (7.45)	‹ 0.001
SYMBOL SEARCH Error	0.95 (1.30)	1.54 (1.88)	0.008
SYMBOL SEARCH Raw Score	29.57 (9.31)	22.00 (7.69)	‹ 0.001
SYMBOL SEARCH Standard score	10.46 (3.12)	8.10 (2.83)	‹ 0.001
ARITHMETICS Raw score	13.79 (3.93)	11.32 (3.21)	‹ 0.001
ARITHMETICS Standard score	10.70 (3.53)	8.43 (3.06)	‹ 0.001
Attention			
D2	163.7 (43.2)	113.0 (44.5)	‹ 0.001
Memory			
CVLT-A1 first attempt	6.91 (2.75)	5.77 (1.92)	0.001
CVLT-A5 fifth attempt	13.38 (2.51)	11.26 (2.93)	‹ 0.001
CVLT-AToT total attempts	53.20 (9.80)	45.8 (11.6)	‹ 0.001
CVLT- Free immediate	12.31 (2.82)	9.77 (3.32)	‹ 0.001
CVLT- Free delayed	12.98 (2.90)	10.32 (3.35)	‹ 0.001
CVLT- Guided	13.64 (2.70)	11.42 (2.38)	‹ 0.001
CVLT- Recognition	15.34 (1.08)	14.20 (2.12)	‹ 0.001
DIGIT SYMBOL Correct	63.10 (19.10)	46.4 (15.8)	‹ 0.001
DIGIT SYMBOL Standard score	10.26 (3.26)	7.34 (2.86)	‹ 0.001
DIGITS Direct	9.33 (2.10)	8.11 (2.21)	‹ 0.001
DIGITS Reverse	8.07 (2.18)	6.71 (2.01)	‹ 0.001
DIGITS Cumulative	8.19 (2.33)	6.64 (2.27)	‹ 0.001
DIGITS Total	25.54 (5.39)	21.42 (5.57)	‹ 0.001
Executive Function			
FAS Direct score correct	36.5 (11.7)	27.3 (11.3)	‹ 0.001
FAS Perseveration errors	0.81 (1.28)	0.78 (1.53)	0.893
FAS Intrusion errors	0.23 (0.633)	0.64 (1.03)	0.001
FAS Derivation errors	0.48 (1.14)	0.577 (0.949)	0.507
ANIMALS Direct Score	21.56 (6.23)	17.14 (4.77)	‹ 0.001
SCWT prop correct	0.9466 (0.0705)	0.887 (0.115)	‹ 0.001
SCWT mean RTCC	1972 (1288)	2654 (1610)	0.001
SCWT mean RTCI	1874 (1170)	3033 (2635)	‹ 0.001
SCWT mean RTCCO	2349 (1921)	3179 (2958)	0.016
SCWT PROPCC	1776 (188)	1459 (1822)	0.133
SCWT_PROPCI	0.9857 (0.0861)	0.846 (0.255)	‹0.001
SCWT_PROPCCO	0.883 (0.179)	0.846 (0.255)	0.255
SCWT mean RT	49 (351)	1181 (1633)	‹ 0.001
WCST Completed categories	4.59 (1.98)	3.08 (2.04)	‹ 0.001
WCST Correct	70.7 (11.3)	67.2 (13.4)	0.042
WCST Error	36.1 (23.3)	54.0 (21.0)	‹0.001
WCST SUMPE	6.77 (3.08)	7.3 (11.0)	0.641
WCST PE	30.2 (21.2)	17.0 (18.2)	‹ 0.001
WCST PR	9.48 (4.41)	9.3 (13.6)	0.882
WCST SFMS	0.90 (1.22)	1.03 (1.28)	0.462

WCST			
TRIAL FIRST	22.6 (26.7)	30.3 (34.3)	0.07
WSCT CI	18.4 (16.8)	22.6 (19.4)	0.096
WCST FI	25.4 (16.2)	33.2 (20.1)	0.002
WSCT NI	28.5 (22.9)	31.6 (26.3)	0.36
WSCT C2	15.8 (15.3)	32 (176)	0.348
WSCT DIFFC1F1	-1315 (13095)	-9.5 (30.3)	0.321
WSCT DIFFF1N1	-1.7 (28.3)	1.5 (36.4)	0.466
WSCT DIFFN1C2	12.2 (24.7)	16.7 (29.1)	0.234
WSCT DIFFC2F2	-0.2 (21.4)	1.7 (22.8)	0.527
IGT Total	2039 (964)	1836 (822)	0.104
IGT CA	49.9 (16.1)	46.5 (15.5)	0.125
IGT CDA	50.1 (16.1)	53.5 (15.5)	0.125
IGT NET 5 AD	10.56 (4.85)	9.72 (4.60)	0.2
IGT NET 5DIS	9.44 (4.85)	10.28 (4.60)	0.2
Automatic processing			
IAT	-0.569 (0.515)	-0.483 (0.480)	0.215

Note. SD: Standard deviation; SCWT: prop correct: Proportion of correct total responses; mean RTCC: Mean response time for congruent correct responses; mean RTCI: Mean response time for incongruent correct responses; mean RTCCO: Mean response time for correct responses; PROPCC: Proportion of congruent correct responses; PROPCI: Proportion of incongruent correct responses; PROPCCO: Proportion of correct responses; mean RT: Mean response time for total correct responses; IGT: Total: Total score achieved; CA: Correct responses; CDA: Incorrect responses; NET 5 AD: Correct responses in the last 20 trials; NET 5 DIS: Incorrect responses in the last 20 trials; WCST: SUMPE: Sum of all incorrect attempts with errors; PE: Percentage of perseverative errors; PR: Perseveration percentage in the tests; SFMS: Total number of occasions in which an incorrect card is selected; TRIAL FIRST: Number of trials needed to complete the first category after at least 5 correct; CI: Percentage of errors in the first color category; NI: percentage of errors in the first number category; FI: Percentage of errors in the first form category; C2: Percentage of error rate in the second color category; DIFF: Difference in error percentages between adjacent categories.

compromised, due not only to excessive drinking but also to smoking more and over a greater number of years. It is clear that not only impulsivity and lack of executive function play a role in maintaining tobacco addiction among patients with alcohol use disorder; other genetic, neurobiological and environmental factors are also involved and without doubt contribute significantly (Koob, 2003; Koob & Volkow, 2010; Volkow et al., 2016).

It was not observed that any variable related to the IGT permitted discrimination between patients and healthy controls. Although several studies initially found significant differences in this test measuring cognitive functions such as cognitive flexibility and decision making, most recent research in fact predominantly indicates that this test has little discriminative capacity when distinguishing between patients with alcohol use disorder and healthy controls (Hagen et al., 2016). In essence, performing the test correctly requires excellent cognitive function. This is why the results obtained by a representative control group well-matched to a group of patients like ours are poor. The analysis of variables reflecting the results of the last 20 trials of the test confirm this; Table 3 shows that in these IGT variables (IGT 5 NET AD, showing the number of correct responses in the last 20 trials, and IGT 5 NET DIS, measuring the opposite) the control group obtains results approaching the mark which shows that the necessary learning to correctly perform the test did not take place. Thus, if the control group obtains poor results, there can only be significant differences if the results of patients are catastrophically bad; this may be the case in patients with severe brain damage or suffering dementia, but is not applicable to patients participating in this study. It must be remembered that these are non-institutionalized outpatients with sufficient cognitive capacity to sign informed consent and participate in the study. The study assessment protocol was carried out at a time when this test had not yet been questioned by the most recent research and was therefore included.

With regard to the other test which did not achieve significant results in the comparison between patients and controls, the IAT, the results yielded by the study of correlations with clinical variables (Table 4) explain this lack of significance. The IAT measures the automatic and implicit preference of a person towards a particular category, in this study alcoholic beverages. When this automatic preference exists, response times when matching words related to the study category with words having positive or negative valence are modified compared with a neutral response. In this study, we expected to see response times indicating a preference of patients over controls for alcoholic beverages, but this was not initially observed. However, significant differences were observed in the patient group when

Table 4. *Significant correlations between variables related to alcohol use and impulsivity and cognitive variables in the patient group.*

Alcohol use / impulsivity variables	**Cognitive variables with significant correlation**
Years of alcohol dependence	D2 (-0.2. p= 0.032) CVLT A5 (-0.28. p = 0.0029) CVLT AToT (-0.23. p = 0.013) CVLT Free immediate (-0.27. P = 0.004) CVLT Free delayed (-0.21. P = 0.0027) Symbol Search correct (-0.31. P = 0.0007) Symbol Search total score (-0.28. P = 0.0024) Arithmetic standard score (-0.25. P = 0.0063) WCST SUMPE (0.23. P = 0.012).
Percentage of lifespan with alcohol dependence	CVLT A5 (-0.19. p = 0.004) CVLT Free immediate (-0.19. p = 0.036) Symbol Search correct (-0.23. p = 0.014) Symbol Search total score (-0.22. p = 0.018) Symbol Search standard score (-0.19. p = 0.046) WCST SUMPE (0.19. p = 0.036) IAT (0.21. p = 0.025)
SDUs	Arithmetic standard score (-0.20. p = 0.033)
GOT	No significant correlation found
GPT	SWCT PROPCC (-0.21. p = 0.024)
GGT	No significant correlation found
MCV	Arithmetic raw score (-0.19. p = 0.038) Arithmetic standard score (-0.20. p = 0.0036)
OCDS-Obsessive	Animals raw score (0.18. p = 0.049) WCST correct (-0.18. p = 0.049)
OCDS-Impulsive	Symbol Search standard score (-0.29. p = 0.0019) WCST completed categories (-0.20. p = 0.027) WCST correct (-0.26. p = 0.0046) WCST error (0.26. p = 0.0048) WCST DIFF2N2 (-0.22. p = 0.019
OCDS-Total	Symbol Search standard score (-0.25. p = 0.0075) IGT CA (0.20. p = 0.03) IGT CDA (-0.26. p = 0.03) WCST correct (-0.26. p = 0.0054) WCST error (0.25. p = 0.0084) WCST DIFF2N2 (-0.21. p = 0.023) IAT (0.18. p = 0.048)
BIS-Cognitive	CVLT guided (0.19. p = 0.038) SCWT mean RTCC (-0.29. P = 0.001) SCWT mean RTCI (-0.23. p = 0.012) SCWT PROPCI (0.23. p = 0.012) SCWT mean RT (-0.3. p = 0.0012) FAS correct raw score (-0.2. p = 0.032) Digits reverse (-0.24. p = 0.009) Digits cumulative (-0.31. p = 0.0008) Digits total (-0.24. p = 0.01) WCST completed categories (-0.31. p = 0.0009) WCST correct (-0.39. p <0.001) WCST error (0.36. p <0.001)
BIS-Motor	SCWT mean RTCI (-0.25. p = 0.007) SCWT PROPCI (0.19. p = 0.042) SCWT mean RT (-0.38. p <0.001) FAS correct raw score (-0.2. p = 0.032) WCST completed categories (-0.24. p = 0.0088) WCST correct (-0.26. p = 0.0056) WCST error (0.35. p = 0.0065) WCST FI (-0.3. p = 0.0011) WCST DIFF1N1 (-0.22. p = 0.019)
BIS-Non-planning	SWCT mean RTCC (-0.33. p = 0.0004) SWCT mean RTCI (-0.31. p = 0.0008) SCWT PROPCI (0.23 p = 0.011) SCWT mean RT (-0.38. p <0.001) Digits cumulative (-0.18. p= 0.047)

	WCST completed categories (-0.38. p<0.001) WCST correct (-0.45. p <0.001) WCST error (0.40. p <0.001) WCST C1 (-0.25 p = 0.008) WCST F1 (-0.28 p = 0.002) WCST C2 (-0.2 p = 0.033) WCST DIFF1N1 (-0.23. p = 0.019) WCST DIFF2N2 (-0.18. p = 0.0029) IAT (0.20. p = 0.047).
BIS-Total	SCWT mean RTCC (-0.31. p = 0.0007) SWCT mean RTCI (-0.30. p = 0.001) SCWT mean RT (-0.30. p <0.001 FAS correct raw score (-0.21. p = 0.024) Digits inverse(-0.19. p = 0.044) Digits cumulative (-0.25. p = 0.0065) Total digits (-0.22. p = 0.02) WCST completed categories (-0.36. p <0.001) WCST correct (-0.45. p <0.001) WCST error (0.40. p <0.001) WCST C1 (-0.20. p = 0.0034) WCST F1 (-0.27. p = 0.003) WCST DIFFF1N1 (-0.23. p = 0.014) WCST DIFFF2N2 (-0.18. p = 0.047) IAT (0.20. p = 0.031)

Note. SDUs: Standard drink units; BIS: Barratt Impulsiveness Scale; OCDS: Obsessive Compulsive Drinking Scale; GOT: glutamate oxalacetate transaminase; GPT: glutamate pyruvate transaminase; GGT: gamma glutamyl transferase; MCV: medium corpuscular volume; SCWT: prop correct: Proportion of correct total responses; mean RTCC: Mean response time for correct congruent responses; mean RTCI: Mean response time for incongruent correct responses; mean RTCCO: Mean response time for correct responses; PROPCC: Proportion of correct congruent responses; PROPCI: Proportion of incongruous correct responses; PROPCCO: Proportion of correct responses; mean RT: Mean response time for total correct responses; WCST: SUMPE: Sum of all incorrect attempts with errors; PE: Percentage of perseverative errors; PR: Perseveration percentage in the tests; SFMS: Total number of times an incorrect letter is selected; TRIAL FIRST: Number of trials needed to complete the first category after at least 5 correct; CI: Percentage of errors in the first color category; NI: Percentage of errors in the first number category; FI: Percentage of errors in the first form category; C2: error rate in the second color category; DIFF: Difference in error percentages between adjacent categories.

Table 5. *Matrix of correlations between the variables related to alcohol consumption and impulsivity in the baseline assessment of patients.*

	Years	**%**	**UBEs**	**GOT**	**GPT**	**GGT**	**VCM**	**BIS 11 C**	**BIS 11 M**	**BIS 11 N**	**BIS 11 T**	**OCDS O**	**OCDS C**	**OCDS T**
Years	**1**	0.904**	-0.034	-0.016	-0.057	0.080	0.207*	-0.158	-0.183	0.002	-0.121	-0.034	0.008	-0.009
%		**1**	0.0161	-0.019	-0.040	0.053	0.175	-0.091	-0.091	0.118	-0.011	-0.003	0.097	0.055
UBEs			**1**	0.246*	0.144	0.232*	0.149	0.146	0.192*	0.222*	0.200*	0.213*	0.298*	0.288*
GOT				**1**	0.710**	0.535**	0.248*	-0.133	-0.082	-0.109	-0.152	0.117	0.258*	0.215*
GPT					**1**	0.307*	0.112	-0.070	-0.059	-0.067	-0.084	-0.016	0.168	0.077
GGT						**1**	0.354*	-0.122	-0.122	0.014	-0.102	0.058	0.100	0.093
VCM							**1**	0.014	-0.047	0.102	0.037	0.139	0.073	0.133
BIS11 C								**1**	0.606**	0.562**	0.865**	0.404**	0.194*	0.341*
BIS11 M									**1**	0.585**	0.824**	0.338*	0.234*	0.318*
BIS11 N										**1**	0.846**	0.252*	0.219*	0.271*
BIS 11 T											**1**	0.388**	0.247*	0.361*
OCDS O												**1**	0.510**	0.884**
OCDS C													**1**	0.849**
OCDS T														**1**

Note. Years: Years of alcohol dependence; %: Percentage of life with alcohol dependence; SDU: Standard Drink Unit; BIS: Barratt Impulsiveness Scale (C: cognitive, M: motor, N: non-planning, T: total); OCDS: Obsessive Compulsive Drinking Scale (O: obsessive, C: Compulsive, T: Total); GOT: glutamate oxalacetate transaminase; GPT: glutamate pyruvate transaminase; GGT: gamma glutamyl transferase; MCV: medium corpuscular volume.
*p ‹ 0.05; **p ‹ 0.0001

taking into account the percentage of years of alcohol dependence, total OCDS, non-planning BIS and total BIS. These results indicate that the IAT is discriminative when the alcohol craving of patients is consolidated, intense and related to impulsivity. Alcohol is a psychoactive substance with low addictive power compared to tobacco, cocaine or morphine derivatives. Our group of patients presents moderate alcohol dependence, with daily consumption of about 90 grams of ethanol and an average period alcohol dependence of 13 years, with large standard deviations, as can be seen in Table 1. That is to say, it is not a group with extreme dependence and alcohol craving, which makes the sample more heterogeneous and leads to a substantial percentage of patients not yielding significant results in the IAT. In summary, the results seem to indicate that the IAT is discriminative in those patients with severe and prolonged alcohol dependence and craving, accompanied by significant impulsiveness.

It is important for health care staff in their daily work involving alcohol detoxification and cessation to know which variables related to alcohol use have a significant relationship with cognitive deterioration produced by ARBD. These variables, easily gathered in the initial diagnostic interviews, act as risk markers, the presence of which would indicate the need to perform a more exhaustive neuropsychological analysis. The SDUs consumed daily during the last month is a marker of recent consumption, alongside the parameters measuring the negative consequences of abusive alcohol consumption in blood tests (GOT, GPT, GGT and MCV). Of the latter, hepatic transaminases (GOT, GPT and GGT) are related to the alcohol drunk over the previous month, thus coinciding with the SDUs, while the parameter related to red blood cells, MCV, is linked to lower specificity than GGT and SDUs, to alcohol consumption over the three months prior to the assessment (Niemela, 2016). As indicated by the correlation study (Table 4), these markers of recent consumption are not strongly related to the cognitive functioning of patients, and appear to be only weakly related to the arithmetic test.

However, the variables related to long-term alcohol use (years of alcohol dependence, alcohol percentage of lifespan with alcohol dependence, OCDS and BIS-11) are more significantly related to cognitive function. The longer the alcohol dependence, the worse the attention, anterograde memory, processing speed and abstract reasoning. Higher scores on the OCDS, which indicate the presence of a more intense and consolidated alcohol craving, are related to declining processing speed, verbal fluency, abstract reasoning and cognitive flexibility. Higher scores in BIS-11, indicating the presence of greater impulsivity, are particularly associated with worsening executive function (verbal fluency, resistance to interference, divided attention, abstract reasoning and cognitive flexibility) and short term memory.

The results obtained in the correlation matrix with respect to BIS-11 are highly significant, conspicuous among them the strong correlation with worse executive functioning. It should be remembered that this test measures impulsivity in a global way, that is, it does not differentiate between the impulsiveness which may have caused the cognitive deterioration associated with alcohol use and the impulsiveness which patients may have had previously and which contributed to their developing alcohol dependence. Previous evidence confirms that both scenarios are possible and compatible. Patients with greater alcohol dependence whose problematic use started earlier display an increased tendency to impulsivity at both the individual and family levels (Bernstein et al., 2015; Jakubczyk et al., 2013), and patients in this study have a significantly greater family tendency to problematic alcohol use (Table 2).

What our study clearly shows is that the BIS-11 correlates especially well with the OCDS (Table 5), highlighting a close relationship between impulsivity and alcohol craving. It is these two psychopathological dimensions which are most closely related to cognitive impairment in this study (Table 4). This relationship is most likely bidirectional, with greater impulsivity and craving leading to more drinking and therefore greater cognitive impairment; the greater the cognitive impairment, the worse the executive function and therefore the greater the impulsivity and alcohol craving.

Our data confirm previous research indicating that the intensity of cognitive impairment associated with alcohol use is determined by the lifetime history of drinking, and not by the most recent use, however intense this may have been (Hayes et al., 2016; Horton et al., 2015).

The results of the present study therefore indicate that compared to healthy controls, patients with alcohol use disorder have worse planning capacity and less cognitive flexibility, added to which are attentional and anterograde memory impairments. These disorders would clearly pose serious problems for the patients when following a program of planned alcohol cessation, in which they would have to adhere to psychopharmacological guidelines and structured psychotherapeutic interventions. In addition, these cognitive impairments would favor relapses in alcohol use. Our results thus confirm the findings of previous research (Evren, Durkaya, Evren, Dalbudak, & Cetin, 2012; Romero-Martinez et al., 2018). It is important to remember, as is confirmed in our study, which found no cut-off point to differentiate patients from healthy controls at an individual level in any of the cognitive tests, that cognitive deterioration associated with alcohol use is dimensional, and, therefore, the deterioration each patient may present will be variable. This deterioration can be predicted through the alcohol use history obtained in the initial clinical interview, but its intensity and possible prognostic repercussions can be only clearly known by performing a battery of systematized cognitive tests.

The present study has limitations which should be noted, the most important of which being the transversal nature of the design. This transversality does not allow the exact relationship between impulsivity measured with the BIS-11 and alcohol use disorder to be clarified, nor the influence on the evolution and prognosis of the cognitive disorders detected to be determined. A further issue associated with the cross-sectional design is the difficulty in retrospectively measuring alcohol use to great detail. The cognitive deterioration of patients with a history of alcohol use disorder of equal duration may have been produced by different patterns of alcohol use. Given the heterogeneity of patients in terms of their history of alcohol use (Table 2), a larger sample size would have provided stronger confirmation of the results obtained. Finally, the inclusion and exclusion criteria used in this study meant that patients with alcohol use disorder of low severity were excluded, and the conclusions of this study are therefore only applicable to patients with moderate or serious alcohol use disorder.

Despite these limitations, we can affirm that the present study substantiates the presence of cognitive deterioration in patients with moderate or severe alcohol use disorder starting outpatient alcohol cessation treatment. Such deterioration causes cognitive impairment which affects these patients' attentional capacity, anterograde memory and cognitive function, and, depending on the intensity of the cognitive deterioration presented by each patient, jeopardizes their chances of achieving abstinence and consolidating it by avoiding relapse. We found cognitive deterioration to be related to the duration of dependence, rather than recent consumption, and to the presence of impulsivity. Moreover, these two factors determine the presence of a more favorable implicit attitude towards alcoholic beverages, which also implies a higher risk of relapse. Given the heterogeneity in the history of alcohol use shown by patients with alcohol use disorder who start outpatient treatment, it is advisable to assess the presence of cognitive impairment individually with a battery of systematized cognitive tests.

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Conflict of interests

The authors declare no conflicts of interest in relation to the study, its authorship, and/or the publication of this manuscript.

References

Aharonovich, E., Campbell, A. N. C., Shulman, M., Hu, M. C., Kyle, T., Winhusen, T. & Nunes, E. V. (2018). Neurocognitive Profiling of Adult Treatment Seekers Enrolled in a Clinical Trial of a Web-delivered Intervention for Substance Use Disorders. *Journal of Addiction Medicine, 12*, 99-106. doi:10.1097/adm.0000000000000372.

Anton, R. F. (2000). Obsessive-compulsive aspects of craving: development of the Obsessive Compulsive Drinking Scale. *Addiction, 95 (Suppl. 2)*, 211-217.

Bech, P. (1990). Psychometric developments of the Hamilton scales: the spectrum of depression, dysthymia, and anxiety. *Psychopharmacology Series, 9*, 72-79.

Bernstein, M. H., McSheffrey, S. N., van den Berg, J. J., Vela, J. E., Stein, L. A., Roberts, M. B., … Clarke, J. G. (2015). The association between impulsivity and alcohol/drug use among prison inmates. *Addictive Behaviors, 42*, 140-143. doi:10.1016/j.addbeh.2014.11.016.

Briere, F. N., Rohde, P., Seeley, J. R., Klein, D. & Lewinsohn, P. M. (2014). Comorbidity between major depression and alcohol use disorder from adolescence to adulthood. *Comprehensive Psychiatry, 55*, 526-533. doi:10.1016/j.comppsych.2013.10.007.

Carmona-Perera, M., Sumarroca-Hernandez, X., Santolaria-Rossell, A., Perez-Garcia, M., & Reyes Del Paso, G. A. (2018). Blunted autonomic responses to emotional stimuli in alcoholism: relevance of impulsivity. *Adicciones*. Advance publication online. doi:10.20882/adicciones.1146.

del Ser Quijano, T., Sanchez Sanchez, F., Garcia de Yebenes, M. J., Otero Puime, A., Zunzunegui, M. V. & Munoz, D. G. (2004). [Spanish version of the 7 Minute screening neurocognitive battery. Normative data of an elderly population sample over 70]. *Neurologia, 19*, 344-358.

Draper, B., Karmel, R., Gibson, D., Peut, A. & Anderson, P. (2011). Alcohol-related cognitive impairment in New South Wales hospital patients aged 50 years and over. *Australian and New Zealand Journal of Psychiatry, 45*, 985-992. doi:10.3109/00048674.2011.610297.

Elwood, R. W. (1995). The California Verbal Learning Test: psychometric characteristics and clinical application. *Neuropsychology Review, 5*, 173-201.

Erdozain, A. M., Morentin, B., Bedford, L., King, E., Tooth, D., Brewer, C., … Carter, W. G. (2014). Alcohol-related brain damage in humans. *PloS One, 9*, e93586. doi:10.1371/journal.pone.0093586.

Evren, C., Durkaya, M., Evren, B., Dalbudak, E. & Cetin, R. (2012). Relationship of relapse with impulsivity, novelty seeking and craving in male alcohol-dependent inpatients. *Drug and Alcohol Review, 31*, 81-90. doi:10.1111/j.1465-3362.2011.00303.x.

Florez, G., Espandian, A., Villa, R. & Saiz, P. A. (2019). Clinical implications of cognitive impairment and alcohol

dependence. *Adicciones, 31*, 3-7. doi:10.20882/adicciones.1284.

Galvin, R., Brathen, G., Ivashynka, A., Hillbom, M., Tanasescu, R. & Leone, M. A. (2010). EFNS guidelines for diagnosis, therapy and prevention of Wernicke encephalopathy. *European Journal of Neurology, 17*, 1408-1418. doi:10.1111/j.1468-1331.2010.03153.x.

Golpe, S., Isorna, M., Barreiro, C., Brana, T. & Rial, A. (2017). Binge drinking among adolescents: prevalence, risk practices and related variables. *Adicciones, 29*, 256-267. doi:10.20882/adicciones.932.

Hagen, E., Erga, A. H., Hagen, K. P., Nesvag, S. M., McKay, J. R., Lundervold, A. J. & Walderhaug, E. (2016). Assessment of Executive Function in Patients With Substance Use Disorder: A Comparison of Inventory- and Performance-Based Assessment. *Journal of Substance Abuse Treatment, 66*, 1-8. doi:10.1016/j.jsat.2016.02.010.

Hayes, V., Demirkol, A., Ridley, N., Withall, A. & Draper, B. (2016). Alcohol-related cognitive impairment: current trends and future perspectives. *Neurodegenerative Disease Management, 6*, 509-523. doi:10.2217/nmt-2016-0030.

Horton, L., Duffy, T., Hollins Martin, C. & Martin, C. R. (2015). Comprehensive assessment of alcohol-related brain damage (ARBD): gap or chasm in the evidence? *Journal of Psychiatric and Mental Health Nursing, 22*, 3-14. doi:10.1111/jpm.12156.

Jakubczyk, A., Klimkiewicz, A., Mika, K., Bugaj, M., Konopa, A., Podgorska, A., . . . Wojnar, M. (2013). Psychosocial predictors of impulsivity in alcohol-dependent patients. *Journal of Nervous and Mental Disease, 201*, 43-47. doi:10.1097/NMD.0b013e31827aaf9d.

Koob, G. F. (2003). Alcoholism: allostasis and beyond. *Alcoholism, Clinical and Experimental Research, 27*, 232-243. doi:10.1097/01.alc.0000057122.36127.c2.

Koob, G. F. & Volkow, N. D. (2010). Neurocircuitry of addiction. *Neuropsychopharmacology, 35*, 217-238. doi:10.1038/npp.2009.110.

Laramee, P., Leonard, S., Buchanan-Hughes, A., Warnakula, S., Daeppen, J. B. & Rehm, J. (2015). Risk of All-Cause Mortality in Alcohol-Dependent Individuals: A Systematic Literature Review and Meta-Analysis. *EBioMedicine, 2*, 1394-1404. doi:10.1016/j.ebiom.2015.08.040.

Litten, R. Z., Ryan, M. L., Falk, D. E., Reilly, M., Fertig, J. B. & Koob, G. F. (2015). Heterogeneity of alcohol use disorder: understanding mechanisms to advance personalized treatment. *Alcoholism, Clinical and Experimental Research, 39*, 579-584. doi:10.1111/acer.12669.

Maharasingam, M., Macniven, J. A. & Mason, O. J. (2013). Executive functioning in chronic alcoholism and Korsakoff syndrome. *Journal of Clinical and Experimental Neuropsychology, 35*, 501-508. doi:10.1080/13803395.2013.795527.

Moretti, R., Caruso, P., Dal Ben, M., Gazzin, S. & Tiribelli, C. (2017). Thiamine and Alcohol for Brain Pathology: Super-imposing or Different Causative Factors for Brain Damage? *Current Drug Abuse Reviews, 10*, 44-51. doi:10.2174/1874473711666180402142012.

Mujica-Parodi, L. R., Carlson, J. M., Cha, J. & Rubin, D. (2014). The fine line between 'brave' and 'reckless': amygdala reactivity and regulation predict recognition of risk. *Neuroimage, 103*, 1-9. doi:10.1016/j.neuroimage.2014.08.038.

Niemela, O. (2016). Biomarker-Based Approaches for Assessing Alcohol Use Disorders. *International Journal of Environmental Research and Public Health, 13*, 166. doi:10.3390/ijerph13020166.

Nyhus, E. & Barcelo, F. (2009). The Wisconsin Card Sorting Test and the cognitive assessment of prefrontal executive functions: a critical update. *Brain and Cognition, 71*, 437-451. doi:10.1016/j.bandc.2009.03.005.

Ostafin, B. D., Marlatt, G. A. & Greenwald, A. G. (2008). Drinking without thinking: an implicit measure of alcohol motivation predicts failure to control alcohol use. *Behaviour Research and Therapy, 46*, 1210-1219. doi:10.1016/j.brat.2008.08.003.

Patton, J. H., Stanford, M. S. & Barratt, E. S. (1995). Factor structure of the Barratt impulsiveness scale. *Journal of Clinical Psychology, 51*, 768-774.

Rehm, J., Allamani, A., Aubin, H. J., Della Vedova, R., Elekes, Z., Frick, U., . . . Wojnar, M. (2015). People with alcohol use disorders in specialized care in eight different European countries. *Alcohol and Alcoholism, 50*, 310-318. doi:10.1093/alcalc/agv009.

Rehm, J., Allamani, A., Della Vedova, R., Elekes, Z., Jakubczyk, A., Landsmane, I., . . . Wojnar, M. (2015). General practitioners recognizing alcohol dependence: a large cross-sectional study in 6 European countries. *Annals of Family Medicine, 13*, 28-32. doi:10.1370/afm.1742.

Rehm, J., Rehm, M. X., Shield, K. D., Gmel, G. & Gual, A. (2013). Alcohol consumption, alcohol dependence and related harms in Spain, and the effect of treatment-based interventions on alcohol dependence. *Adicciones, 25*, 11-18.

Rehm, J., Shield, K. D., Gmel, G., Rehm, M. X. & Frick, U. (2013). Modeling the impact of alcohol dependence on mortality burden and the effect of available treatment interventions in the European Union. *European Neuropsychopharmacology, 23*, 89-97. doi:10.1016/j.euroneuro.2012.08.001.

Rickham, P. P. (1964). Human Expermentation, Code of Ethics of the World Medical Association. Declaration of Hensinki. *British Medical Journal, 2*, 177.

Ridley, N. J., Draper, B. & Withall, A. (2013). Alcohol-related dementia: an update of the evidence. *Alzheimer's Research & Therapy, 5*, 3. doi:10.1186/alzrt157.

Romero-Martinez, A., Vitoria-Estruch, S. & Moya-Albiol, L. (2018). Cognitive profile of long-term abstinent alcoholics in comparison with non-alcoholics. *Adicciones*. Advance publication online. doi:10.20882/adicciones.1079.

Sachdeva, A., Chandra, M., Choudhary, M., Dayal, P. & Anand, K. S. (2016). Alcohol-Related Dementia and Neurocognitive Impairment: A Review Study. *International Journal of High Risk Behaviors & Addictions, 5*, e27976. doi:10.5812/ijhrba.27976.

Scarpina, F. & Tagini, S. (2017). The Stroop Color and Word Test. *Frontiers in Psychology, 8*, 557. doi:10.3389/fpsyg.2017.00557.

Shoval, G., Shmulewitz, D., Wall, M. M., Aharonovich, E., Spivak, B., Weizman, A. & Hasin, D. (2014). Alcohol dependence and suicide-related ideation/behaviors in an Israeli household sample, with and without major depression. *Alcoholism, Clinical and Experimental Research, 38*, 820-825. doi:10.1111/acer.12290.

Stavro, K., Pelletier, J. & Potvin, S. (2013). Widespread and sustained cognitive deficits in alcoholism: a meta-analysis. *Addiction Biology, 18*, 203-213. doi:10.1111/j.1369-1600.2011.00418.x.

Steinborn, M. B., Langner, R., Flehmig, H. C. & Huestegge, L. (2018). Methodology of performance scoring in the d2 sustained-attention test: Cumulative-reliability functions and practical guidelines. *Psychological Assessment, 30*, 339-357. doi:10.1037/pas0000482.

Steingroever, H., Wetzels, R., Horstmann, A., Neumann, J. & Wagenmakers, E. J. (2013). Performance of healthy participants on the Iowa Gambling Task. *Psycholological Assessment, 25*, 180-193. doi:10.1037/a0029929.

Volkow, N. D., Koob, G. F. & McLellan, A. T. (2016). Neurobiologic Advances from the Brain Disease Model of Addiction. *New England Journal of Medicine, 374*, 363-371. doi:10.1056/NEJMra1511480.

Wollenweber, F. A., Halfter, S., Brugmann, E., Weinberg, C., Cieslik, E. C., Muller, V. I., . . . Eickhoff, S. B. (2014). Subtle cognitive deficits in severe alcohol addicts–do they show a specific profile? *Journal of Neuropsychology, 8*, 147-153. doi:10.1111/jnp.12001.

Zahr, N. M. & Pfefferbaum, A. (2017). Alcohol's Effects on the Brain: Neuroimaging Results in Humans and Animal Models. *Alcohol Research: Current Reviews, 38*, 183-206.