# Learning and verbal memory: A comparison between patients with alcohol use disorder and major depressive disorder

## Aprendizaje y memoria verbal: Comparación entre pacientes con trastorno por consumo de alcohol y trastorno de depresión mayor

Rocío Villa\*,\*\*,\*\*\*, Julia Rodríguez-Revuelta\*,\*\*,\*\*\*, Ashkan Espandian\*\*\*\*, Isabel Menéndez-Miranda\*,\*\*, Francesco Dal Santo\*,\*\*,\*\*\*, María Paz García-Portilla\*,\*\*,\*\*\*,\*\*\*\*\*, Gerardo Flórez\*\*\*\*\*,\*\*\*\*\*\*, Julio Bobes\*,\*\*,\*\*\*,\*\*\*\*\*, Pilar A. Sáiz\*,\*\*,\*\*\*,\*\*\*\*\*.

\* Servicio de Salud del Principado de Asturias (SESPA), España.
\*\* Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), España.
\*\*\* Área de Psiquiatría, Universidad de Oviedo, España.
\*\*\*\* Servicio de Psiquiatría del Hospital del Bierzo. Servicio de Salud Mental de Castilla y León (SACYL), España.
\*\*\*\*\* Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), España.
\*\*\*\*\*\* Unidad de Conductas Adictivas, Complejo Hospitalario Universitario de Ourense, España.

## Abstract

Brain damage related to alcohol consumption is associated with impairments in cognitive functions, among which memory and verbal learning stand out. The main objective is to evaluate memory and verbal learning in a sample of 111 patients with alcohol use disorder (AUD) versus 78 with major depressive disorder (MDD) and 100 healthy controls. The evaluation included sociodemographic and clinical variables, the Hamilton Depression Scale (HDRS) and the California Verbal Learning Test (CVLT). One-way ANOVA was used for comparisons between the 3 groups and two-way ANCOVAS including different covariates. The one-way ANOVA shows that patients with AUD and MDD had scores similar to each other and lower than those of the control group (p <0.001), with the exception of the Cued CVLT (worse scores in MDD vs AUD, p <0.001). After including age, sex and years of completed studies as covariates, the differences between the AUD and MDD groups persisted compared to the control group (p ≤ 0.003) in all indices except for the Immediate Free CVLT and the Cued CVLT (worse performance in MDD vs AUD, p = 0.022 and p = 0.035, respectively). In the second ANCOVA, after controlling for depression severity, differences were only detected between AUD patients and healthy controls (p ≤ 0.007). Patients with AUD present a significant impairment in learning and verbal memory when compared with patients with MDD and with healthy people.
*Key words:* Alcohol use disorder; California Verbal Learning Test; major depressive disorder; verbal learning; verbal memory.

## Resumen

El daño cerebral relacionado con el consumo de alcohol se asocia a alteraciones de las funciones cognitivas, entre las que destacan memoria y aprendizaje verbal. El objetivo principal es evaluar memoria y aprendizaje verbal en una muestra de 111 pacientes con trastorno por consumo de alcohol (TCA) versus 78 con trastorno de depresión mayor (TDM) y 100 controles sanos. La evaluación incluyó variables sociodemográficas y clínicas, la Escala de Hamilton para la Depresión (HDRS) y el Test de Aprendizaje Verbal de California (CVLT). Se utilizó ANOVA de un factor para comparaciones entre los 3 grupos y ANCOVAS bidireccionales incluyendo diferentes covariables. El ANOVA de un factor muestra que los pacientes con TCA y TDM obtienen puntuaciones similares entre sí e inferiores a las del grupo control (p < 0,001), con excepción del CVLT Guiado (peores puntuaciones en TDM vs TCA, p < 0,001). Tras incluir como covariables la edad, sexo y los años de estudios completados, persisten las diferencias entre los grupos de TCA y TDM frente al grupo control (p ≤ 0,003) en todos los índices con excepción del CVLT Libre Inmediato y del CVLT Guiado (peor rendimiento en TDM vs TCA, p = 0,022 y p = 0,035, respectivamente). En el segundo ANCOVA, tras controlar por gravedad de la depresión, únicamente se detectan diferencias entre los pacientes con TCA y los controles sanos (p ≤ 0,007). Los pacientes con TCA presentan una importante alteración en aprendizaje y memoria verbal al compararlos con pacientes con TDM y con personas sanas.
*Palabras clave:* Aprendizaje verbal; California Verbal Learning Test; memoria verbal; trastorno de depresión mayor; trastorno por consumo de alcohol.

Most studies in patients with mental disorders in general and with substance use disorder in particular focus on psychopathological aspects. However, little attention has been paid to the cognitive deficits linked to such disorders, despite their importance and the impact they have on patients' quality of life and their social and professional integration (Millan et al., 2012).

There is ample evidence that prolonged and excessive alcohol use can cause structural and functional brain damage (Crowe, Cammisuli & Stranks, 2019; Le Berre, Fama & Sullivan, 2017; Stavro, Pelletier & Potvin, 2013; Toledo-Nunes, Kipp, Reitz & Savage, 2019) with potential effects ranging from subtle impairments to more serious and lasting cognitive disorders such as dementia (Brust, 2010; Hayes, Demirkol, Ridley, Withall & Draper, 2016; Svanberg & Evans, 2013; Toledo-Nunes et al., 2019). Such brain dysfunction linked to alcohol is caused by two toxic mechanisms acting in combination (Moretti, Caruso, Dal Ben, Gazzin & Tiribelli, 2017). On the one hand, the direct neurotoxic effect of ethanol (Stavro et al., 2013; Wollenweber et al., 2014) and, on the other hand, that associated with thiamine deficiency that gives rise to Wernicke/Korsakoff Syndrome, the core symptom of which is serious memory disorder (Kuźma, Llewellyn, Langa, Wallace & Lang, 2014; Maharasingam, Macniven & Mason, 2013; Sachdeva, Chandra, Choudhary, Dayal & Anand, 2016). Moreover, the belief that moderate alcohol consumption has a neuroprotective effect has recently been called into question, with evidence of harm in moderate drinkers compared to abstainers (Topiwala et al., 2017).

It should be noted that brain damage related to drinking alcohol is a frequently underdiagnosed health problem (Sachveda et al., 2016; Hayes et al., 2016), one that is associated with impairment in the following cognitive functions: attention, processing speed, visuospatial tasks, anterograde memory, working memory and executive function (verbal fluency, resistance to interference, abstract reasoning and cognitive flexibility) (Erdozain et al., 2014; Spear, 2018; Stavro et al., 2013; Villa et al., 2021).

The degree of deterioration is influenced not only by the amount of alcohol but also by the drinking pattern (Florez, Espandian, Villa & Saiz, 2019; Hayes et al., 2016). It is noteworthy, for example, that binge drinking can produce more intense neuronal effects in the hippocampus, hypothalamus and cerebellum, which would interfere with learning and memory capacity (Ridley, Draper & Withall, 2013).

Similarly, cognitive dysfunction in major depression disorder (MDD) affects different domains, including, among others, executive function, verbal memory and attention (Bortolato et al., 2016; Fossatti, Coyette, Ergis & Allilaire, 2002; Marazziti, Consoli, Picchetti, Carlini & Faravelli, 2010; Roca, Vives, López-Navarro, García-Campayo & Gili, 2015).

Previous studies suggest that cognitive impairment in MDD may be an independent symptom domain, rather than an epiphenomenon of mood-related symptoms (Gregory et al., 2020; Rock, Roiser, Riedel & Blackwell, 2014). The deterioration of memory and verbal learning that is found both in patients with unipolar and bipolar depression, is usually interpreted as a reflection of the inability to transfer information from short-term storage to long-term storage (Marazziti et al., 2010).

Previous data in patients with alcohol use disorder (AUD) has shown impairment in the different indices of the California Verbal Learning Test (CVLT) (Ros-Cucurull et al., 2018; Van Geldorp, Bergman, Robertson, Wester & Kessels, 2012; Villa et al., 2021a; Villa et al., 2021b; Wester, Roelofs, Egger & Kessels, 2014). Although some studies have analyzed cognitive function in alcohol and depression comorbidity (Hunt, Baker, Michie, & Kavanagh, 2009; Hunt, Kay-Lambkin, Baker & Michie, 2015; Lee et al., 2015), there is no research to date comparing memory and verbal learning impairment in patients with AUD compared to patients with MDD and healthy controls, which represents the main innovation of this study.

The main objective of the present study is to evaluate memory and verbal learning in a sample of AUD patients compared to MDD patients and healthy controls. Based on the literature, our working hypothesis is that patients with AUD disorders will present a greater degree of deterioration in these functions than the rest of the sample (MDD and healthy controls).

## Material and methods

### Participants

The final sample comprised 111 patients with active AUD (DSM-5 criteria) (American Psychiatric Association, 2013) at the time of recruitment, 78 patients with MDD (DSM-5 criteria) (American Psychiatric Association, 2013) and 100 healthy controls. Participants with AUD were recruited from three health facilities: the La Calzada mental health centre in Gijón, the addictive behaviours unit of the psychiatry department at the Ourense Hospital Complex, and the Institute of Neuropsychiatry and Addictions, Parc de Salut Mar, in Barcelona. Patients with an MDD diagnosis were recruited at the Mental Health Centre II, La Corredoria, in Oviedo.

The AUD patients met DSM-5 criteria for moderate or severe alcohol use disorder, quantified as active consumption of > 60 grams of ethanol/day in men and > 40 grams of ethanol/day in women over the past month, and expressed a clear desire to control their drinking. Noteworthy among the inclusion criteria for patients with AUD was having no previous history of depressive episodes and scoring < 5 on the 17-item Hamilton Depression Scale (HDRS) (Hamilton, 1960). The main inclusion criterion

Rocío Villa, Julia Rodríguez-Revuelta, Ashkan Espandian, Isabel Menéndez-Miranda, Francesco Dal Santo, María Paz García-Portilla, Gerardo Flórez, Julio Bobes, Pilar A. Sáiz

for the group of patients with MDD was a score of ≥ 15 points on the HDRS scale, while key exclusion criteria for both groups of patients (AUD and MDD) were comorbidity with another psychiatric disorder according to DSM-5 criteria, (except tobacco use disorder), intellectual disability or any serious physical illness.

The control group included people with no current or past history of mental disorder and no family history of AUD or MDD. In addition, it was required that alcohol consumption did not exceed 30 grams of ethanol/day during the previous month.

All study participants were aged over 18 years, agreed to participate in the study and signed the corresponding informed consent. The study was approved by the following Research Ethics Committees: Pontevedra - Vigo - Ourense (2016-313), Principado de Asturias (61/14, 06/17 and 142/19) and Parc de Salut Mar (2017-7221 -I) and was developed in line with the ethical and legal regulations on the protection of personal data and studies with humans, complying with the Declaration of Helsinki guidelines (World Medical Association General Assembly, 2013).

### Assessment instruments

An ad-hoc questionnaire (sociodemographic and clinical variables) and the Spanish version of the HDRS scale (Hamilton, 1960; validation in Spanish by Bobes et al., 2003) were used for the purposes of assessing the sample. Finally, the California Verbal Learning Test (CVLT) (Delis, Kramer, Kaplan & Ober, 1987) was used to measure different indices of verbal memory such as encoding, free and cued recall, and recognition presented orally. For this purpose, the examiner reads a list of 16 nouns aloud (List A), at one second intervals, in fixed order, during five learning trials, with the sum of the correct answers forming the CVLT Total Attempts score. Next, a list of interferences is presented (List B) and subjects are asked if they remember List A (CVLT Immediate Free Recall). After 20 minutes, subjects were asked to remember as many words as possible (CVLT Delayed Recall), after which the examiner gave semantic signals or clues (CVLT Cued Recall). Finally, a recognition test was presented in which the participants had to discriminate the List A words from the distractors (CVLT Recognition).

### Data analysis

Data were analyzed using the SPSS 24.0 statistical package (SPSS, Armonk, NY: IBM Corp.). Data are presented using means (M) and standard deviations (SD) for numerical variables and frequencies and percentages for categorical variables.

The chi-square test $(\chi^2)$ was used for categorical variables, with Fisher's exact test used to establish statistically different groups, provided that the degrees of freedom (df) were greater than 1, and the analysis of variance was carried out with a one-factor ANOVA with post hoc Bonferroni correction to make the comparison of numerical variables across the 3 groups. Subsequently, two bidirectional analyses of covariance (ANCOVA) were carried out. Fixed factors in the first of the ANCOVAs were sample group membership and gender, and covariates were those variables shown in the literature as influencing the results of the different CVLT indices, age and completed years of education. In the second ANCOVA, depression severity according to the HDRS was added as another covariate. The level of statistical significance established in all cases was α = 0.05 (2 tails).

## Results

The total sample was made up of 289 individuals, 111 of whom had an AUD diagnosis [mean age (SD)= 49.07 (8.41); males: n = 87 (78.4%)], 78 with MMD [mean age (SD) = 52.28 (10.63); males: n = 32 (41.0%)] and 100 healthy controls [mean age (SD) = 48.66 (9.57); males: n = 74 (74.0%)]. The main sociodemographic characteristics of the sample are summarized in Table 1. Key results in the group of patients with AUD were 15.45 (9.92) mean years (SD) of dependence and consumption of 9.61 (6.43) SDUs/day in the previous month. Meanwhile, in patients with MDD, mean severity (SD) of depression measured with the HDRS was 21.03 (4.09), in line with the clinical picture of major depression according to the Bech (1996) criteria. The corresponding analysis based independently on sex in each of the groups studied, found no statistically significant differences between men and women in the different sociodemographic and clinical variables included in the study.

To compare the results obtained in the different CVLT indices across the three study groups, an exploratory ANOVA was first carried out. This revealed that the scores obtained by AUD and MDD groups were similar to each other and statistically lower than those of the group of healthy controls (p < 0.001) with the exception of the scores obtained in the CVLT Cued index, in which all groups were different from each other and the patients with MDD were those who obtained the lowest scores (p < 0.001) (see table 2). Two consecutive ANCOVAS were subsequently performed, with the first considering sample group membership and sex as fixed factors, and age and completed years of education as covariates, and the second adding severity of depression according to HDRS as a new covariate (Table 2). After the first ANCOVA, it can be observed that the differences in the scores obtained between the AUD and MDD groups persisted as compared to the control group (p ≤ 0.003) in all indices except for CVLT Immediate Free and CVLT Cued, in which there were also differences between the scores obtained by patients with AUD and MDD (p = 0.022 and p = 0.035,

Table 1. *Sociodemographic and clinical variables of the study groups.*

| | Alcohol[1] (n = 111) | Depression[2] (n = 78) | Controls[3] (n = 100) | X² (df) / F (df) | p |
|---|---|---|---|---|---|
| Sex [n (%)] Male | 87 (78.4%) | 32 (41.0%) | 74 (74.0%) | 32.403 (2)* | ‹ 0.001 (1 y 3 ≠ 2)*** |
| Age [M (SD)] | 49.07 (8.41) | 52.28 (10.63) | 48.66 (9.57) | 3.749 (288)** | 0.035 (2 ≠ 3)**** |
| Marital status [n (%)] Single Married / partner Separated / divorced Widowed | 28 (25.2%) 46 (41.4%) 33 (29.7%) 4 (3.6%) | 2 (2.6%) 52 (66.7%) 19 (24.4%) 5 (6.4%) | 27 (27.0%) 56 (56.0%) 15 (15.0%) 2 (2.0%) | 28.960 (6)* | ‹ 0.001 ‹ 0.001 (1 y 3 ≠ 2)*** ≤ 0.039 (1 ≠ 2 y 3)*** 0.032 (1 ≠ 3)*** NS |
| Completed years of study [M (SD)] | 13.30 (2.88) | 13.32 (4.76) | 12.76 (2.42) | 0.865 (288)** | 0.422 |
| HDRS [M (SD)] | 1.97 (2.02) | 21.03 (4.09) | 1.22 (1.76) | 1505.96 (288)** | ‹ 0.001 (1 y 3 ≠ 2)**** |
| Age of dependence onset [M (SD)] | 33.62 (9.15 | – | – | – | – |
| Years of dependence [M (SD)] | 15.45 (9.92) | – | – | – | – |
| SDUs/day(previous month) [M (SD)] | 9.61 (6.43) | – | – | – | – |

*Note.* *Chi-squared; **Analysis of variance; ***Statistically different groups after Fisher exact test; ****Statistically significant groups after post-hoc Bonferroni correction; df = degrees of freedom; M =mean; SD = standard deviation; HDRS = Hamilton Depression Rating Scale; SDU = standard drink unit; NS = not significant.

Table 2. *Means, adjusted means, standard deviations and standard errors for the different indices of the California Verbal Learning Test in the different groups.*

| | Alcohol[1] (n = 111) | Depression[2] (n = 78) | Controls[3] (n = 100) | F (df) | p (*****) |
|---|---|---|---|---|---|
| CVLT Total Attempts [M (SD)] | 45.76 (11.61) | 45.56 (12.16) | 53.20 (9.80) | 14.826 (2. 286)*** | ‹ 0.001 (1 y 2 ≠ 3) |
| CVLT Total Attempts [Madjusted (SE)]* | 47.84 (1.19) | 45.62 (1.21) | 54.42 (1.19) | 14.599 (2. 281)**** | ‹ 0.001 (1 y 2 ≠3) |
| CVLT Total Attempts [Madjusted (SE)]** | 46.16 (1.64) | 50.56 (3.52) | 52.44 (1.78) | 7.149 (2. 280)**** | 0.001 (1 ≠ 3) |
| CVLT Immediate Free [M (SD)] | 9.77 (3.32) | 9.08 (3.41) | 12.31 (2.82) | 26.838 (2. 286)*** | ‹ 0.001 (1 y 2 ≠ 3) |
| CVLT Immediate Free [Madjusted (SE)]* | 10.40 (0.34) | 9.09 (0.34) | 12.70 (0.34) | 28.451 (2.281)**** | ‹ 0.001 (1 y 2 ≠ 3) 0.022 (1 ≠ 2) |
| CVLT Immediate Free [Madjusted (SE)]** | 10.19 (0.47) | 9.70 (1.01) | 12.45 (0.51) | 11.155 (2. 280)**** | ‹ 0.001 (1 ≠ 3) |
| CVLT Delayed Free [M (SD)] | 10.32 (3.35) | 9.56 (3.37) | 12.98 (2.90) | 29.394 (2. 286)*** | ‹ 0.001 (1 y 2 ≠ 3) |
| CVLT Delayed Free [Madjusted (SE)]* | 10.79 (0.35) | 9.67 (0.36) | 13.25 (0.35) | 26.575 (2. 281)**** | ‹ 0.001 (1 y 2 ≠ 3) |
| CVLT Delayed Free [Madjusted (SE)]** | 10.39 (0.49) | 10.87 (1.05) | 12.78 (0.53) | 11.341 (2. 280)**** | ‹ 0.001 (1 ≠ 3) |
| CVLT Cued [M (SD)] | 11.42 (2.83) | 10.56 (2.99) | 13.64 (2.70) | 29.171 (2. 286)*** | ‹ 0.001 (1 ≠ 2 ≠ 3) |
| CVLT Cued [M (SE)]* | 11.75 (0.32) | 10.64 (0.32) | 13.87 (0.32) | 26.911 (2. 281)**** | ‹ 0.001 (1 y 2 ≠ 3) 0.035 (1 ≠ 2) |
| CVLT Cued [M (SE)]** | 11.62 (0.44) | 10.99 (0..94) | 13.71 (0.47) | 11.088 (2. 280)**** | ‹ 0.001 (1 ≠ 3) |
| CVLT Recognition [M (SD)] | 14.20 (2.12) | 13.94 (2.37) | 15.34 (1.08) | 14.502 (2. 286)*** | ‹ 0.001 (1 y 2 ≠ 3) |
| CVLT Recognition [M (SE)]* | 14.37 (0.22) | 13.89 (0.22) | 15.40 (0.22) | 12.351 (2. 281)**** | 0.003 (1 ≠ 3) ‹ 0.001 (2 ≠ 3) |
| CVLT Recognition [M (SE)]** | 13.94 (0.30) | 15.16 (0.64) | 14.89 (0.32) | 5.495 (2. 280)**** | 0.007 (1 ≠ 3) |

*Note.* *Covariates: age and completed years of education; **Covariates: age, completed years of education and score on Hamilton Depression Rating Scale (HDRS); ***Analysis of variance; ****Analysis of covariance; *****Statistically significant groups after post-hoc Bonferroni correction; CVLT = California Verbal Learning Test; M = mean; SD = standard deviation; df = degrees of freedom; SE = standard error.

respectively) (Table 2). It should be noted that women obtained statistically higher scores than men in all indices and in all groups (p ≤ 0.017) (Table 3). A statistically significant interaction between sex and group was not observed in any of the indices after controlling for age and completed years of education [CVLT Total Attempts: F (2, 281) = 0.569, $p$ = 0.567, partial η² = 0.004; CVLT Immediate Free: F (2, 281) = 0.252, $p$ = 0.777, partial η² = 0.002; CVLT

Delayed Free: F (2, 281) = 0.617, $p$ = 0.540, partial η² = 0.004; CVLT Cued: F (2, 281) = 0.224, $p$ = 0.800, partial η² = 0.002; CVLT Recognition: F (2, 281) = 0.467, $p$ = 0.628, partial η² = 0.003] (Table 3).

As mentioned above, the second of the ANCOVAS carried out also included the total score on the HDRS scale as a covariate. Figure 1 shows that for all indices, women obtained significantly higher scores than men, regardless of

Rocío Villa, Julia Rodríguez-Revuelta, Ashkan Espandian, Isabel Menéndez-Miranda, Francesco Dal Santo, María Paz García-Portilla, Gerardo Flórez, Julio Bobes, Pilar A. Sáiz

the group to which they belong (CVLT Total Attempts: $p < 0.001$; CVLT Immediate Free: $p < 0.001$; CVLT Delayed Free: $p = 0.001$; CVLT Cued: $p = 0.006$; CVLT Recognition: $p = 0.027$) (Table 3). Table 2 shows how after controlling for the depression severity, statistically significant differences were only detected between the group of patients with AUD and healthy controls ($p \leq 0.007$). Finally, it should be noted that there was no statistically significant interaction between sex and group for any of the indices after the corresponding controls for age, completed years of education and HDRS score [CVLT Total Attempts: $F (2, 280) = 0.702$, $p = 0.497$, partial $\eta^2 = 0.005$; CVLT Immediate Free: $F (2, 280) = 0.286$, $p = 0.751$, partial $\eta^2 = 0.002$; CVLT Delayed Free: $F (2, 280) = 0.748$, $p = 0.474$, partial $\eta^2 = 0.005$; CVLT Cued: $F (2, 280) = 0.249$, $p = 0.780$, partial $\eta^2 = 0.002$; CVLT Recognition: $F (2, 280) = 0.384$, $p = 0.682$, partial $\eta^2 = 0.003$] (Table 3).

## Discussion

The main objective of this study was to compare the verbal memory performance of patients with AUD and MDD and healthy controls using the CVLT. As might be expected, patients with AUD or MDD performed worse than healthy controls in all indices assessed in this test.

Initial exploratory analysis shows that the impairment in learning, immediate recall and delayed recall was similar in patients with AUD and MDD, with significantly lower scores in both cases than those detected in healthy people. These data coincide with those reported in previous studies comparing patients with AUD versus healthy controls (Ros-Cucurull et al., 2018; Stavro et al., 2013; Van Geldorp et al., 2012; Villa et al., 2021a; Villa et al., 2021b; Wester et al., 2014) and MDD patients versus healthy controls (Lee, Hermens, Porter & Redoblado-Hodge, 2012; Marazziti et al., 2010; Mesholam-Gately et al., 2012; Roca et al., 2015). Furthermore, patients with MDD obtained worse scores in the cued free recall index, that is, in the index in which categorical clues are provided to facilitate recall. Various authors argue that the results obtained in the CVLT may be mediated by executive functioning (Mesholam-Gately et al., 2012; Moreira, Santos, Sousa & Costa, 2015). It could be hypothesized that recall guided by categorical clues would require frontal intervention for the semantic association that favours recall and this could be behind the poorer performance in MDD patients, since notable impairment of executive function has been described in depression (Nuño, Gómez-Benito, Carmona & Pino, 2021; Rock et al., 2014). However, it should be noted that other authors have not found significant differences in delayed cued recall between patients with MDD and healthy controls (Fossatti, Deweer, Raoux & Allilaire, 1995).

After controlling for confounding factors in the subsequent ANCOVA analysis, it can be observed that the performances in recent memory and recognition continue to be similar and significantly lower in patients with AUD and MDD compared to healthy controls, with the exception of worse performance in immediate free recall and in cued recall in patients with MDD (versus AUD and controls).

Table 3. *Means, adjusted means, standard deviations and standard errors for the different indices of the California Verbal Learning Test in the different groups by sex.*

| | Men | | | Women | | | Effect (p) | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | Alcohol[1] (n = 87) | Depression[2] (n = 32) | Controls[3] (n = 74) | Alcohol[1] (n = 24) | Depression[2] (n = 46) | Controls[3] (n = 26) | Sex | Grupo*sexo Iteration |
| CVLT Total Attempts [M (SD)] | 43.99 (10.95) | 41.41 (8.41) | 51.96 (9.94) | 52.17 (11.90) | 48.46 (13.55) | 56.73 (8.54) | - | - |
| CVLT Total Attempts [Madjusted (SE)]* | 43.66 (1.11) | 43.07 (1.86) | 51.71 (1.21) | 52.03 (2.12) | 48.18 (1.53) | 57.12 (2.04) | ‹ 0.001 | 0.567 |
| CVLT Total Attempts [Madjusted (SE)]** | 41.96 (1.59) | 48.23 (3.92) | 49.80 (1.76) | 50.36 (2.39) | 52.89 (3.51) | 55.09 (2.45) | ‹ 0.001 | 0.497 |
| CVLT Immediate Free [M (SD)] | 9.24 (3.25) | 7.72 (3.29) | 11.85 (2.93) | 11.71 (2.85) | 10.02 (3.21) | 13.62 (2.02) | - | - |
| CVLT Immediate Free [Madjusted (SE)]* | 9.18 (0.32) | 8.17 (0.53) | 11.76 (0.34) | 11.63 (0.60) | 10.02 (0.44) | 13.63 (0.58) | ‹ 0.001 | 0.777 |
| CVLT Immediate Free [Madjusted (SE)]** | 8.97 (0.45) | 8.81 (1.12) | 11.52 (0.50) | 11.42 (0.68) | 10.60 (1.00) | 13.38 (0.70) | ‹ 0.001 | 0.751 |
| CVLT Delayed Free [M (SD)] | 9.90 (3.27) | 8.84 (3.23) | 12.64 (2.98) | 11.83 (3.25) | 10.07 (3.40) | 13.96 (2.44) | - | - |
| CVLT Delayed Free [Madjusted (SE)]* | 9.84 (0.33) | 9.27 (0.55) | 12.54 (0.36) | 11.75 (0.63) | 10.07 (0.46) | 13.97 (0.60) | 0.001 | 0.540 |
| CVLT Delayed Free [Madjusted (SE)]** | 9.43 (0.47) | 10.52 (1.17) | 12.08 (0.52) | 11.35 (0.71) | 11.21 (1.04) | 13.47 (0.73) | 0.001 | 0.474 |
| CVLT Cued [M (SD)] | 11.14 (2.83) | 9.94 (2.85) | 13.39 (2.83) | 12.46 (2.62) | 11.00 (3.03) | 14.35 (2.15) | - | - |
| CVLT Cued [M (SE)]* | 11.09 (0.30) | 10.24 (0.50) | 13.34 (0.32) | 12.42 (0.56) | 10.97 (0.41) | 14.39 (0.54) | 0.005 | 0.800 |
| CVLT Cued [M (SE)]** | 10.95 (0.42) | 10.64 (1.05) | 13.19 (0.47) | 12.29 (0.64) | 11.33 (0.94) | 14.23 (0.65) | 0.006 | 0.780 |
| CVLT Recognition [M (SD)] | 14.06 (2.16) | 13.38 (2.87) | 15.27 (1.16) | 14.71 (1.92) | 14.33 (1.87) | 15.54 (0.76) | - | - |
| CVLT Recognition [M (SE)]* | 14.05 (0.20) | 13.45 (0.34) | 15.25 (0.22) | 14.69 (0.39) | 14.33 (0.28) | 15.54 (0.37) | 0.017 | 0.628 |
| CVLT Recognition [M (SE)]** | 13.61 (0.29) | 14.78 (0.72) | 14.76 (0.32) | 14.27 (0.44) | 15.54 (0.64) | 15.02 (0.45) | 0.027 | 0.682 |

*Note.* *Covariates: age and completed years of education; **Covariates: age, completed years of education and score on Hamilton Depression Rating Scale (HDRS); CVLT = California Verbal Learning Test; M = mean; SD = standard deviation; SE = standard error.
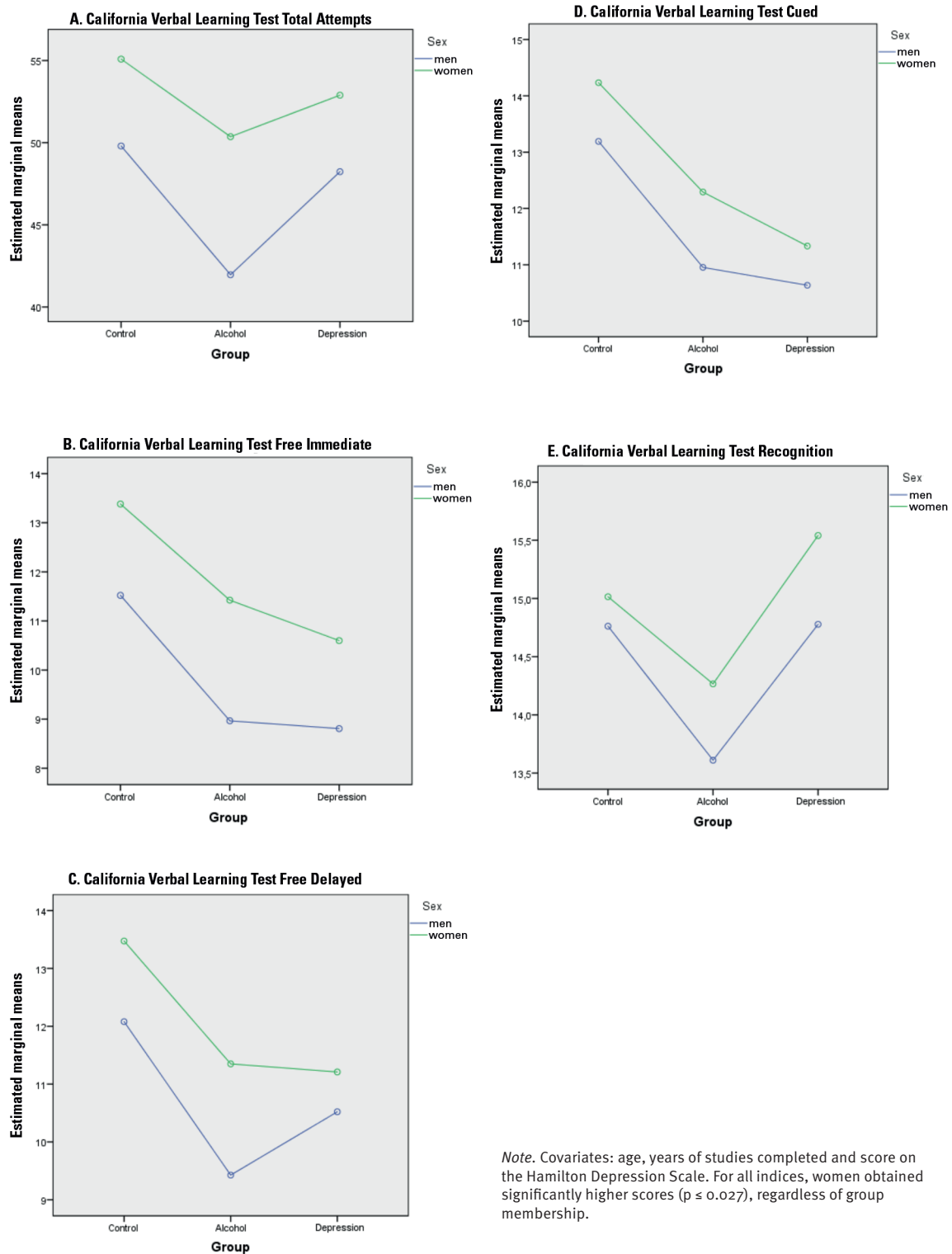
## A. California Verbal Learning Test Total Attempts



## D. California Verbal Learning Test Cued



## B. California Verbal Learning Test Free Immediate



## E. California Verbal Learning Test Recognition



## C. California Verbal Learning Test Free Delayed



*Note.* Covariates: age, years of studies completed and score on the Hamilton Depression Scale. For all indices, women obtained significantly higher scores (p ≤ 0.027), regardless of group membership.

*Figure 1.* Adjusted means for the different indices of the California Verbal Learning Test by sex and group membership.

Previous data have shown that depressed patients have difficulties with immediate free verbal memory tasks (Fossatti et al., 1995), and there is broad agreement that they may be secondary to other dysfunctions, such as attention deficit, cognitive interference from pessimistic ruminative thoughts, the lack of motivation, as well as the difficulty of maintaining sustained effort (Marazzitti et al., 2010; Millan et al., 2012 ).

This first analysis shows that MDD patients had persistently greater difficulty in cued recall, with the implication that recall facilitated by clues is not influenced by the confounding factors taken into account (age, sex and/or educational level).

Furthermore, it is interesting to note that, in all groups (AUD, MDD and healthy controls) and in all test

Rocío Villa, Julia Rodríguez-Revuelta, Ashkan Espandian, Isabel Menéndez-Miranda, Francesco Dal Santo, María Paz García-Portilla, Gerardo Flórez, Julio Bobes, Pilar A. Sáiz

indices, women performed better than men. A statistically significant interaction between sex and group was not observed in any of the indices after the corresponding control for age and completed years of education. Previous studies have highlighted that women outperform men in learning and verbal recall in all age ranges using the CVLT, which is consistent with the hypothesis linking oestrogen level and verbal memory performance (Kramer et al., 2019; Lundervold, Wollschläger & Wehling, 2014).

After controlling for the severity of depression, statistically significant differences were only detected between the group of AUD patients and healthy controls. In our sample, therefore, depression severity stands out as a determining factor in the impairment of verbal memory in patients with MDD. Our data confirm earlier findings that the severity of depression is associated with a deficit in verbal learning and memory in depressed patients (Lee et al., 2015; Marazziti et al., 2010; McDermott & Ebmeier, 2009). Moreover, the initial working hypothesis was confirmed since AUD patients presented a greater degree of deterioration in all CVLT test indices when compared to MDD patients and healthy controls. Previous studies have shown that AUD patients seeking treatment present clear cognitive impairment which includes executive dysfunction and memory deficits (Oscar-Berman et al., 2014; Stavro et al., 2013; Sullivan, Rosenbloom, Lim & Pfefferbaum, 2000). Alcohol abuse damages brain tissue causing a marked generalized brain atrophy, as well as specific damage in the areas responsible for learning and memory (Ridley et al., 2013; Stavro et al., 2013; Zahr & Pfefferbaum, 2017). In patients with AUD there are deficits in the coding and verbal retrieval processes (Bernardin, Maheut-Bosser & Paille, 2014; Noël et al, 2001; Pitel et al., 2007) and the learning of verbal and non-verbal information may be affected (Kopera et al., 2012). Our results confirm what has been previously described regarding the impairment of verbal memory in AUD (Ros-Cucurull et al., 2018; Van Geldorp et al., 2012; Villa et al., 2021a; Villa et al., 2021b; Wester et al., 2014). However, it should be noted that the studies carried out to date compare AUD with healthy controls, without including another group of patients classically associated with significant impairment in cognition, such as patients with MDD. Our results are therefore more relevant both at clinical and therapeutic levels. Memory and executive functioning are cognitive domains closely linked to treatment outcomes and maintenance of abstinence (Bates, Buckman & Nguyen, 2013). Dysfunction in learning and memory could interfere with the adequate assimilation of psychotherapeutic interventions, potentially reducing their effectiveness, and making it difficult to achieve the goal of quitting alcohol (Bates et al., 2013; Florez et al., 2019; Sachdeva et al., 2016). It should be noted that, although some studies have reported data that could be promising in the improvement of such cognitive dysfunction, using

both psychopharmacological approaches (Bell, Pittman, Petrakis & Yoon, 2020; Sachdeva et al., 2016) as well as psychotherapeutics (Frias-Torres et al., 2018; Hayes et al., 2016; Rupp, Kemmler, Kurz, Hinterhuber & Fleischhacker, 2012; Sachdeva et al., 2016; Svanberg et al., 2013), the results of these studies are not conclusive at present.

The main limitation of this study is its cross-sectional design, which does not allow the prognosis of memory dysfunction to be assessed in the medium/long term. Another limitation associated with the cross-sectional design is the difficulty of retrospectively measuring alcohol use with a greater degree of accuracy. Moreover, it should be noted that a premorbid IQ measurement was not made, which may in turn have an influence on test performance. Finally, it should be noted that the interference in cognition of the pharmacological treatments used was not analyzed. However, the various strengths of the study can also be highlighted. Chief among them is that this is the first study of its kind to assess verbal learning and memory in a sample of AUD patients compared to MDD patients and healthy controls. Similarly, the selection of the sample was very strict, excluding patients with other psychiatric comorbidities, in order to allow the specific factors associated with verbal memory in patients with AUD and MDD to be established.

Finally, it should be pointed out that AUD patients in our sample presented significant impairment in verbal learning and memory when compared with patients with MDD and with healthy individuals. These results raise the need for future studies to analyze the extent to which this verbal mnesic disorder can negatively influence the results of an alcoholic cessation program. Thus, it may be relevant to adapt the therapeutic interventions to the cognitive level of each patient to favour their effectiveness.

## Acknowledgments

## 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

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders,* 5th ed. *(DSM-5).* Arlington, VA: American Psychiatric Publishing.

Bates, M. E., Buckman, J. F. & Nguyen, T. T. (2013). A role for cognitive rehabilitation in increasing the effectiveness of treatment for alcohol use disorders. *Neuropsychology Review, 23,* 27-47. doi:10.1007/s11065-013-9228-3.

Bech, P. (1996). *The Bech, Hamilton and Zung scales for mood disorders: Screening and listening,* 2nd ed. Berlin: Springer.

Bell, M. D., Pittman, B., Petrakis, I. & Yoon, G. (2020). Donepezil and cognitive remediation therapy to augment treatment of alcohol use disorder related mild cognitive impairment (AUD-MCI): An open label pilot study with historical controls. *Substance abuse.* Advance publication online. doi:10.1080/08897077.2020.1844847.

Bernardin, F., Maheut-Bosser, A. & Paille, F. (2014). Cognitive impairments in alcohol-dependent subjects. *Frontiers in Psychiatry, 16,* 78. doi:10.3389/fpsyt.2014.00078.

Bobes, J., Bulbena, A., Luque, A., Dal-Re, R., Ballesteros, J. & Ibarra, N. (2003). Grupo de validación en español de escalas psicométricas. Evaluación psicométrica comparativa de las versiones en español de 6, 7 y 21 ítems de la Escala de valoración de Hamilton para la evaluación de la depresión. *Medicina Clínica, 120,* 693-700.

Bortolato, B., Miskowiak, K. W., Köler, C. A., Maes, M., Fernandes, B. S., Berk, M. & Carvalho, A. F. (2016). Cognitive remission: A novel objective for the treatment of major depression? *BMC Medicine, 14,* 9. doi:10.1186/s12916-016-0560-3.

Brust, J. C. M. (2010). Ethanol and cognition: Indirect effects, neurotoxicity and europrotection: A review. *International Journal of Environmental Research and Public Health, 7,* 1540-1557. doi:10.3390/ijerph7041540.

Crowe, S. F., Cammisuli, D. M. & Stranks, E. K. (2019). Widespread cognitive deficits in alcoholism persistent following prolonged abstinence: An updated meta-analysis of studies that used standardised europsychological assessment tools. *Archives of Clinical Neuropsychology, 35,* 31-45. doi:10.1093/arclin/acy106.

Delis, D. C., Kramer, J. H., Kaplan, E. & Ober, B. A. (1987). *California Verbal Learning Test. Research edition manual.* New York: Psychological Corporation.

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.* doi:10.1371/journal.pone.0093586.

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.

Fossatti, P., Deweer, B., Raoux, N. & Allilaire, J. F. (1995). Deficits in memory retrieval: An argument in favor of frontal subcortical dysfunction in depression. *L'Encephale, 21,* 295-305.

Fossatti, P., Coyette, F., Ergis, A. M. & Allilaire, J. F. (2002). Influence of age and executive functioning on verbal memory of inpatients with depression. *Journal of Affective Disorders, 68,* 261-271. doi:10.1016/s0165-0327(00)00362-1.

Frias-Torres, C., Moreno-Espana, J., Ortega, L., Barrio, P., Gual, A. & Teixidor Lopez, L. (2018). Remediation therapy in patients with alcohol use disorders and neurocognitive disorders: A pilot study. *Adicciones, 30,* 93-100. doi:10.20882/adicciones.757.

Gregory, E., Torres, I. J., Ge, R., Blumberger, D. M., Downar, J. H., Daskalakis, Z. J.,... Vila-Rodriguez, F. (2020). Predictors of cognitive impairment in treatment-resistant depression. *Journal of Affective Disorders, 274,* 593-601. doi:10.1016/j.jad.2020.05.10.

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology Neurosurgery and Psychiatry, 23,* 56-62. doi:10.1136/jnnp.23.1.56.

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.

Hunt, S. A., Baker, A. L., Michie, P. T. & Kavanagh, D. J. (2009). Neurocognitive profiles of people with comorbid depression and alcohol use: Implications for psychological interventions. *Addictive behaviors, 34,* 878-886. doi:10.1016/j.addbeh.2009.03.036.

Hunt, S. A., Kay-Lambkin, F. J., Baker, A. L. & Michie, P. T. (2015). Systematic review of neurocognition in people with co-occurring alcohol misuse and depression. *Journal of affective disorders, 179,* 51-64. doi:10.1016/j.jad.2015.03.024.

Kopera, M., Wojnar, M., Brower, K., Glass, J., Nowosad, I., Gmaj, B. & Szelenberger, W. (2012). Cognitive functions in abstinent alcohol-dependent patients. *Alcohol, 46,* 666-671. doi:10.1016/j.alcohol.2012.04.005.

Kramer, A. O., Casaletto, K. B., Umlauf, A., Staffaroni, A. M., Fox, E., You, M. & Kramer, J. H. (2019). Robust normative standards for the California Verbal Learning Test (CVLT) ages 60–89: A tool for early detection of memory impairment. *Clinical Neuropsychologist, 34,* 384-405. doi:10.1080/13854046.2019.1619838.

Kuźma, E., Llewellyn, D. J., Langa, K. M., Wallace, R. B. & Lang, I. A. (2014). History of alcohol use disorders and risk of severe cognitive impairment: A 19-year prospective cohort study. *American Journal of the Geriatric Psychiatry, 22,* 1047-1054. doi:10.1016/j.jagp.2014.06.001.

Rocío Villa, Julia Rodríguez-Revuelta, Ashkan Espandian, Isabel Menéndez-Miranda, Francesco Dal Santo, María Paz García-Portilla, Gerardo Flórez, Julio Bobes, Pilar A. Sáiz

Le Berre, A. P., Fama, R. & Sullivan, E. V. (2017). Executive functions, memory, and social cognitive deficits and recovery in chronic alcoholism: A critical review to inform future research. *Alcoholism, Clinical and Experimental Research, 41,* 1432-1443. doi:10.1111/acer.13431.

Lee, R. S., Dore, G., Juckes, L., De Regt, T., Naismith, S. L., Lagopoulos, J.,… Hermens, D. F. (2015). Cognitive dysfunction and functional disability in alcohol-dependent adults with or without a comorbid affective disorder. *Cognitive neuropsychiatry, 20,* 222-231. doi:10.1080/13546805.2015.1014031.

Lee, R. S., Hermens, D. F., Porter, M. A. & Redoblado-Hodge, M. A. (2012). A meta-analysis of cognitive deficits in first-episode major depressive disorder. *Journal of Affective Disorders, 140,* 113-124. doi:10.1016/j.jad.2011.10.023.

Lundervold, A. J., Wollschläger, D. & Wehling, E. (2014). Age and sex related changes in episodic memory function in middle aged and older adults. *Scandinavian Journal of Psychology, 55,* 225-232. doi:10.1111/sjop.12114.

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.

Marazziti, D., Consoli, G., Picchetti, M., Carlini, M. & Faravelli, L. (2010). Cognitive impairment in major depression. *European Journal of Pharmacology, 626,* 83-86. doi:10.1016/j.ejphar.2009.08.046.

McDermott, L. M. & Ebmeier, K. P. (2009). A meta-analysis of depression severity and cognitive function. *Journal of Affective Disorders, 119, 1-8.* doi:10.1016/j.jad.2009.04.022.

Mesholam-Gately, R. I., Giuliano, A. J., Zillmer, E. A., Barakat, L. P., Kumar, A., Gur, R. C.,… Moberg, P. J. (2012). Verbal learning and memory in older adults with minor and major depression. *Archives of Clinical Neuropsychology, 27,* 196-207. doi:10.1093/arclin/acr106.

Millan, M. J., Agid, Y., Brüne, M., Bullmore, E. T., Carter, C. S., Clayton, N. S.,… Young, L. J. (2012). Cognitive dysfunction in psychiatric disorders: Characteristics, causes and the quest for improved therapy. *Nature Reviews Drug Discovery, 11,* 141-168. doi:10.1038/nrd3628.

Moreira, P. S., Santos, N. C., Sousa, N. & Costa, P. S. (2015). The use of canonical correlation analysis to assess the relationship between executive functioning and verbal memory in older adults. *Gerontology and Geriatric Medicine, 1.* doi:10.1177/2333721415602820.

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.

Noël, X., Van der Linden, M., Schmidt, N., Sferrazza, R., Hanak, C., Le Bon, O.,… Verbanck, P. (2001). Supervisory attentional system in nonamnesic alcoholic men. *Archives of General Psychiatry, 58,* 1152. doi:10.1001/archpsyc.58.12.1152.

Nuño, L., Gómez-Benito, J., Carmona, V. R. & Pino, O. (2021). A systematic review of executive function and information processing speed in major depression disorder. *Brain Sciences, 11,* 147. doi:10.3390/brainsci11020147.

Oscar-Berman, M., Valmas, M. M., Sawyer, K. S., Ruiz, S. M., Luhar, R. B. & Gravitz, Z. R. (2014). Profiles of impaired, spared, and recovered neuropsychological processes in alcoholism. *Handbook of Clinical Neurology, 125,* 183-210. doi:10.1016/B978-0-444-62619-6.00012-4.

Pitel, A. L., Beaunieux, H., Witkowski, T., Vabret, F., Guillery-Girard, B., Quinette, P.,… Eustache, F. (2007). Genuine episodic memory deficits and executive dysfunctions in alcoholic subjects early in abstinence. *Alcoholism, Clinical and Experimental Research, 31,* 1169-1178. doi:10.1111/j.1530-0277.2007.00418.x.

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

Rock, P. L., Roiser, J. P., Riedel, W. J. & Blackwell, A. D. (2014). Cognitive impairment in depression: A systematic review and meta-analysis. *Psychological Medicine, 44,* 2029-2040. doi:10.1017/S0033291713002535.

Roca, M., Vives, M., López-Navarro, E., García-Campayo, J. & Gili, M. (2015). Cognitive impairments and depression: A critical review. *Actas Españolas de Psiquiatría, 43,* 187-193.

Ros-Cucurull, E., Palma-Alvarez, R. F., Cardona-Rubira, C., Garcia-Raboso, E., Jacas, C., Grau-Lopez, L.,… Roncero, C. (2018). Alcohol use disorder and cognitive impairment in old age patients: A 6 months follow-up study in an outpatient unit in Barcelona. *Psychiatry Research, 261,* 361-366. doi:10.1016/j.psychres.2017.12.069.

Rupp, C. I., Kemmler, G., Kurz, M., Hinterhuber, H. & Fleischhacker, W. W. (2012). Cognitive remediation therapy during treatment for alcohol dependence. *Journal of studies on alcohol and drugs, 73,* 625-634. doi:10.15288/jsad.2012.73.625.

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 and Addiction, 5.* doi:10.5812/ijhrba.27976.

Spear, L. P. (2018). Effects of adolescent alcohol consumption on the brain and behaviour. *Nature Reviews Neuroscience, 19,* 197-214. doi:10.1038/nrn.2018.10.

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.

Sullivan, E. V., Rosenbloom, M. J., Lim, K. O. & Pfefferbaum, A. (2000). Longitudinal changes in cognition, gait, and balance in abstinent and relapsed alcoholic men: Relationships to changes in brain structure. *Neuropsychology, 14,* 178-188.

Svanberg, J. & Evans, J. J. (2013). Neuropsychological rehabilitation in alcohol-related brain damage: A systematic review. *Alcohol and Alcoholism, 48,* 704-711. doi:10.1093/alcalc/agt131.

Toledo-Nunes, P., Kipp, T. K., Reitz, N. L. & Savage, L. M. (2019). Aging with alcohol-related brain damage: Critical brain circuits associated with cognitive dysfunction. *International Review of Neurobiology, 148,* 101-168. doi:10.1016/bs.irn.2019.09.002.

Topiwala, A., Allan, C. L., Valkanova, V., Zsoldos, E., Filippini, N., Sexton, C.,… Ebmeier, K. P. (2017). Moderate alcohol consumption as risk factor for adverse brain outcomes and cognitive decline: Longitudinal cohort study. *BMJ, 357.* doi:10.1136/bmj.j2353.

Van Geldorp, B., Bergman, H. C., Robertson, J., Wester, A. J. & Kessels, R. P. C. (2012). The interaction of working memory performance and episodic memory formation in patients with Korsakoff's amnesia. *Brain Research, 1433,* 98-103. doi:10.1016/j.brainres.2011.11.036.

Villa, R., Espandian, A., Saiz, P. A., Astals, M., Valencia, J. K., Martinez-Santamaria, E.,… Florez G. (2021a). Cognitive functioning in patients with alcohol use disorder who start outpatient treatment. *Adicciones, 33,* 161-174. doi:10.20882/adicciones.1326.

Villa, R., Espandian, A., Saiz, Rodriguez-Revuelta, J., Garcia-Portilla, P., Bobes, J. & Florez, G. (2021b). Cognitive functioning after six months of follow-up in a sample of alcohol use disorder outpatients. *Adicciones.* Advance publication online. doi:10.20882/adicciones.1672.

Wester, A. J., Roelofs, R. L., Egger, J. I. M. & Kessels, R. P. C. (2014). Assessment of alcohol-related memory deficits: A comparison between the Rivermead Behavioural Memory Test and the California Verbal Learning Test. *Brain Impairment, 15,* 18-27. doi:10.1017/BrImp.2014.6.

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.

World Medical Association. (2013). World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects. *JAMA, 310,* 2191-2194. doi:10.1001/jama.2013.281053.

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.