Research article

Cognitive impairment in the co-occurrence of alcohol dependence and major depression: neuropsychological assessment and event-related potentials analyses

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HIGHLIGHTS

- Dual diagnosis (DD) patients exhibited a distinctive pattern of cognitive impairments compared to single diagnosis subjects.
- The ERP alterations identified were not shared among affected groups.
- Dual patients exhibited idiosyncratic behavioral responses.
- Impaired executive functions in DD subjects improved with SSRI medication.
- Neuropsychological and behavioral alterations are not explained as the sum of negative contributions of individual diagnosis.

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ABSTRACT

To evaluate the putative detrimental effect of Major Depressive Disorder (MDD) on the cognitive impairment associated with Alcohol Dependence (AD), we contrasted the neuropsychological profile and behavioral responses of AD subjects, MDD individuals, and in those with a co-occurring AD-MDD diagnosis (DD). Patients and healthy subjects completed a comprehensive neuropsychological battery and were recorded for P200, P300, and N450 event-related potentials during memory and Stroop tasks. AD subjects exhibited a generalized detrimental neuropsychological performance; in contrast, in MDD individuals, impairment was limited to discrete domains. Notably, the deficits were distinctive in DD cases. A P200 increased amplitude in MDD, a decrease in P300 amplitude in AD, and increased latency of P300 in DD patients were the overt electrophysiological abnormalities identified. Dual patients also exhibited a distinct pattern of behavioral responses, particularly apparent during high-demand cognitive tasks. Specific ERP adjustments were associated with the short-term fluoxetine treatment in DD and MDD subjects; the SSRI also improved altered baseline performance in learning and cognitive flexibility in DD subjects. In conclusion, the neuropsychological and behavioral alterations detected in the co-occurrence of AD-MDD did not seem to be merely the sum of the negative contributions of the independent disorders.

1. Introduction

Alcohol dependence (AD) and major depression disorder (MDD) are among the most frequent, recurring, and disturbing mental health problems, generating a heavy social and financial burden to the affected individual. Epidemiological studies show a substantial comorbidity between alcohol use disorders and mood disorders (Merikangas et al., 1998).

Clinicians concur those individuals exhibiting a co-occurring dual AD-MDD diagnosis (that henceforth shall be named with the acronym DD) show more disruptive behavior, poorer adherence to pharmacological treatments and a troublesome recovery with frequent relapses and
hospitlizations, as compared to subjects displaying diagnoses in solitary (Drake, 2004). This multifaceted adverse clinical scenario underscores the imperative necessity to develop mental health services to cope with these unique challenges (Hughes, 2006). All the above lead to consider if the clinical uneasiness, behavioral disturbances, and distress experienced by DD patients could be linked to significantly undermined cognition.

Numerous research papers have documented the impaired cognitive status in individuals affected by alcohol dependence or major depressive disorder (e.g., AD: Noël et al., 2012; Sullivan et al., 2002; MDD: Jaeger et al., 2006; McDermontt and Ebmeier 2009; Baune et al., 2010; Withall et al., 2010; Rock et al., 2014). In short, these studies exhibit a broad set of deficits in the performance of executive functions, some of which seem to share.

Therefore, it might be plausible to assume that the cognitive impairment in DD patients should be just the reflection of the summed negative contributions of each disorder. However, conflicting results emerge from the few studies that have evaluated the neuropsychological profile of AD patients with or without a comorbid affective disorder. Some authors describe an attentional bias to alcohol-related words (Fridici et al., 2014), an exacerbated impulsivity dependent on the severity of depressive symptoms (Jakubczyk et al., 2012) or a poorer performance in visual memory tasks and subtle deficits in executive function as compared to those without the affective comorbidity (Liu et al., 2010). Others instead have been unable to identify an added negative contribution of depression on the already impaired cognitive profile of alcoholics (Uekermann et al., 2003; Fridici et al., 2014). More perplexing is the description of a non-altered neuropsychological performance in individuals with hazardous use of alcohol and depressive symptoms in the severe range (Hunt et al., 2009).

It is worth noting that although neuropsychological tasks provide standardized metrics sensitive to brain-behavior relationships, their capability to evaluate the accuracy and speed of behavioral responses is limited. In this regard, measures of electrical brain activity such as event-related brain potentials (ERPs) can provide valuable insight into the nature of cognitive processes; this electrophysiological measures allow monitoring in “live” the information processing in diverse clinical populations; is a non-invasive and dynamic method that records the associated brain electrical activity to cognitive operations in specific modalities of information processing (e.g., auditory discrimination acuity, expectancy, semantic processing) during the execution of particular task. Moreover, as certain ERP components have been draft to specific brain systems, deviations in relevant parameters (i.e., amplitude, latency, scalp distribution) may even point to the nature and location of the brain dysfunction, providing information of clinical relevance in the conditions of depression, alcohol consumption and dual diagnosis.

Unfortunately, few studies have recorded the electrophysiological activity of neural markers of stimulus processing in the co-occurrence of alcohol use problems and depression. A noteworthy exception is Maugraje et al. (2008) which reported that although alcoholics, depressed individuals, and alcoholics with an added MD diagnosis showed similar deficits in identifying facial expressions with emotional content, only those with alcohol use disorder showed early perceptual deficits in information processing flow, irrespective of comorbid depression.

Given the inconsistent results mentioned above, we aimed to test the hypothesis that the cognitive profile in the co-occurrence of alcoholism and depression is not just the cumulative effect of the impairments displayed in patients with a single diagnosis but instead associated with a distinctive pattern of deficits. In such a scenario, DD individuals, although would manifest deficits displayed in patients with a single diagnosis, would also show non-shared impairments. To this purpose, we contrasted the results of the neuropsychological evaluation of a broad set of cognitive and executive functions (i.e., memory, attention, learning, cognitive flexibility), in individuals with a single AD or MDD diagnosis, and those with a co-occurring AD-MDD diagnosis.

Additionally, since there is substantial evidence that working memory and attention domains are altered in major depression and alcohol use disorders we recorded event-related potentials associated to relevant neural processes. Particularly, P200 and P300 evoked potential recordings were carried out to establish whether over-processing of irrelevant stimuli that has been documented in subjects with a single diagnosis of MDD or AD, could also be displayed in patients with comorbidity. Finally, during a Stroop task, we evaluated the N450 potential as an electrophysiological marker of deficits in cognitive conflict detection and executive control related to the negative affect (West et al., 2010).

On the other hand, it has been noticed a beneficial adjustment in the cognitive profile of MDD patients after pharmacological treatment with serotonin reuptake inhibitors. For instance, Levkovitz et al. (2002) registered improved memory performance in depressive patients treated with fluoxetine. Similarly, a positive bias in episodic memory measurements and, to a lesser extent, in working memory and mental processing speed was observed by Herrera-Guzmán et al. (2009) after 24 weeks of pharmacotherapy with escitalopram. To our knowledge, there are no similar reports concerning the AD-MDD co-occurrence. We, therefore, examined in these dual patients, if their altered cognitive performance could be modified after short-term treatment with fluoxetine.

2. Method

2.1. Sample

Sixty male outpatients who attended the Instituto Nacional de Psiquiatría in Mexico City participated voluntarily in this protocol. All participants were informed of the objectives and gave a written informed consent. Research and the Bioethics Committees granted approval for study. Procedures performed in the human participants were in accordance with the Code of Ethics of the World Medical Association (https://www.wma.net/policies-post/wma-international-code-of-medical-ethics/).

Following the psychiatric examination, 20 subjects met DSM-IV criteria for MDD and 40 for AD, from which half was also diagnosed with a concurrent major depressive episode (i.e. DD group). Two DD participants initially enrolled were subsequently excluded as they showed either, a concomitant cocaine substance abuse, or a coexisting additional psychiatric disorder additional. A medical disability, the clinical evidence of dementia, psychosis or neurological disease, or the antecedent or co-morbidity of a DSM-IV axis I disorder (other than anxiety disorder) was discarded in all subjects. The final clinical sample consisted of forty-eight subjects: 17 with DD; 14 MDD and 17 AD. Additionally, 17 male individuals without physical illness, psychiatric or neurological disorder and who were free of any current medication were evaluated as a reference group.

2.2. Procedure

All neuropsychological and electrophysiological evaluations were performed by a trained psychologist, in a sound-attenuated and temperature controlled room, in a single session that lasted approximately 120 min. Participants in this study did not receive monetary compensation, although an individualized report of their neuropsychological assessment performance was given if were requested.

2.3. Measurements

2.3.1. Assessment of severity of depression and alcohol dependence

The 21-item Hamilton Depression Scale (HAMD) (Hamilton, 1967), the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) and the Beck Depression Inventory (BDI) (Beck et al., 1961), were administered at baseline and fortnightly during the eight weeks of pharmacological treatment to assess the severity of depressive symptoms.
Alcohol dependence severity were estimated through the Spanish-translated version of the Alcohol Dependence Scale (ADS) (Solís et al., 2007). The Obsessive-Compulsive Drinking Scale (OCDS) was used as a proxy of alcohol craving (Anton and Moak, 1995).

As stated the DD and control populations, both completed all clinical assessments. Meanwhile, MDD patients completed all the mood and anxiety symptom assessments, but not the ADS. In this particular case the alcohol severity dependence measure was skipped from the clinical battery as a recommendation of the internal ethics committee, who considered it irrelevant and unnecessary to apply it to subjects that did not meet the criteria for AD.

2.3.2. Neuropsychological measurements

Memory: The Wechsler Memory Scale for logical, visual and verbal short-term memory (Wechsler, 1997b).

Attention: The Corsi Block-Tapping Test (forward) (Milner, 1971; Wechsler, 1997a), the Digit Span (forward) from the Wechsler Adult Intelligence Test (WAIS) (Wechsler, 1997a) and the Single Letter Cancellation Task (Diller et al., 1974).

Processing Speed: The Digit Symbol and Symbol Search subtests of the WAIS (Wechsler, 1997a)

Learning: California Verbal Learning Test (Delis et al., 2000).

Working memory: Digit Span backward subtest of the WAIS (Wechsler, 1997a) and Corsi Block-Tapping Test (backward) (Milner, 1971).

Executive function: Phonological Verbal Fluency (Artiola I Fortuny et al., 1999), Trail Making Test (Partington and Leiter, 1949) and the Wisconsin Card Sorting Test (Berg, 1948).

2.3.3. ERP paradigm

For eliciting P200 and P300 potentials, a visual dual-task paradigm of working memory was generated using the STIM2 software (Neuroscan Inc), as described in Hernández-Balderas et al. (2012). A typical trial began with the presentation of a matrix with three (low cognitive demand) or six (high cognitive demand) white points for 10 s; participants performed subsequently an oddball task, in which the arrows were displayed in a random order, asking them to respond to the infrequent arrow as quickly as they could by pressing a key selectively. A total of 360 stimuli were exhibited, 288 frequent and 72 infrequent. At the end of this secondary task, three examples of the matrix were displayed for recognition. All subjects had a training assay before performing the task.

To elicit the N450 wave, a modified Stroop task was applied. In this case, 82 congruent, 82 incongruent and 40 control stimuli were presented; (for further details on this experimental paradigm, see Coderre et al. (2011).

2.4. EEG recording and signal pre-processing

SCAN 4.3.1 software (Neuroscan Inc.) was used for the digital EEG with a bandwidth of 0.01–30 Hz, with a sampling rate of 500 Hz, using a NuAmps digital monopolar amplifier (Neuroscan Inc.).

The electrical activity was registered from 19 electrodes (10–20 International System) attached to an elastic cap (ElectroCap Inc.), using linked ear lobes as the reference and keeping the impedance below 5 kohm. Eye movements were recorded with two electrodes in the external and sub-orbital canthus of the left eye. Ocular activity was reduced from the EEG using the editing software of SCAN 4.3.1.

ERP’s were obtained off-line. EEG epochs of 1180 ms for working memory task and 1800 for Stroop task both were generated with a pre-stimulus interval of 100 ms, were detrended and baseline corrected. The average potentials were obtained separately with at least 25 epochs for both frequent/infrequent or congruent/incongruent stimulus. In adherence to the guidelines for using human event-related potentials to study cognition, we excluded from the analyses all EEG segments with ±50 μV artifacts in any electrode, with noise from visual inspection and those associated with incorrect responses (Duncan et al., 2009).

Mean voltage amplitudes were measured in all electrodes with respect to the highest peaks in CZ for P200 and N450, and PZ for P300 (Picton et al., 2000). Maximum peak latency was obtained from CZ, and PZ electrodes separately for all ERP’s using SCAN Edit software. P200 was defined as the largest positive wave with the 125–175 ms interval following the presentation of the arrow. P300 (p3b) was defined as the largest positive wave between 250 and 400 ms; N450 was defined as the larger negative wave between 300 and 550 ms post-stimulus. All latency measurements were taken from the peaks present in the ERP waveform. Peaks detection and mean amplitudes and latencies calculation were made by automatic procedures using the Scan 4.3 software (Neuroscan Inc). Correct responses and reaction times to frequent, infrequent, congruent, incongruent and control stimulus were recorded.

2.5. Post-pharmacological evaluations

Following the initial neuropsychological and electrophysiological evaluations, treatment with fluoxetine was initiated in those DD and MDD patients (20 mg per day for the first week, 30mg/day for the second week, and 40 mg per day from week 3 to onwards). Along these two months, no other clinical intervention was assayed. After the end of the 8 weeks of pharmacological trial, patients were re-evaluated with the same clinical and experimental paradigms.

2.6. Statistical analysis

All analyses were performed with SPSS, version 20. Statistical significance was set at p < 0.05. When required, the Bonferroni post-hoc test was applied. ANOVA was used for comparing the scores on the age, educational level, and clinical scales between groups. ANCOVA was used to compare neuropsychological scores between groups, using age as a covariate.

Latencies of the three components were examined using ANOVA. Repeated measures of analysis of variance (Greenhouse-Geisser correction) and posthoc comparison (least significant difference test) was used to analyze each component with the stimulus (frequent/infrequent; congruent/incongruent) anterior-posterior (Frontal, Central and Parietal derivations), lateral distribution (left, right and midline derivation) of the electrodes as within-subject factors and the group as the between-subject factor. MANOVA was applied to analyze the amplitudes of each potential after pharmacological treatment, using time variables. In all cases, statistical significance was set at p < 0.05.

3. Results

3.1. Demographics

Demographic and clinical data are shown in Table 1, Panel A. Scores for depression and alcohol dependence scales are given in Table 1, Panel B.

Subjects following were adults between the 20 and 55 years old, mostly with an education level of junior high or high school. Mean age was not equal among the four groups analyzed (F (3) = 3.15, p = 0.03); particularly, depressive individuals were younger than those with a diagnosis of AD (Bonferroni posthoc test: mean difference = 10.7, p = 0.04).

DD subjects and those with major depression showed similar scores for HAMD, MADRS, and BDI. It is worth noting that AD patients showed more depressive symptoms as evidenced by their scores in the BDI. Finally, the severity of alcohol dependence was similar in AD or DD patients, as assessed by the ADS (mean difference = 1.2, p = 0.98).

A significant reduction in depression and anxiety scores was detected in both medicated groups at the end of the pharmacological intervention (Table 2).
### Table 1. Demographic and clinical characteristics of the groups analyzed.

|                  | DD                  | MDD                 | AD                  | CT                  | F       |
|------------------|---------------------|---------------------|---------------------|---------------------|---------|
|                  | N = 17              | N = 14              | N = 17              | N = 17              |         |
| **Panel A**      |                     |                     |                     |                     |         |
| Age (years)      | 43 ± 12             | 33 ± 12             | 44 ± 10             | 37 ± 11             | 3.2*    |
| Years of education | 10 ± 2              | 12 ± 3              | 12 ± 3              | 12 ± 4              | 2.2     |
| Number of previous depressive episodes | 2 ± 2 | 2 ± 2 | 1 ± 1 | 0 | 5.8** |
| Age of the first depressive episode (years) | 31 ± 17 | 26 ± 13 | 26 ± 17 | NA | 0.4 |
| Age of onset of alcohol consumption (years) | 15 ± 2 | 17 ± 3 | 15 ± 5 | 17 ± 3 | 1.2 |
| Age of onset of alcohol dependence (years) | 25 ± 8 | NA | 26 ± 10 | NA | 0.04 |
| Number of abstinence periods | 5 ± 5 | NA | 7 ± 7 | NA | 0.9 |
| Consumption of alcohol per day in the last month (standard drinks) | 3 ± 8 | NA | 3 ± 8 | NA | 0.8 |
| **Panel B**      |                     |                     |                     |                     |         |
| ADS              | 23 ± 12             | NA                  | 22 ± 8              | 2 ± 4               | 20.7**  |
| HAMD             | 22 ± 5              | 25 ± 7              | NA                  | 3 ± 3               | 59.1**  |
| MADRS            | 26 ± 6              | 30 ± 11             | NA                  | 3 ± 2               | 44.5**  |
| BDI              | 31 ± 14             | 31 ± 7              | 17 ± 9              | 4 ± 4               | 29.5**  |
| HAS              | 15.3 ± 6            | 21 ± 7              | NA                  | 5 ± 4               | 29.3**  |

Data represent mean ± standard deviation.
DD: co-occurring diagnosis of alcohol dependence (AD) and Major depressive disorder (MDD); CT: Control subjects; ADS: Alcohol Dependence Scale; HAMD: Hamilton Depression Scale; MADRS: Montgomery-Asberg Depression Rating Scale; BDI: Beck Depression Inventory; HAS Hamilton Anxiety Scale; NA: not applicable. p < 0.05*; p < 0.01**.

### Table 2. Mean score of severity of depression (HAMD, MADRS, BDI), anxiety (HAMS) and obsessiosity and compulsivity related to craving and drinking behavior (OCDS), at baseline (W0) and after eight weeks (W8) treatment with the serotonin reuptake inhibitor, fluoxetine.

|                  | MDD W0 | DD W0 | MDD W8 | DD W8 | MANCOVA F | MDD DD |
|------------------|--------|-------|--------|-------|-----------|--------|
| HAMD             | 24 ± 7 | 22 ± 5 | 7 ± 8  | 17.2 ± 2** | 14.3 ± 2** |
| MADRS            | 28 ± 11 | 27 ± 7 | 8 ± 9  | 18.8 ± 4** | 18.3 ± 3** |
| BDI              | 31 ± 6 | 32 ± 15 | 11 ± 14 | 18.5 ± 5** | 20 ± 4** |
| HAS              | 20 ± 7 | 15 ± 7 | 5 ± 5  | 13 ± 2** | 10 ± 2** |
| OCDS             | 22 ± 15 | 6 ± 7  | 16 ± 14** |

Data represent mean ± standard deviation.
DD: co-occurring diagnosis of alcohol dependence and Major depressive disorder (MDD).
MANCOVA (year as covariable).
HAMD: Hamilton Depression Scale; MADRS: Montgomery-Asberg Depression Rating Scale; BDI: Beck Depression Inventory; HAMS: Hamilton Anxiety Scale; OCDS Obsessive Compulsive Drinking Scale. MDD (Major Depressive Disorder, N = 10); DD (co-occurring diagnosis of alcohol dependence and MDD, N = 15).
*p < 0.05; **p < 0.01.

#### 3.2. Neuropsychological results

Table 3 shows the data summary of ANCOVA analysis for the neuropsychological assessment at baseline.

In comparison to healthy subjects, patients with alcoholism (regardless of co-occurrence of the mood disorder) showed a meager execution on the logic, verbal, visual tasks of the Wechsler Memory Scale. Also, their processing speed was slower, and they slipped up more frequently at trying to identify the cue letters in Diller’s Single Letter Cancellation Test (LCT). Moreover, they performed poorly on tasks associated with the California Verbal learning test. Finally, they were less competent at remembering the backward recall task of Corsi’s block-tapping test, a deficit that was also seen in depressive patients. Interestingly, as compared with alcoholics without comorbidity, DD patients showed the poorest performance in most of the memory Wechsler tests, made fewer hits and more errors in the Digits Symbols task, and missed more cue letters in the LCT.

Furthermore, they took more time in planning tasks, scored the lowest in the cognitive flexibility (Visual attention/switching) task (Trail Making Test B), and showed less verbal fluency. Most remarkably, they committed a higher number of incorrect responses, perseverative errors, and had more failures to maintain the set in the WCST.

#### 3.3. Effect of pharmacological treatment on neuropsychological profile

Table 4 summarizes the neuropsychological assessment results after 8-weeks of fluoxetine. Both MDD and DD groups showed a significant amelioration of the performance of the different tests included in the memory domain. Interestingly, only the comorbidity group displayed an improvement in the executive functions of learning and cognitive flexibility.

#### 3.4. Event-related potentials at baseline

**P200:** A stimulus* anterior-posterior* diagnosis interaction was found (F(3) = 3.70, p = 0.009), among the comparison groups. The post-hoc analysis showed a statistically significant increment in P200 amplitude elicited by the non-target stimulus during the high-demanding cognitive task, along the central and parietal zones, for those with a diagnosis of MDD as compared with the control group: central (C3, C2 derivation) and parietal zone (P3, PZ, P4 derivation). Amplitude values are shown in Table 5a.

**P300:** At low cognitive demand task, a significant effect in stimulus* diagnosis interaction was found (F(3) = 3.01, p = 0.036), which was attributed to a decrement in amplitude in parietal and frontal zone in AD, DD and MDD patients as compared with the control group (Table 5b) (Amplitudes for all components are shown in Supplementary table). Additionally, a significant difference in latency between DD (512 ± 54 ms) and control (457 ± 41 ms) groups in CZ derivation was found (mean difference: 55.4, p = 0.04).

**N450:** No significant main or interaction effects were found for any of the comparisons.
### 3.5. Behavioral results

The reaction time (RT in milliseconds) to the infrequent stimulus in the low cognitive demand task was different among the groups evaluated: CT: 467 ± 90, MDD: 479 ± 55, AD: 510 ± 101; (F(3) = 3.02, p = 0.03). Particularly, DD patients showed significantly longer RTs than control subjects for congruent, incongruent, and control stimuli (Table 6, Panel A). Furthermore, all but the DD group displayed the anticipated Stroop effect (Table 6, Panel B).

### 3.6. ERPs after 8 weeks of pharmacological treatment

**P200.** (Low cognitive demand task): Main effects for the time (F(N = 1) 5.37; p = 0.03), time*anterior posterior (F(N = 1) 17.6; p<0.01), and time*anterior posterior*lateral (F(N = 1) 3.2; p = 0.045) interactions were observed. The post-hoc analysis showed a decrease in amplitude (mean difference: -2.3 p = 0.02) and earlier latency (F(N = 1) 28, p<0.01) in the CZ derivation for frequent stimulus in patients with the concurrent AD-MDD diagnoses.

**P300.** (Low cognitive demand): A main effect was observed for time (F(N = 1) 6.61; p<0.01) and time*anteriorposterior*dagnosis (F(N = 1) 0.83; p = 0.05). The post-hoc analysis showed reduced amplitudes of central and parietal zones in MDD patients after pharmacological treatment (Table 7).

**N450.** A significant difference for time*stimulus*lateral*dagnosis interaction was found (F(N = 1) 3.37, p = 0.05); however, it did not reach statistical significance after the post-hoc analysis.

### Figures A and B show the P200 and P300 potentials elicited during the visual dual-task paradigm of working memory, while Figure C shows the topographic distribution of P300 at mild and high difficulty levels of dual-task.

### Table 3. Comparison of mean scores for the different neuropsychological tests/tasks assessed among comparison groups.

|                        | DD (n = 17) | MDD (n = 14) | AD (n = 17) | CT (n = 17) | ANCOVA F( p)  | Post-hoc       |
|------------------------|------------|--------------|------------|-------------|---------------|----------------|
| **Memory**             |            |              |            |             |               |                |
| Logic memory I         | 7 (2.5)    | 9.1 (4)      | 8.1 (1.8)  | 10 (2)      | 4.1**         | DD < MDD**     |
| Logic memory II        | 5.3 (2.1)  | 8 (2.1)      | 6.5 (2.4)  | 9 (2.4)     | 7.2**         | DD < MDD*, CT**; AD < CT* |
| Verbal memory I        | 6.2 (1.5)  | 6.5 (2.1)    | 5.3 (1.6)  | 7.7 (1.6)   | 4.3**         | AD < CT**      |
| Verbal memory II       | 7.5 (0.3)  | 8.5 (0.3)    | 8.5 (0.3)  | 9.5 (0.3)   | 4.6**         | DD < CT**      |
| Verbal memory total    | 22.8 (4)   | 25 (3.1)     | 22 (3)     | 26.3 (3.2)  | 3.9**         | AD < CT**      |
| Visual memory I        | 1.5 (1)    | 2.4 (1.8)    | 1.2 (1.4)  | 3 (1.7)     | 3.1*          | AD < CT*       |
| Visual memory II       | 2.5 (1.6)  | 3.7 (1.9)    | 2.9 (1.2)  | 4.6 (1.4)   | 4.3**         | DD < CT**; AD < CT* |
| Visual memory III      | 3.3 (2)    | 4.6 (2)      | 3 (1.6)    | 5.1 (1.6)   | 3.3*          | DD < CT*; AD < CT** |
| Visual memory total    | 7.5 (3.8)  | 10.7 (4.9)   | 7 (2.4)    | 12.7 (3.6)  | 6.3**         | DD, AD < CT**  |
| **Attention**          |            |              |            |             |               |                |
| TGL hits               | 84 (1.6)   | 85 (0.6)     | 84 (1.2)   | 85 (0.7)    | 4.2**         | DD, AD < CT**  |
| TGL misses             | 1.8 (1.5)  | 0.5 (0.6)    | 1 (0.7)    | 0           | 9.3**         | DD > CT**, MDD**; AD < CT* |
| **Speed processing**   |            |              |            |             |               |                |
| Digits hits            | 48 (10)    | 63 (14)      | 57 (13)    | 63 (15)     | 3.3*          | DD < CT**, MDD** |
| Digits errors          | 0.4 (0.8)  | 0            | 0.1 (0.5)  | 0           | 3.7**         | DD > CT**, MDD**; AD** |
| **Learning**           |            |              |            |             |               |                |
| Essay 2                | 7.5 (1.8)  | 10.7 (1.6)   | 8.1 (3.1)  | 10.7 (1.7)  | 5.5**         | DD < MDD*CT**; AD < CT* |
| Recognition essay      | 40.6 (0.5) | 41 (0.5)     | 40.1 (0.5) | 42.2 (0.5)  | 2.6*          | AD < CT*       |
| **Working memory**     |            |              |            |             |               |                |
| Corsi Cubes sequences  | 6.7 (1.7)  | 6.4 (1.4)    | 5.9 (0.9)  | 8.3 (2.6)   | 5.3**         | AD, MDD < CT*  |
| **Executive function** |            |              |            |             |               |                |
| TMT B (seconds)        | 126 (48)   | 77 (17)      | 115 (52)   | 78 (25)     | 4**           | DD > CT*MDD*   |
| Verbal fluency         | 14 (3)     | 15 (4)       | 15 (4)     | 17 (3)      | 2.7**         | DD < CT*       |
| WCST essay             | 128 (0)    | 111 (23)     | 110 (19)   | 103 (22)    | 4**           | DD > CT**AD*   |
| WCST errors            | 56 (18)    | 43 (27)      | 39 (3)     | 33 (20)     | 2.9*          | DD > CT*       |
| WCST perseverative answers | 37 (16)   | 25 (16)      | 22 (15)    | 20 (13)     | 4*            | DD > CT*, AD*  |
| WCST perseverative errors | 33 (14)   | 23 (14)      | 20 (13)    | 18 (11)     | 4**           | DD > CT**AD*   |
| Categories generated   | 3.2 (2)    | 4.2 (2)      | 4.2 (2)    | 5.7 (0.5)   | 4.4**         | DD > CT**      |
| Failures to maintain the set | 1.5 (1) | 0.25 (0.4)   | 0.67 (0.6) | 0.71 (0.7)  | 6.2**         | DD > CT*, MDD**; AD** |

Data represent mean score (standard deviation).

DD: co-occurring diagnosis of alcohol dependence (AD) and Major depressive disorder (MDD) patients; CT: Control subjects.

Post-hoc comparisons using Bonferroni ANCOVA adjusted by age; *p < 0.05; **p < 0.01.

LCT: Letter Cancellation Test, TMT: Trail Making Test, WCST: Wisconsin Card Sorting Test.

a Number of items that were identified as being correctly recalled.

b Number of sequences that were identified as correctly reproduced.

c Number of accurately recognized words.

d Number of words beginning with a specific consonant, generated in a minute.
Table 4. Neuropsychological test scores at baseline (W0) and after eight weeks (W8) treatment with the serotonin reuptake inhibitor, fluoxetine.

|                | MDD     | W0     |   | DD     | W8     | MANCOVA F |
|----------------|---------|--------|---|---------|--------|-----------|
|                |         |        |   |         |        | MDD       |
|                |         |        |   |         |        | DD        |
|                |         |        |   |         |        |           |
| **Memory**     |         |        |   |         |        |           |
| Logic Memory I | 8.4 (4.4)| 12.1 (3.7)|   | 6.7 (2.4)| 8.4 (2.8)| 3.6**     |
| Logic Memory II| 7.6 (3.8)| 10.8 (3.3)|   | 5.1 (2.1)| 7.2 (2.6)| 3.1**     |
| Verbal Memory I| 6.1 (2.2)| 7.1 (0.9)|   | 6.2 (1.6)| 6.9 (1.2)| 1.4*      |
| Verbal Memory II| 8.6 (1.7)| 9.2 (0.7)|   | 7.4 (1.8)| 8.1 (1.3)| 0.7       |
| Verbal Memory III| 10.2 (3.2)| 9.7 (0.4)|   | 8.8 (1.4)| 9.5 (0.9)| 0.3       |
| Visual Memory I | 24 (4.4)| 26 (1.5)|   | 22.6 (4.1)| 25.6 (3)| 2.9**     |
| Visual Memory II| 2.2 (1.5)| 3.7 (2.1)|   | 1.7 (2.1)| 2.7 (1.6)| 1.0       |
| Visual Memory III| 3.3 (2)| 4.9 (1.3)|   | 2.2 (1.4)| 3 (1.7)| 1.5*      |
| Verbal Memory total | 9.5 (4.9)| 13.7 (4.4)|   | 6.9 (3.7)| 9.4 (5)| 3.6**     |
| **Learning**   |         |        |   |         |        |           |
| Essay I        | 6.3 (2)| 8.1 (3)|   | 6.3 (2)| 8.7 (2)| 2.5**     |
| Essay 2        | 10.4 (1.7)| 11.3 (2.7)|   | 8.4 (2.9)| 11.2 (2.3)| 1.2       |
| Essay 3        | 11.9 (2.2)| 12.8 (1.9)|   | 10.4 (3.3)| 12.5 (2.5)| 1.0       |
| Essay 4        | 12.9 (1.9)| 12.6 (2.8)|   | 11.9 (3.1)| 13 (2.6)| 0.6       |
| STR            | 12.8 (2)| 13.8 (1.9)|   | 12 (2.2)| 13.4 (2.5)| 0.8       |
| STRc           | 13 (2)| 14.5 (1.7)|   | 12.5 (2.2)| 14 (2.4)| 0.6       |
| LTRc           | 13.8 (1.7)| 14.5 (1.6)|   | 12.2 (2.8)| 13.8 (2.3)| 0.9       |
| **Executive Function** | | | | | | |
| TMT A (seconds) | 47 (14)| 38 (13)|   | 58 (15)| 47 (18)| 7.1       |
| Verbal fluency | 14.5 (3.8)| 17 (4)|   | 14 (2.5)| 16 (3)| 1.7       |
| WCST trails    | 110 (24)| 102 (25)|   | 123 (12.4)| 115 (23)| 4.3       |
| WCST errors    | 45 (28)| 32 (29)|   | 57 (22)| 50 (26)| 6.6       |
| WCST perseverative | 27 (18)| 17 (13)|   | 44 (27)| 32 (20)| 9.5       |
| WCST perseverative errors | 24 (15)| 15 (11)|   | 38 (20)| 30 (17)| 7.0       |
| Categories generated | 4 (2)| 4 (3)|   | 3 (2)| 4 (2)| 0.01      |
| Failures to maintain the set | 1.1 (1.7)| 1.3 (1.3)|   | 1.6 (0.9)| 1 (1.3)| 0.28      |

Data represent mean (standard deviation).
DD: co-occurring diagnosis of alcohol dependence (AD) and Major depressive disorder (MDD) patients.
MANCOVA (year as covariable) F, df = 1; *p ≤ 0.05; **p ≤ 0.01, post-hoc comparisons using Bonferroni.
STR: short-term retrieval; STRc: short-term retrieval with retrieval cues; LTRc: long-term retrieval with retrieval cues. TMT A: Trail Making Test, version A; WCST: Wisconsin Card Sorting Test.

Table 5. Comparison of mean scores for P200 and p300 amplitude among clinical and control groups.

|                | A P200 non-target stimulus amplitude | MD Posthoc |
|----------------|--------------------------------------|-----------|
|                | Mean (standard deviation)             |           |
|                | CT MDD AD DD                          |           |
|                | C3 −0.40 (2.44) 1.8 (2.5) 0.99 (2.1) 1.2 (1.7) 2.28 p = .009 TDM-CT |
|                | Cz 0.34 (1.91) 2.9 (3.3) 2.28 (2.4) 1.7 (2.02) 2.57 p = .009 TDM-CT |
|                | C4 −0.06 (1.8) 2.08 (3.1) 1.4 (2.12) .92 (1.5) 2.15 p = .01 TDM-CT |
|                | F3 −2.1 (3.2) 0.77 (1.9) −2.3 (3) −0.37 (3.5) 3.15 p = .02 TDM-AD |
|                | Pr −0.53 (2.4) 2.2 (2.7) −0.24 (3.3) 1.16 (3.2) 2.79 p = .01 TDM-CT |
|                | P4 −1.7 (2.6) 1.01 (2.2) 0.7 (7.4) .06 (3.1) 2.78 p = .04 TDM-CT |
|                | B P300: At low cognitive demand task |           |
|                | Mean (standard deviation)             |           |
|                | CT MDD AD DD                          |           |
|                | F3 5.33 (5.80) 3.40 (3.69) 3.22 (2.64) 2.54 (2.64) 2.78 p = .07 CT-DD |
|                | F3 7.56 (4.55) 4.79 (4.40) 5.03 (3.48) 5.02 (3.99) 2.76 p = .09 CT-DD |
|                | Pr 10.05 (5.46) 7.70 (4.90) 5.93 (4.27) 6.99 (3.96) 4.12 p = .06 CT-AD |
|                | P4 6.88 (4.91) 4.62 (2.69) 5.27 (2.58) 4.79 (3.97) 3.05 p = .08 CT-DD |
Electrophysiological recordings raw data can be consulted at https://osf.io/gzu3f/

4. Discussion

In this study, we examined the hypothesis that the cognitive impairment displayed in DD patients could be not only the manifestation of the summed negative contributions of each disorder. As expected, the neuropsychological assessment revealed a broad set of impairments across the different cognitive domains examined. Notwithstanding, these shortcomings were unevenly distributed among the clinical groups; for example, the group of MDD affected subjects exhibited discrete cognitive failures in attention and executive functions, akin to that described in individuals with mild cognitive impairment (Zihl et al., 2010; Lee et al., 2015). On the other hand, the deficits identified in the groups with a diagnosis of alcohol dependence were more noticeable, covering a broader spectrum of impairments (i.e., memory, attention, processing speed, executive functions). Heavy alcohol use has been linked to visuospatial deficits and deterioration in fluid cognitive abilities (such as concept formation, abstraction, and problem solving) (Bates et al., 2002). Given the cross-sectional case-control strategy employed in our experimental design, it is uncertain whether the identified impairments are linked to premorbid risk traits or alcohol-induced neurobiological changes (Vaidyanathan et al., 2015).

Remarkably, patients with the AD-MDD co-occurrence were those with deficits more severe. Moreover, certain executive function tasks (as assessed by the WCST), were altered only in this comorbid group; among them, we identified the slowing in their processing speed, distorted cognitive flexibility, and the failure to maintain the set. Additionally, the Stroop effect was absent in these patients, a feature which might be reflecting a compromised inhibitory control (Noel et al., 2012).

This discrepancy cannot be credited to differences in the age of onset of alcohol consumption, the onset of dependence, the number of periods of abstinence, or daily use of alcohol since patients with the affective comorbidity also displayed similar attributes. Other variables, such as the pattern of consumption or maximum alcohol consumed per occasion, might partially explain these differences. In any case, all these taint features would influence negatively the proper behavioral tuning in response to environmental feedback. Moreover, it might be linked to the frequent relapses, disruptive behavior, poor pharmacological...
commitment, or high prevalence of suicide reported in these dual patients (Drake and Wallach, 2000).

Of noting, the impairments above mentioned are primarily associated with the activity of the dorsolateral prefrontal cortex (Ardila, 2008). Hence, further examination of other “cold” executive functions associated with this brain area, such as problem-solving, concept development, and commitment, or high prevalence of suicide reported in these dual patients (Drake and Wallach, 2000).

4.1. Electrophysiological outcomes

4.1.1. P200 and P300 ERPs

To explore putative neurophysiological mechanisms underlying the identified neuropsychological deficits, we recorded three ERPs associated with sequential stages of information processing during the execution of behavioral tasks.

First of all, we evaluated the early sensory evoked potential P200 as a proxy of attention modulation of non-target stimuli and stimulus classification (Novak et al., 1992). Notwithstanding that its functional significance is only partially understood in comparison to other ERPs, current evidence suggests that this evoked potential belongs to a sensory gating system at the early stages of filtering and processing of stimuli that allow their proper discrimination, facilitating the allocation of attention (Crowley and Colrain, 2004; Liijffijt et al., 2009).

We anticipate recording changes in the P200 amplitude and or latency parameters associated with an affective disorder based on previous reports describing that relative to non affected controls, subjects with major depression expressed, during a classic two-tone auditory oddball task, a heightened P200 amplitude (Vandoolaeghe et al., 1998) or a longer latency (Patterson et al., 2016). Similarly, an exaggerated P200 amplitude to both target (signal) and non-target (noise) tone stimuli was also reported in affected MDD subjects (Kemp et al., 2009).

Interestingly enough, notwithstanding the severity of depression was equivalent between DD and MDD patients, only in the latter was overtly evident an increase in the P200 amplitude elicited by the non-target stimulus during the high-demanding cognitive task.

On the other hand, published reports on alcohol use disorders and P200 are scarce, being more frequent identify studies oriented to examine the acute effects of alcohol. For example, Hari et al. (1999) reported a discrete reduction in the amplitude of P200 at low doses of alcohol (although authors debated whether this probably represented the effect of the drug on an even earlier wave, the N120). On the contrary, Sklar and Nixon (2014) did not find evidence that low to moderate doses of alcohol altered P200, although ethanol significantly decreased earlier P50 and N100 gating potentials relative to placebo. Similarly to Maes et al. (2001), we do not identified any visible alteration in this particular event-related potential in abstinent alcohol-dependent patients.

On the other hand, P300 was analyzed as an index of the neural system at the early stages of system updating and evidence that low to moderate doses of alcohol altered P200, although ethanol significantly decreased earlier P50 and N100 gating potentials relative to placebo. Similarly to Bruder et al. (2009), notwithstanding many studies report reduced P300 amplitudes associated with depression, this effect is not unanimously observed, with some investigations reporting no difference (Himani et al., 1999; Vandoolaeghe et al., 1998) or even an increased P3 amplitude in response to specific high-demand cognitive tasks (Nandrino et al., 2004; Krompinger and Simons, 2011). Interestingly, in Nadrino’s report, the exaggerated amplitude was coupled with slower and more variable response times, suggesting the activation of a behavioral compensatory adjust to increase the signal to noise ratio.
We detected a statistically significant decrement in the P300 amplitude in PZ derivation in AD patients compared with the control group. However, notwithstanding having a similar alcohol dependence severity, the expected amplitude P300 reduction was not as overtly apparent in those patients with concurrent depression. Fein and Cardenas (2017) reported that, in contrast to the lower P3b amplitudes seen in long term abstinent alcoholics (LTAAs) without a current MDD (either with no lifetime MDD or a lifetime, but not current MDD), in those LTAAs with a current MDD its amplitudes did not differ from controls.

Moreover, we distinguish that those with the co-occurrence AD-MDD expressed a prolonged P3b latency, a flaw also noted previously by Maes et al. (2001) in recently detoxified alcohol-dependent patients. This observation, in connection with its more delayed reaction times in response to the target stimulus, suggests a critical affectation in the association cortex of the allocation of attentional resources required for updating context in the process of working memory and decision-making, which is especially noticeable during a task requiring an intense cognitive demand. In contrast, MDD patients appeared to retain the ability to recruit a sufficient amount of cognitive resources needed to achieve an adequate behavioral response. A recurrent finding in heavy alcohol users and depressive subjects is their impaired performance of cognitive control processes, such as interference and inhibitory control and conflict monitoring, requiring adaptive behavioral adjustments (Jakubczyk et al., 2012; Vanderhasselt and De Raedt, 2009; West et al., 2010). We noted a generalized slowdown in the response time to the different stimuli (i.e., congruent, incongruent, control) in those patients with alcohol use problems, a behavioral impairment notably aggravated in those with the dual AD-MDD diagnosis. Furthermore, the diminished ability to inhibit pre-potent responses during a standard Stroop task or in other cognitive abilities trials, which has been extensively documented in alcohol-dependent subjects (Curtin and Fairchild 2003; Noel et al., 2012) as well as in depressive individuals (Holmes and Pizzagalli, 2008; Krompinger and Simons, 2011), was unexpectedly absent in DD patients.

To evaluate the cognitive information processes in our patients, the ERP’s brain activity during a standard Stroop task was recorded. We focused specifically on the negative deflection around 450 ms since there is substantial evidence that this component covaries when the response conflict has been detected, requiring cognitive control (i.e., conflict monitoring). (Chen et al., 2011).

Reductions of this frontal component and other elements of the ERP (e.g., NSW negative slow wave), allegedly indexing evaluative and regulative cognitive control processes, have been described after an intoxicating alcohol dose (Curtin and Fairchild, 2003). Similarly, a reduction in the N450 amplitude in response to incongruent stimuli in depressive subjects was described by Holmes and Pizzagalli (2008). Of noting, Vanderhasselt and De Raedt (2009) reported that the N450 conflict-related modulation in response to a modified Stroop task detected in healthy subjects was significantly reduced in remitted depressed patients, particularly in those highly recurrent episodes. Interestingly, they noticed a positive association between the number of previous depressive episodes with the exacerbation of the above-cited impairment, suggesting that each depressive episode generates a progressive reduction of the process of cognitive control or interfere gradually in the ability to use effortful strategies.

Notwithstanding the cited above, we did not detect significant alterations in the amplitude or latency of the N450 wave among the different clinical groups analyzed. Differences between experimental procedures like the Stroop version used or the percentage of presented stimuli would somewhat explain our discrepancy with the above-cited studies. Moreover, the temporal window used in our analysis of the N450 wave could have limited our capacity to identify relevant changes. In this regard, it is worth noting that some authors differentiate two Stroop task components related to cognitive control: a first one between 300 and 500 ms, most probably related to conflict monitoring (Chen et al., 2011; Holmes and Pizzagalli, 2008) and a second factor, between 600 – 1000 ms, defined as a slow conflict potential (SP), involving the selection of response or resolution of the conflict. Future studies should extend the temporal window of analysis to evaluate the late stage of processing.

4.2. Effects of pharmacological treatment

As presumed, MDD patients improved their depressive symptoms (assessed by three different scales) after the short-term fluoxetine treatment. Interestingly, those in the co-occurrence of depression and alcohol dependence also showed a similar amelioration after the SSRI treatment. The effectiveness of antidepressants for treating people with co-occurring depression and alcohol dependence is currently under evaluation (reviewed in Pettinati, 2014; Agabio et al., 2018). The effect of the anti-depressive drug ran in parallel with a favorable adjustment in their short-term memory performance. While a beneficial cognitive outcome in depressive patients was previously informed (Herrera-Guzman et al., 2009, 2010), it had not been reported to our knowledge for the AD-MDD co-occurrence. Moreover, the increased scores in learning and cognitive flexibility tests displayed by these affected subjects at the end of the fluoxetine treatment are worth noting.

In contrast, we could not detect in MDD patients an improvement in their attention and working memory as reported by others (Cassano et al., 2002; Jaeger et al., 2006). The electrophysiological data also revealed a differential response pattern to pharmacological treatment, with those with a comorbid alcohol disorder exhibiting a P200 diminished amplitude and an earlier latency. An enlargement in the amplitude at this early evoked-potential in non-responders to antidepressant therapy relative to healthy subjects and responders was reported by Vandooolaege et al. (1998). Furthermore, while a decrease along all scalp derivations in the P300 amplitude was detected in fluoxetine-treated MDD subjects, this effect was restricted to a single area in DD patients. Trejo et al. (2007) conjectured that an increase in the amplitude of P300 could be associated with cognitive fatigue in healthy subjects. Therefore, in our study, the generalized decrease in amplitude in depressive subjects after pharmacological treatment in conjunction with a better performance in the visual working memory might indicate cognitive improvement.

Therefore, these different electrophysiological outcomes may represent distinct strategies to recruit the neurocognitive resources required to properly execute a task. Hence, whereas in patients with a single diagnosis of depression, the pharmacological treatment could impinge upon late electrophysiological stages associated with selective attention processes and context updating; in dual diagnosis population, the adjustment might be oriented to modify early attention processes and discrimination and categorization of stimuli.

Another intriguing observation in dual patients was the noticeable decrease of their craving scores as assessed by the OCDs after fluoxetine treatment (Table 2) and the inverse correlation with the cognitive flexibility test. As Tiffany and Conklin (2000) suggest, high-order cognitive functions may modulate craving intensity in patients with chronic consumption histories. Therefore, it might be that adjusting their cognitive setup facilitates a more appropriate behavioral response to environmental demands through better regulation strategies and the generation of alternative plans for consumption. Importantly, cognitive flexibility might be a better predictor of change in the pattern of substance consumption compared to other functions such as verbal fluency, inhibition of stimulii, or attentional set change (Hunt et al., 2015).

It is necessary to acknowledge that this work is not without shortcomings. Mainly, the limited number of MDD and DA patients evaluated could have potential masked differences in comparing their cognitive performance profiles. Moreover, since only male outpatients were examined, data should not be extrapolated to females, more severe cases, or those DD patients whose initial diagnosis was depression. Economic constraints restricted the inclusion of larger samples and a more extended pharmacological
follow-up. Ethical issues also impeded the inclusion of a placebo group. In addition, although anxiety levels were not significant between the clinical groups, we do not exclude the possibility that this symptomatology may be an uncontrolled variable in the analyses. Finally, our experimental design does not allow us to determine whether cognitive alterations were a consequence of the co-morbid state or whether these features might have preceded their clinical manifestation.

In summary, the results of the neuropsychological evaluation and electrophysiological recordings do not support the notion that AD and MDD in comorbidity are merely the consequence of the sum of the negative contributions of the single clinical entities. More important, these findings could have encouraging clinical implications for alcohol disorders treatment, where a therapeutic intervention should consider the presence or absence of affective comorbidity. One can envision, for example, that an adequate neurocognitive adjustment might impinge on beneficial learning responses, promoting a better pharmacological adherence and psychotherapy attachment. All this, in consequence, would help to restore social structures and the acquisition of skills for the maintenance of abstinence, stability, and self-control in consumption. In any case, these cognitive changes open a field of research with promising scopes in the clinical treatment area of patients with the dual AD-MDD diagnosis.

Declarations

Author contribution statement

Yvonne Flores-Medina: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Yaneth Rodríguez-Agudelo, Jorge Bernal-Hernández: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Carlos S. Cruz-Fuentes: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Data availability statement

Data associated with this study has been deposited at Open Science Framework https://osf.io/gzu3f/

Declaration of interest’s statement

The authors declare no conflict of interest.

Additional information

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