

Gender Differences in Affects and Craving in Alcohol-Dependence: A Study During Alcohol Detoxification

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Background: Alcohol craving is a major cause of relapse in alcohol-dependent (AD) patients. It is closely related to the high depression and anxiety symptoms that are frequently observed at the early stages of abstinence, and these comorbid symptoms might thus constitute a relapse factor when they persist after detoxification. As these negative affects are known to evolve during the detoxification process, the aim of this study was to investigate the course of the relation between affects and craving during detoxification, with a particular attention given to gender in light of the known differences in affects between AD men and women.

Methods: AD patients ($n = 256$) undergoing a detoxification program were evaluated for positive (PA) and negative affectivity (NA), depression and anxiety symptoms, and craving, twice within a 3-week interval (on the first [T1] and the eighteenth day [T2] of abstinence).

Results: Detoxification course was associated with improvements regarding NA, depression and anxiety symptoms, and craving. Moreover, these negative affects were related to craving intensity. However, for men, the relation was only present at the beginning of detoxification, while, for women, it persisted at the end of detoxification as did high levels of depression. Furthermore, only with women was the level of craving at T2 proportional to negative affects reported at T1, and depression symptoms experienced at T1 were reliable predictors of craving at T2.

Conclusions: Given the importance of craving in relapse, special care should be given to improve depressive symptoms in AD women to promote long-term abstinence. Also, the remaining portion of AD women who still exhibit substantial symptoms of anxiety and depression at the end of detoxification could benefit from an integrated treatment simultaneously tackling mood and alcohol-dependence disorders.

Key Words: Alcohol Dependence, Craving, Affects, Detoxification, Gender.

THE VERY HIGH rate of alcohol consumption relapse following detoxification represents a major clinical problem in alcohol-dependence treatment (Brandon et al.,

2007). Craving, the persistent urge or desire to use a substance, has been reintroduced as a criterion of the DSM-5 (American Psychiatric Association, 2013) definition of alcohol use disorder, underlining its crucial role in treatment dropout and relapse (e.g., Mo and Deane, 2016). The description of the determinants of craving and the ways to deal with them therefore represent key targets in alcohol-dependence research and might constitute an innovative lever to reduce relapse rates. Craving is a complex construct that has been explored extensively in the addiction field, leading to several theoretical models. The most influential ones have placed negative affects at the center of the addiction motivational process (Baker et al., 2004; Koob and Le Moal, 2001; Stasiewicz and Maisto, 1993; Verheul et al., 1999), as chronic drug users progressively learn that substance use can help (temporarily) with getting rid of negative emotional states. Craving will then occur when the addict is caught up with negative emotions while not being able to use the substance. The idea that craving is closely linked to attempts at dealing with negative affects has gained considerable empirical support from clinical, laboratory, and ecological momentary assessment studies (e.g., Cleveland and Harris, 2010; Cordovil de Sousa Uva et al., 2010a,b; Gordon et al., 2006; Oslin et al., 2009; Tiffany, 2010; de Timary et al., 2013).

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Alcohol detoxification constitutes a crucial initial step in the treatment of alcohol-dependent (AD) patients, and it is accompanied by major changes in emotional and motivational dimensions. The level of craving decreases between the beginning and the end of detoxification treatment (Andersohn and Kiefer, 2004; Cordovil de Sousa Uva et al., 2010a, b; de Timary et al., 2008, 2013), and these changes occur in parallel to substantial declines in negative affects, depressive, and anxious symptoms (Andersohn and Kiefer, 2004; Cordovil de Sousa Uva et al., 2010a,b). Studying the progression of negative affects and craving, and their relation during the transition period of detoxification, is therefore of major interest.

In this regard, the study of gender-related particularities may constitute a promising and interesting area of research. There is strong evidence for gender differences in the epidemiology, etiopathology, and progression of alcohol use disorders (Wilsnack and Wilsnack, 2013). Addicted men and women differ in their clinical picture, with women exhibiting higher depression and anxiety symptoms rates than men (e.g., Conway et al., 2006). These comorbidities often play an important role in craving and relapse in women, while in men, drinking is more often due to social pressure (e.g., Boykoff et al., 2010; Chaplin et al., 2008; Luminet et al., 2016; for a review, see Erol and Karpyak, 2015). While men and women appear to differ in terms of emotional and motivational aspects related to alcohol use, the development of these differences in the course of AD, and especially during the first steps of abstinence, has however been explored very little to date. Yet, understanding the factors underlying craving and the different trajectories they may follow in men and women is crucial for effective alcohol use disorder prevention programs, diagnosis, and therapies, as well as related issues specific to both genders.

In summary, in light of (i) the role played by craving in relapse among AD individuals, (ii) the role of negative affects in craving, (iii) the turning point state of detoxification in regard to both emotional and motivational dimensions, and (iv) the difference between AD men and women in terms of comorbidity patterns, there is a need for further investigation of the course of craving and affects during detoxification, particularly as far as their gender-based modulations are concerned.

The first aim of this study was hence to evaluate how positive (PA) and negative affectivity (NA), depression symptoms, and anxiety symptoms are related to craving and how this relation evolves in both transversal and longitudinal ways during a detoxification program in AD patients. A second goal was to explore whether gender differences could be seen in regard to these links. To address these aims, AD patients were evaluated twice, at the beginning and at the end of the detoxification program (i.e., within a 3-week interval) in terms of emotional dimensions and craving. We first hypothesize that AD patients would exhibit positive associations between craving and affects at both of the evaluation times. Second, we hypothesized that

the reported intensity on emotional scales on the first day of abstinence would be positively associated with subjective craving at the end of the detoxification. Last, we expected that these relationships would be stronger for women than men.

MATERIALS AND METHODS

Participants

The total sample comprised 256 AD patients. They were selected by a psychiatric interview according to DSM-IV criteria (American Psychiatric Association, 1994), and they were recruited to participate in the study either at the alcohol departments of the Clinique Universitaire Saint-Luc or the Clinique Europe Saint-Michel or the Clinique La Ramée, Brussels, Belgium, at the start of their 3-week detoxification program. Exclusion criteria were the existence of other Axis I DSM-IV diagnoses of major cognitive impairments (i.e., a score of ≤ 10 on the MMSE; Folstein et al., 1975), or of current consumption of drugs other than alcohol or nicotine. Only patients who had consumed alcohol on the day of their admission or on the previous day were included in the study. The patients received benzodiazepine medication (diazepam: 40 to 60 mg per day) at treatment onset, and it was progressively reduced during detoxification. As data were collected across different studies, which focused on various cognitive and affective measures, the number of participants varied for the different questionnaires and also for some demographic and clinical variables. Also, for a subset of patients, the severity of withdrawal symptoms was rigorously assessed by nurses from our inpatient unit, with the Cushman scale (Cushman et al., 1985). For these patients, the exact amount of benzodiazepine taken at the beginning of treatment was also known. The number of participants for each variable is specified in Tables 1 and 2. The study was approved by the ethics committees of the 3 hospitals identified above, and the patients signed an informed consent form.

Procedure and Measures

All patients were tested twice within their 3-week detoxification stay: on the first and the eighteenth day of abstinence, with the exact same procedure: After describing the study and obtaining informed consent, demographic data were obtained and the participants then had to fill out questionnaires assessing 4 state-related dimensions, namely craving, depression symptoms, anxiety symptoms, and affective states.

Table 1. Sociodemographic Data for Both Genders

	Men (<i>n</i> = 175)	Women (<i>n</i> = 81)
Age (year, mean $\pm$ SD)	47.5 (10.5) ^d	51.9 (9.7) ^d
Years of addiction (mean $\pm$ SD)	9.9 (8.6)	9.9 (9.0)
Alcohol intake prior detoxification (U/d, mean $\pm$ SD) ^a	17.4 (12.5) ^d	11.0 (6.4) ^d
Education level (year, mean $\pm$ SD) ^b	14.1 (3.3)	13.6 (3.2)
Diazepam (mg/d, mean $\pm$ SD) ^c	45.62 (13.06)	48.21 (15.64)
Cushman score (mean $\pm$ SD)	3.06 (2.42)	4.50 (3.58)

Number of participants for each variable by gender: Age: M (*n* = 174)/F (*n* = 80); Years of addiction: M (*n* = 46)/F (*n* = 24); Alcohol intake: M (*n* = 108)/F (*n* = 56); Education level: M (*n* = 100)/F (*n* = 55); Diazepam: M (*n* = 40)/F (*n* = 14); Cushman score: M (*n* = 40)/F (*n* = 14).

^aOne unit (U) represents 10 g of alcohol.

^bNumber of years of education since completing primary school.

^cDose received the second day of abstinence.

^dDifference between genders at *p* < 0.05.

Table 2. Motivational and Emotional Data (Means and Standard Deviations in Parentheses) for Both Genders and Both Evaluation Times

Variables	T1			T2		
	M	W	Total	M	W	Total
OCDS Obsessions	11.03 (4.00)	11.80 (4.62)	11.27 (4.21)	4.79 (3.09)	5.80 (4.43)	5.10 (3.58)
OCDS Compulsions	7.78 (2.55)	8.52 (2.59)	8.01 (2.58)	3.26 (2.36)	3.56 (2.73)	3.35 (2.48)
OCDS Total	18.81 (5.95)	20.32 (6.60)	19.29 (6.919)	8.02 (5.02)	9.42 (6.84)	8.46 (5.68)
BDI	24.03 (9.06)	31.50 (12.32)	26.13 (10.60)	12.44 (7.02)	19.25 (12.34)	14.36 (9.32)
STAI	50.57 (10.87)	56.56 (10.47)	52.27 (11.06)	44.66 (10.03)	49.44 (10.25)	46.03 (10.29)
PANAS PA	29.00 (8.30)	24.93 (5.92)	25.56 (7.78)	32.17 (7.09)	30.02 (7.65)	31.41 (7.34)
PANAS NA	19.77 (7.20)	21.70 (8.80)	20.45 (7.83)	16.90 (5.97)	18.11 (8.18)	17.33 (6.83)

M, men; W, women; OCDS, Obsessive and Compulsive Drinking Scale (obsessive and compulsive factors and total score); BDI, Beck Depression Inventory; STAI, State-Trait Anxiety Inventory, state version; PANAS, Positive Affectivity Negative Affectivity Schedule; PA, positive affectivity; NA, negative affectivity.

T1 corresponds to the first day of abstinence.

T2 corresponds to the eighteenth day of abstinence.

Number of participants for each variable by gender: PANAS: M ($n = 104$)/F ($n = 57$); OCDS: M ($n = 175$)/F ($n = 80$); BDI: M ($n = 154$)/F ($n = 60$); STAI: M ($n = 113$)/F ($n = 45$).

The Obsessive Compulsive Drinking Scale. The Obsessive Compulsive Drinking Scale (OCDS; Anton et al., 1995, 1996; for the French version, Ansseau et al., 2000) is a self-report questionnaire in regard to craving that investigates obsessive (e.g., How much of your time when you're not drinking is occupied by ideas, thoughts, impulses, or images related to drinking?) and compulsive (e.g., How much of an effort do you make to resist consumption of alcoholic beverages?) dimensions of craving during the previous week. A modified version (with 10 items, 6 obsessive-related and 4 compulsive-related) excluding the items related to current alcohol consumption was provided, as patients were undergoing detoxification and hence did not consume alcohol. All items were rated on a 5-point Likert scale (0 = least, 4 = most) referring to 5 statements that express the degree of the severity of craving. Obsessions scores can range from 0 to 24, and compulsion scores, from 0 to 16.

The Beck Depression Inventory. The Beck Depression Inventory (BDI; Beck et al., 1998) is a 21-item self-report inventory designed to measure the severity of depressive symptoms. Scores can range from 0 to 63, and cutoff scores for the severity of symptoms may be used: 0 to 11: minimum; 12 to 19: mild; 20 to 27: moderate; 28 to 63: severe. This test covers the period going from 2 weeks prior to the day of the experiment (this one being also included).

The State Anxiety Items of the State-Trait Anxiety Inventory. The State-Trait Anxiety Inventory (STAI; Spielberger et al., 1983; for the French version, Bruchon-Schweitzer and Paulhan, 1993) is a self-reported questionnaire divided into two 20-item subsections measuring state and trait anxiety, respectively. We only used the state subsection (how one feels at the moment) in this study. Scores can range from 20 to 80, and cutoff scores for the severity of symptoms may be used: ≤ 35 : very low; 36 to 45: low; 46 to 55: moderate; 56 to 65: high; >65 : very high.

The Positive Affectivity Negative Affectivity Schedule. The Positive Affectivity Negative Affectivity Schedule (PANAS; Watson et al., 1988; for the French version, Gaudreau et al., 2006) is a 20-item questionnaire where the participant has to rate to which extent words describing positive (e.g., enthusiastic) or negative (e.g., upset) feelings correctly represent their recent (previous week) positive and negative affects. The scores can range from 10 to 50 for both negative and positive affects.

The Cushman Scale. The Cushman scale (Cushman et al., 1985) allows to assess the severity of the withdrawal symptoms. The Cushman score is based on the evaluation of several clinical variables:

pulse, systolic blood pressure, respiratory rate, tremor, sweating, agitation, and sensorial disorders. Each category is rated from 0 to 3, depending on specific criteria that reflect the degree of severity or disturbance of each parameter. The maximal total score is 18. The Cushman score we report in the study is related to the second day of detoxification, during which the nurses performed an evaluation of withdrawal symptoms every 6 hours. The total score is a mean score of the different evaluations.

Statistical Analyses

Differences for sociodemographic variables between genders were tested using independent *t*-tests. For experimental measurements, analyses of variance (ANOVAs) were computed with Gender as between-subject variable and Time of evaluation as within-subject variable. Bonferroni post hoc independent and paired *t*-tests were used to probe interactions. Pearson's correlations (corrected using the Benjamini and Hochberg procedure; Benjamini and Hochberg, 1995) were then used to test the links between experimental variables for the 2 testing sessions (transverse and longitudinal analyses). The gender effect on these links was explored using correlations, the significance of the differences between correlations among men and women being determined by Fisher's *Z*-test (Fisher, 1921). Additional analyses included correlational analyses to control for the possible relationship between demographic variables (age, years of addiction, alcohol consumption, and level of education) and craving, and the addition of age as a covariate in the ANOVAs for experimental measures as the variable differed between genders. The potential influence of the severity of withdrawal symptoms and the amount of benzodiazepine on the results concerning depression symptoms and craving was also explored in a subset of patients. The discovery of significant correlations between withdrawal symptoms and/or benzodiazepines and depression symptoms and/or craving level led to reconduct ANOVAs with the addition of Cushman scores or quantity of benzodiazepine as covariate(s) (ANCOVAs) where appropriate and to carry out semipartial correlation between depression symptoms and craving with controlling for the effect of any variable (Cushman or benzodiazepine) that significantly covaried with 1 of the variables of interest. Last, for female, hierarchical multiple regression analysis was used to go beyond correlation links and test whether the affective variables (measured on the first day [T1] of abstinence) that were associated with craving on the eighteenth day [T2] of abstinence were also significant predictors of craving in T2. Collinearity was checked with a matrix of Pearson's correlations with $r \geq 0.8$ in at least 1 correlation as the criterion for

multicollinearity and with the variance inflation factor (VIF) (exclusion of multicollinearity if all VIF <10). All analyses were conducted with IBM SPSS Statistics for Windows (version 22.0; IBM Corp., Armonk, NY), with the level of significance at 0.05.

RESULTS

Demographics

Independent *t*-tests did not reveal any difference between genders for the level of education, $t(153) = 1.011$, $p = 0.313$, the severity of withdrawal symptoms, $t(52) = 1.676$, $p = 0.100$, the amount of benzodiazepine received at the beginning of detoxification, $t(52) = 0.606$, $p = 0.547$, and the duration of the addiction, $t(68) = 0.021$, $p = 0.983$. However, the women were significantly older than the men, $t(252) = 3.175$, $p = 0.002$, and their alcohol consumption before detoxification was, unsurprisingly, lower, $t(161.946) = 4.360$, $p < 0.001$. Demographic values are presented in Table 1.

Modulation of the State Variables as a Function Time and Gender

Craving for Alcohol. Total Craving Score—Our analyses revealed a main effect of Time, $F(1, 253) = 468.231$, $p < 0.001$, $\eta^2 = 0.649$, and a main effect of Gender, $F(1, 253) = 5.455$, $p = 0.020$, $\eta^2 = 0.021$. Total craving scores were lower at T2 compared to T1, and women reported more craving than men.

Obsessions for Alcohol—We found a main effect of Time, $F(1, 253) = 332.219$, $p < 0.001$, $\eta^2 = 0.568$, and a main effect of Gender, $F(1, 253) = 4.781$, $p = 0.030$, $\eta^2 = 0.019$. Obsessions for alcohol were lower at T2 compared to T1, and women reported more obsessions for alcohol than men.

Compulsions for Alcohol—Our analyses revealed a main effect of Time, $F(1, 253) = 466.855$, $p < 0.001$, $\eta^2 = 0.649$, and a main effect of Gender, $F(1, 253) = 3.946$, $p = 0.048$, $\eta^2 = 0.015$. Compulsions for alcohol were lower at T2 compared to T1, and women reported more compulsions for alcohol than men.

Depression Symptoms. Our analyses revealed a main effect of Time, $F(1, 212) = 308.655$, $p < 0.001$, $\eta^2 = 0.593$, and a main effect of Gender, $F(1, 212) = 31.417$, $p < 0.001$, $\eta^2 = 0.129$. The level of depression symptoms was lower in T2 compared to T1, and women reported more depression symptoms than men. Based on the cutoff scores for the BDI, we can tell that 35% of the men presented with severe depression symptoms at T1 and only 2% of them still showed severe levels of depression symptoms by the end of the treatment. For women, 60% reported severe depression symptoms at T1 and 23% of the sample still presented with severe symptoms at T2.

Anxiety Symptoms. Our analyses revealed a main effect of Time, $F(1, 156) = 44.262$, $p < 0.001$, $\eta^2 = 0.221$, and a main effect of Gender, $F(1, 156) = 11.970$, $p = 0.001$, $\eta^2 = 0.071$. Anxiety symptoms decreased between T1 and T2, and women experienced more anxious symptoms than the men. Based on the cutoff scores for the STAI, very high levels of anxiety symptoms were found in 9% of the men and 22% of the women at T1, and in none of the men and 11% of the women at T2.

Affective States. Positive Affects—Our analyses revealed a main effect of Time, $F(1, 159) = 38.661$, $p < 0.001$, $\eta^2 = 0.196$, and a main effect of Gender, $F(1, 159) = 9.185$, $p = 0.003$, $\eta^2 = 0.055$. The level of PA increased between T1 and T2, and men had more PA than the women.

Negative Affects—Our analyses revealed a main effect of Time, $F(1, 159) = 28.565$, $p < 0.001$, $\eta^2 = 0.152$, meaning that NA are lower in T2 compared to T1 in the whole sample. No effect of gender was found ($p = 0.136$). Motivational and emotional data are presented in Table 2.

Links Between Affective States and Craving for Alcohol

Correlational Transversal Analysis: Associations Between Craving for Alcohol and the Other State Dimensions in T1 and in T2 and Evaluation of Gender Differences. Evaluation T1—Analysis for the Whole Sample—Our analyses revealed a positive association at T1 between the total craving score and negative affects ($p = 0.001$), depression symptoms ($p < 0.001$), and anxiety symptoms ($p < 0.001$). The positive associations were found for both subscales, except for the correlation between negative affects and compulsions that was not significant (Obs: NA: $p < 0.001$; Dep: $p < 0.001$; Anx: $p < 0.001$; Comp: NA: $p = 0.576$; Dep: $p < 0.001$; Anx: $p < 0.001$).

Analysis by Gender—Total craving for alcohol: When distinguishing between male and female at T1, the significant correlations with anxiety and depression symptoms were still present for both genders (Anx: M: $p < 0.001$; F: $p < 0.001$; Dep: M: $p < 0.001$; F: $p < 0.001$). However, the link between negative affect and total craving was only present with women ($p = 0.001$). Results of Fisher's Z transformations showed that the correlation with depression symptoms was significantly higher for women compared to men ($z = 3.43$, $p < 0.001$).

Obsessions for alcohol: Positive associations with depression and anxiety symptoms observed at the group level were still present for both genders (Dep: M: $p < 0.001$; F: $p < 0.001$; Anx: M: $p < 0.001$; F: $p < 0.001$). However, the link between negative affect and total craving was only significant with women ($p = 0.001$) and nonsignificant after Benjamini and Hochberg's correction for men. The correlations with depression symptoms and anxiety symptoms were

higher for women compared to men (Dep: $z = 3.36$, $p < 0.001$, Anx: $z = 1.83$, $p = 0.033$).

Compulsions for alcohol: The associations with depression and anxiety symptoms observed at the group level were found with both genders (M: Dep: $p < 0.014$; Anx: $p < 0.001$; F: Dep: $p < 0.001$; Anx: $p < 0.001$). The correlation with depression symptoms was higher for women compared to men (Dep: $z = 2.14$, $p = 0.016$). All detailed data relating to correlations in T1 can be found in Table 3.

Evaluation T2—Analysis for the Whole Sample—Our analyses revealed a positive association at T2 between craving and negative affects ($p < 0.001$), depression symptoms ($p < 0.001$), and anxiety symptoms ($p < 0.001$), and a negative association with positive affect ($p = 0.014$). The significant links with negative affects, depression symptoms, and anxiety symptoms were found for obsessions (NA:

$p < 0.001$; Dep: $p < 0.001$; Anx: $p = 0.001$) and for compulsions (NA: $p < 0.001$; Dep: $p = 0.001$; Anx: $p = 0.002$), but only compulsions were significantly negatively linked to positive affects ($p = 0.006$) after Benjamini and Hochberg's correction.

Analysis by Gender—When probing for distinctions between male and female at T2, we found out that in men, no correlations reached significance after Benjamini and Hochberg's correction between any of the affective variables and craving, neither for the total score nor for the 2 subscales. Women presented positive correlations between craving and negative affects (OCDS Tot: $p < 0.001$; Obs: $p < 0.001$; Comp: $p = 0.011$), depression symptoms (OCDS Tot: $p < 0.001$; Obs: $p < 0.001$; Comp: $p < 0.001$), and anxiety symptoms (OCDS Tot: $p < 0.001$; Obs: $p < 0.001$; Comp: $p = 0.001$) as well as negative correlations with positive affects for total craving and compulsions (OCDS Tot: $p = 0.012$; Comp: $p = 0.001$) that were initially observed at the group level. Furthermore, the correlations between depression symptoms and both the total score of craving and obsessions for alcohol were significantly higher for women compared to men (OCDS Tot: $z = 3.35$, $p < 0.001$; Obs: $z = 2.15$, $p = 0.015$). All detailed data related to correlations at T2 can be found in Table 4. Graphs representing the level of total craving according to the levels of depression symptoms and state anxiety symptoms at T2 are displayed in Figs 1 and 2.

Correlational Longitudinal Analysis: Associations Between Measures of Emotional and Affective State Dimensions at T1 and Craving at T2. *Analysis for the Whole Sample—*A positive correlation was found between the total craving score at T2 and scores for negative affects ($p = 0.024$), depression symptoms ($p = 0.001$), and anxiety symptoms ($p = 0.005$) at T1. These 3 correlations were also found for obsessions (NA: $p = 0.003$; Dep: $p = 0.007$; Anx: $p = 0.004$), but only anxiety significantly correlated with compulsions ($p = 0.026$).

Analysis by Gender—In terms of differences between male and female, our results showed that for males, no significant relation existed between affective states at T1 and any of the craving scores or subscores ($p > 0.322$) at T2. Negative affects, depression symptoms, and anxiety symptoms as measured at T1 were significantly correlated with craving at T2 only for women (OCDS Tot: NA: $p = 0.007$; Dep: $p < 0.001$; Anx: $p = 0.001$; Obs: NA: $p = 0.003$; Dep: $p = 0.002$; Anx: $p = 0.003$; Comp: Dep: $p < 0.001$; Anx: $p = 0.001$). All detailed data related to correlations at T1/T2 can be found in Table 5.

Complementary Analyses. Associations Between Craving and Demographical Variables (Age, Years of Addiction, Alcohol Consumption, and Level of Education)—Our results showed that at T1, the total score for craving as well as the 2 subscales negatively correlated with age (Tot: $r = -0.168$,

Table 3. Transversal Correlational Analysis at T1 for the Full Sample and by Gender

Variable 1	Variable 2	<i>R</i> value (<i>p</i> -value)	
OCDS Total T1	Positive affects T1	-0.073 (0.359)	
		σ φ	
	Negative affects T1	-0.102 (0.302)	0.080 (0.553)
		σ φ	0.268 (0.001)
	Depression T1	0.164 (0.096)	0.418 (0.001)
		σ φ	0.528 (<0.001)
OCDS Obsessions T1	Positive affects T1	0.382 (<0.001)	0.732 (<0.001)
		σ φ	0.448 (<0.001)
	Negative affects T1	0.401 (<0.001)	0.518 (<0.001)
		σ φ	-0.076 (0.340)
	Depression T1	-0.112 (0.256)	0.081 (0.549)
		σ φ	0.304 (<0.001)
OCDS Compulsions T1	Positive affects T1	0.206 (0.036)	0.452 (<0.001)
		σ φ	0.513 (<0.001)
	Negative affects T1	0.369 (<0.001)	0.719 (<0.001)
		σ φ	0.394 (<0.001)
	Depression T1	0.322 (<0.001)	0.532 (<0.001)
		σ φ	-0.005 (0.947)
OCDS Anxiety T1	Positive affects T1	-0.060 (0.547)	0.059 (0.662)
		σ φ	0.045 (0.567)
	Negative affects T1	0.063 (0.526)	0.264 (0.047)
		σ φ	0.480 (<0.001)
	Depression T1	0.315 (<0.001)	0.576 (<0.001)
		σ φ	0.466 (<0.001)
OCDS Anxiety T1	Positive affects T1	0.438 (<0.001)	0.362 (0.014)
		σ φ	

OCDS, Obsessive and Compulsive Drinking Scale (obsessive and compulsive factors and total score), T1 corresponds to the first day of abstinence.

Correlational analyses that remained significant after Benjamini and Hochberg (1995)'s correction are printed in bold.

Table 4. Transversal Correlational Analysis at T2 for the Full Sample and by Gender

Variable 1	Variable 2	<i>R</i> value (<i>p</i> -value)	
OCDS Total T2	Positive affects T2	-0.194 (0.014)	
		♂ -0.094 (0.342)	♀ -0.330 (0.012)
	Negative affects T2	0.355 (< 0.001)	
		♂ 0.169 (0.087)	♀ 0.557 (< 0.001)
	Depression T2	0.409 (< 0.001)	
		♂ 0.195 (0.015)	♀ 0.616 (< 0.001)
	Anxiety T2	0.314 (< 0.001)	
		♂ 0.176 (=0.063)	♀ 0.552 (< 0.001)
OCDS Obsessions T2	Positive affects T2	-0.153 (0.052)	
		♂ -0.087 (0.378)	♀ -0.230 (0.085)
	Negative affects T2	0.372 (< 0.001)	
		♂ 0.161 (0.102)	♀ 0.591 (< 0.001)
	Depression T2	0.349 (< 0.001)	
		♂ -0.176 (0.029)	♀ 0.473 (< 0.001)
	Anxiety T2	0.325 (< 0.001)	
		♂ 0.175 (0.064)	♀ 0.563 (< 0.001)
OCDS Compulsions T2	Positive affects T2	-0.217 (0.006)	
		♂ -0.085 (0.393)	♀ -0.439 (0.001)
	Negative affects T2	0.274 (< 0.001)	
		♂ 0.146 (0.140)	♀ 0.446 (0.011)
	Depression T2	0.291 (< 0.001)	
		♂ -0.100 (0.217)	♀ 0.550 (< 0.001)
	Anxiety T2	0.245 (0.002)	
		♂ 0.141 (0.136)	♀ 0.475 (0.001)

OCDS, Obsessive and Compulsive Drinking Scale (obsessive and compulsive factors and total score), T2 corresponds to the eighteenth day of abstinence.

Correlational analyses that remained significant after Benjamini and Hochberg (1995)'s correction are printed in bold.

$p = 0.007$; Obs: $r = 0.143$; $p = 0.024$; Comp: $r = -0.173$, $p = 0.006$). Only compulsions correlated with age at T2 ($p = 0.042$). Years of addiction, baseline alcohol consumption, and years of study did not show any link with craving either. Analyses by gender revealed that the correlations between age and craving were only significant with men.

Control of a Potential Age Effect—Main effects of the covariate age were found for the 3 craving subscales (OCDS Tot: $p < 0.001$; Obs: $p < 0.001$; Comp: $p < 0.001$), all indicating that craving scores decreased with age. Controlling age did not, however, change the time and gender-related effects depicted above, and no interaction was found with any other variable.

Control of Potential Influences of Severity of Withdrawal Symptoms and Amount of Benzodiazepine Received on Depression Symptoms and Craving—The control of the

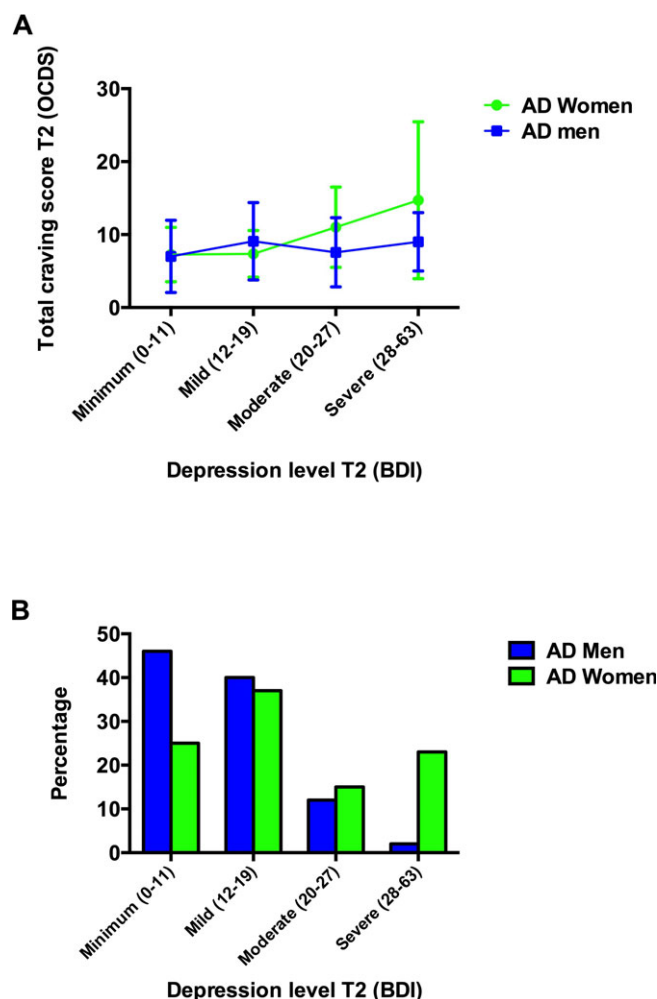


Fig. 1. (A) Mean ($\pm$ SEM) level of total craving (OCDS) according to the level of depression (according to BDI cutoff scores for minimum, mild, moderate, and severe depression) at T2, for men (in blue) and women (in green). (B) Graphs representing the percentage of patients for each level of depression (according to BDI cutoff scores for minimum, mild, moderate, and severe depression) at T2, for men (in blue) and women (in green).

influence of the severity of withdrawal symptoms and/or the amount of benzodiazepine on depression symptoms and/or craving levels and their relationship was conducted in a subset of patients for which we possessed all these information ($N = 40M/14F$). First of all, similar results as those of the whole sample were obtained when conducting 2 (T1 vs. T2) $\times$ 2 (M vs. F) ANOVAs separately on depression symptoms and on total craving level in this subgroup of patients ($N = 54$), with a main effect of Time for both variables, BDI: $F(1, 52) = 104.126$, $p < 0.001$, $\eta^2 = 0.663$, OCDS: $F(1, 52) = 193.867$, $p < 0.001$, $\eta^2 = 0.785$, and an additional effect of Gender for depression, $F(1, 52) = 5.500$, $p = 0.023$, $\eta^2 = 0.094$. We then tested whether the severity of withdrawal symptoms and/or the amount of benzodiazepine received per day was related to depression symptoms and/or craving levels in this sample. The 2 measures only concerned T1 as withdrawal symptoms and benzodiazepine prescription are not present at the end of the 3 weeks of

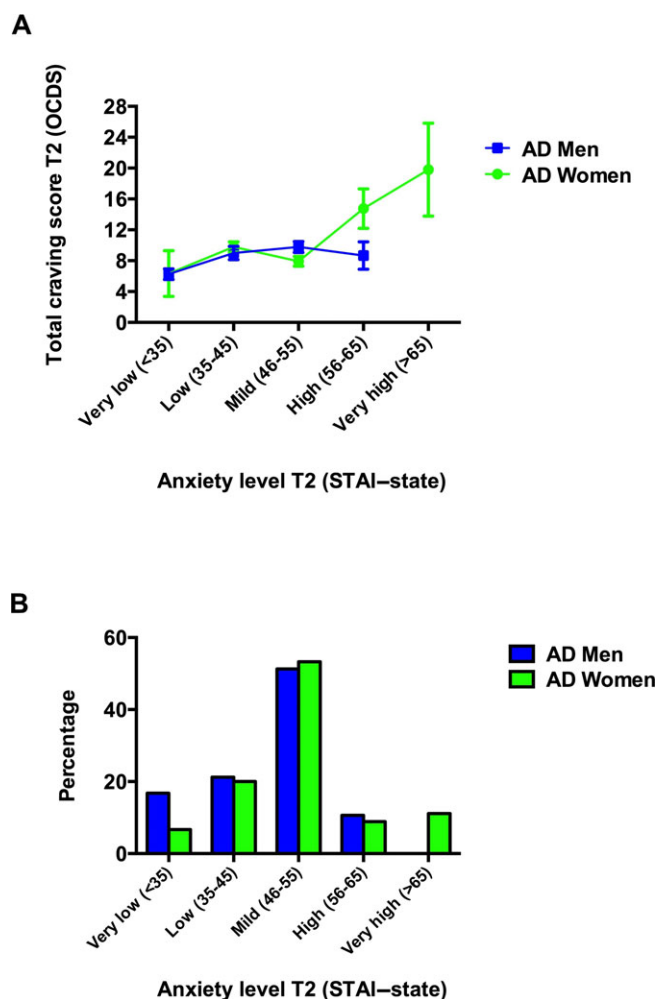


Fig. 2. (A) Mean ($\pm$ SEM) level of total craving (OCDS) according to the level of the state of anxiety (according to STAI cutoff scores for very low anxiety, low anxiety, mild anxiety, high anxiety, and very high anxiety) at T2. (B) Graphs representing the percentage of patients for each level of state anxiety (according to STAI cutoff scores for very low anxiety, low anxiety, mild anxiety, high anxiety, and very high anxiety) at T2, for men (in blue) and women (in green).

detoxification (T2). We conducted correlational analyses for both genders and for both evaluation times, separately. Positive associations between the severity of withdrawal symptoms at T1 and the level of depression symptoms were found at both evaluation times in women only (T1: $r = 0.540$, $p = 0.046$; T2: $r = 0.710$, $p = 0.007$). This means that in women, higher withdrawal symptoms measured at T1 are linked to higher depression symptoms, at T1 and T2. We also observed, for men and in T1 only, positive associations between the level of craving (total score) and both the severity of withdrawal symptoms ($r = 0.346$, $p = 0.029$) and the quantity of benzodiazepine received ($r = 0.443$, $p = 0.004$). This means that for men, the higher the level of craving at T1, the higher the severity of withdrawal symptoms and the amount of benzodiazepine prescribed. Retesting the evolution of depression symptoms for women during detoxification with Cushman scores included as a covariate did not

Table 5. Longitudinal Correlational Analysis (T1–T2) for the Full Sample and by Gender

Variable 1	Variable 2	<i>R</i> value (<i>p</i> -value)	
OCDS Total T2	Positive affects T1	0.032 (0.691)	
		♂ 0.003 (0.975)	♀ 0.116 (0.388)
	Negative affects T1	0.178 (0.024)	
		♂ 0.032 (0.749)	♀ 0.355 (0.007)
	Depression T1	0.222 (0.001)	
OCDS		♂ -0.018 (0.828)	♀ 0.493 (< 0.001)
	Anxiety T1	0.222 (0.005)	
		♂ 0.081 (0.391)	♀ 0.463 (0.001)
	Positive affects T1	0.004 (0.957)	
		♂ -0.047 (0.638)	♀ 0.149 (0.268)
OCDS		0.233 (0.003)	
	Negative affects T1	♂ 0.097 (0.326)	♀ 0.386 (0.003)
	Depression T1	0.183 (0.007)	
		♂ -0.032 (0.691)	♀ 0.385 (0.002)
	Anxiety T1	0.226 (0.004)	
OCDS		♂ 0.091 (0.340)	♀ 0.431 (0.003)
	Positive affects T1	0.063 (0.429)	
		♂ 0.064 (0.518)	♀ 0.055 (0.682)
	Negative affects T1	0.076 (0.336)	
	Depression T1	♂ -0.055 (0.577)	♀ 0.268 (0.044)
OCDS		0.130 (0.058)	
	Anxiety T1	♂ -0.080 (0.322)	♀ 0.4654 (< 0.001)
		0.178 (0.026)	
	Positive affects T1	♂ 0.053 (0.577)	♀ 0.466 (0.001)
		0.053 (0.577)	

OCDS, Obsessive and Compulsive Drinking Scale (obsessive and compulsive factors and total score), T1 corresponds to the first day of abstinence, T2 corresponds to the eighteenth day of abstinence.

Correlational analyses that remained significant after Benjamini and Hochberg (1995)'s correction are printed in bold.

remove the Time effect, $F(1, 11) = 17.476$, $p = 0.002$, $\eta^2 = 0.614$, even though a main effect of Cushman score was observed, $F(1, 11) = 8.490$, $p = 0.014$, $\eta^2 = 0.436$, corroborating the abovementioned correlation finding that depression symptoms covariate with severity of withdrawal symptoms in women. Likewise, adding the Cushman score and the quantity of benzodiazepine received as covariates in the analysis on craving (total score) for men did not remove the main effect of Time, $F(1, 37) = 3.956$, $p = 0.051$, $\eta^2 = 0.097$, despite the main effect of the Cushman score, $F(1, 37) = 7.282$, $p = 0.010$, $\eta^2 = 0.164$, and of the quantity of benzodiazepine, $F(1, 37) = 6.290$, $p = 0.017$, $\eta^2 = 0.145$, in line with correlation results.

Correlation results concerning depression and craving in this reduced sample of patients were also similar to those observed with the original one. Positive correlations between depression symptoms and craving level were found for both genders in T1 (M: $r = 0.335$, $p = 0.032$; F: $r = 0.754$,

$p = 0.001$). They were also observed in T2 (M: $r = 0.361$, $p = 0.020$; F: $r = 0.616$, $p = 0.019$) and in the longitudinal link (i.e., depression symptoms in T1*craving in T2) (M: $r = 0.316$, $p = 0.044$; F: $r = 0.568$, $p = 0.034$). Subsequent analyses controlling for the effect of covariates in the links between depression symptoms and craving were conducted as followed. For T1 and for males, the craving level (total score) in T1 was first regressed on the Cushman score and on the quantity of benzodiazepine to obtain the level of craving that was independent of both these covariables. The obtained residual variable was then correlated with depression symptoms in T1. The correlation obtained was no longer significant ($r = 0.254$, $p = 0.114$). In T1, for women, the depression symptoms in T1 was regressed on the Cushman score and then correlated with the unchanged craving score in T1. The new r and p -values for this corrected correlation were $r = 0.655$, $p = 0.011$. A similar procedure was applied at T2 in women and resulted in the following values for this correlation between depression symptoms in T2 and craving level in T2 controlling for the effect of Cushman score on depression symptoms: $r = 0.996$, $p < 0.001$. The longitudinal correlation between depression symptoms in T1 and craving in T2 was also reconducted for women after controlling for Cushman on depression symptoms, and the new values were $r = 0.709$, $p = 0.007$. No correction was made for the correlation between depression symptoms and craving in T2 and the longitudinal correlation for men as all involved variables in these correlations were not affected by either the Cushman score or the amount of benzodiazepine. Finally, Fisher's Z -test was used to assess differences between these correlations and corrected correlations among men and women. For T2, the correlation was significantly higher for women compared to men (T2: $z = 7.94$; $p < 0.001$).

Predictive Analyses

Three separate multiple hierarchical regression analyses were conducted with the craving scores at T2 entered as outcome variables (i) the total craving score, (ii) the obsession subscore, and (iii) the compulsion subscore. Emotional variables at T1 that correlated with craving in T2 were entered as predictor variables in 3 separate blocks with the more general emotional dimension, that is, negative affects entered as the first factor, followed by the 2 more specific dimensions, that is, anxiety symptoms as the second one and depression symptoms in third place. All correlation coefficients between predictors and the VIF were below the criteria for multicollinearity ($r \leq 0.573$; $VIF < 1.931$).

For the total score for craving, the model as a whole (including all 3 variables) could account for about 26% of the variability in craving, $F(3, 201) = 34.588$, $p < 0.001$. The addition of depression symptoms in the third block accounted for an additional significant ($p = 0.041$) 9.3% compared to negative affects and anxiety symptoms alone. Last, coefficient analysis showed that depression symptoms

was the only variable that made a statistically significant contribution to the modulation of craving ($\beta = 0.423$; $t = 2.125$; $p = 0.041$).

For obsessions, the entire model was able to account for about 23% of the variability in obsessions, $F(3, 36) = 4.541$, $p = 0.009$. Adding depression symptoms in the third block allowed for prediction of an additional ($p = 0.085$) 6.7% of the variance of the outcome compared to negative affects and anxiety symptoms alone, and depression symptoms was the variable that made the highest contribution to the modulation of obsessions ($\beta = 0.361$; $t = 1.773$; $p = 0.085$).

For compulsions, the global model accounted for about 27.3% of the variability in compulsions, $F(3, 36) = 5.516$, $p = 0.003$. The addition of depression symptoms in the third block accounted for an additional significant ($p = 0.024$) 11.2% compared to negative affects and anxiety symptoms alone. Last, coefficient analysis showed that depression symptoms was the only variable that made a statistically significant contribution to the modulation of compulsions ($\beta = 0.466$; $t = 2.360$; $p = 0.024$).

To ascertain the stability of the model used, we changed the order in which the 3 predictors were entered in the regression. All 5 other combinations lead to the finding that depression symptoms was the best remaining predictor.

DISCUSSION

The present study conducted with a population of AD patients sought to explore links between affects and alcohol craving, their progression during a detoxification program, as well as potential gender-specific effects. A clear strength of our study was its ability to address the concept of affects in a broad sense using several different measures (e.g., positive and negative affects, but also anxiety and depression symptoms).

In keeping with what has been reported in the literature, our results showed that regardless of the time of the evaluation, women experienced higher anxiety symptoms, more depressive symptoms, and less positive affects compared to men (Bekker and van Mens-Verhulst, 2007; Karpyak et al., 2016; for a review see Erol and Karpyak, 2015).

Our results also confirm that the levels of obsessions and compulsions for alcohol as well as of depression symptoms, anxiety symptoms, and negative affects decreased between the beginning and the end of the detoxification stay, while the level of positive affects increased simultaneously. This supports the conclusion drawn from previous studies that the detoxification period is a key time for reducing craving and negative emotions (Andersohn and Kiefer, 2004; Cordovil de Sousa Uva et al., 2010a,b; Schuckit, 1994; de Timary et al., 2008, 2013).

Regarding the relations between emotional and motivational dimensions, correlational data first corroborated the existence of associations between depression symptoms and self-reported craving (Andersohn and Kiefer, 2004; Cordovil de Sousa Uva et al., 2010a; de Timary et al., 2013). These

results are consistent with models of substance abuse and relapse (Baker et al., 2004; Koob and Le Moal, 2001; McCarthy et al., 2010; Stasiewicz and Maisto, 1993) that contend that craving responses are closely related to negative emotional states. The further observation that the links between affects and craving are more intense overall for women than for men fits with the general consensus that unpleasant mood states constitute a particular threat to abstinence with women (Erol and Karpyak, 2015; Karpyak et al., 2016). The specific focus of this study on the course of the withdrawal period first showed that, with men, the relation between emotions and craving was only present at the beginning of detoxification, while with women, the relation was maintained both at the beginning and at the end of the detoxification stay. The observation of this distinctive feature may partly address the important clinical question as to whether medical treatment targeting mood disorders should be prescribed in patients presenting both alcohol use disorders and symptoms of depression and anxiety (Pettinati et al., 2013). As predicted from findings in the literature, the majority of women in the present study were able to rid themselves of their anxious and depressive symptoms along with drinking cessation. At the end of the detoxification period, only 23 and 11% of the sample still presented severe depression symptoms and a very high level of anxiety symptoms, respectively. Yet, the women who still presented severe negative affective symptoms were also the ones experiencing the most intense craving. The finding that the correlation between affects and craving remained significant specifically for women after detoxification may thus be indicative of specific cases in which medications targeting both mood disorders and alcohol abuse may be warranted and beneficial. Interestingly, the proportion of men presenting with increased levels of depression symptoms and craving at the end of the detoxification was extremely low. Second, our data revealed that while with men, the levels of negative affects as measured at T1 and T2 were not related to craving at the end of the treatment, with women, affects (and depression in particular) exhibited at T1 had a predictive capacity on the intensity of craving at the time of discharge from the hospital. The finding that among negative affects, depressive symptomatology in particular was able to predict craving in women may be in accordance with some previous works that specifically emphasized the role of depression symptoms over other negative states in relapse and re-initiation of drug use following periods of abstinence (e.g., Curran et al., 2007; Witkiewitz and Villarreal, 2009; Witkiewitz et al., 2011). Our results highlight that this may only be seen with women. Moreover, the idea that depression symptoms influence the level of craving in women at the end of the detoxification is of substantial relevance in light of the demonstrated relation between craving at the end of the detoxification process and future relapse (e.g., Bottlender and Soyka, 2004; Gordon et al., 2006). It stresses the need to pay high attention to emotional dimensions at the very beginning of the steps

toward recovery with female patients. Particular care should be taken with these patients who are at a potentially higher risk of craving and further relapse, and treatments targeting the decrease of depression and alcohol craving should be emphasized. For example, the mindfulness-based relapse prevention (Bowen et al., 2009) has shown promise in helping patients deal with emotional states and craving, thereby breaking down the relations between negative affect, craving, and substance use (Witkiewitz and Bowen, 2010; Witkiewitz et al., 2011).

Future research would greatly benefit from exploring the existence of moderator variables that could play a role in the affects-craving relationships for both genders (e.g., neuroticism; Armeli et al., 2003), emotional intelligence (Cordovil de Sousa Uva et al., 2010b), alexithymia (Luminet et al., 2016), self-consciousness (de Timary et al., 2013), contextual influences, awareness, or cognitive control (McCarthy et al., 2010). Our study also has several limitations that should be addressed in future studies. We tested the influence of the severity of withdrawal symptoms and the use of benzodiazepine on the results, and it allowed to discover that these variables, despite their isolated significant effect on the variables of interest, did not change the general findings on the links between depression symptoms and craving and the general effect of time on both dimensions and most of all did support the idea that the correlation between affect and craving is essentially observed in women. Although depression symptom level was the most central variable in the study as regards the results obtained, these issues remain to be properly tested in the whole sample of patients in future studies and for all affects dimensions, not only depression symptoms. Further studies should also opt for a longitudinal design with postcure measures to confirm the link between affects and craving levels at the end of the detoxification and long-term abstinence/relapse.

In summary, by highlighting differential patterns of association in men and women, this study adds to the level of understanding of the links between affects and alcohol craving during the detoxification period. First, it confirms that the detoxification period is linked to improvements in negative affects and levels of craving. Second, it corroborates evidence that affects are closely linked to craving in both men and women when they initiate the detoxification program. It indicates, however, that at the end of this detoxification, only women still exhibit a link between affects and craving and that their level of craving is proportional to the degree of negative affects reported when they initiate the treatment. Last, it highlights that only in AD women do the depression symptoms experienced at the beginning of the detoxification stay predict craving at the end of it. Given the well-known association between craving at the end of detoxification and relapse, these findings stress the importance of helping female patients deal with symptoms of depression so as to maximize their chances of remaining abstinent in the long run.

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