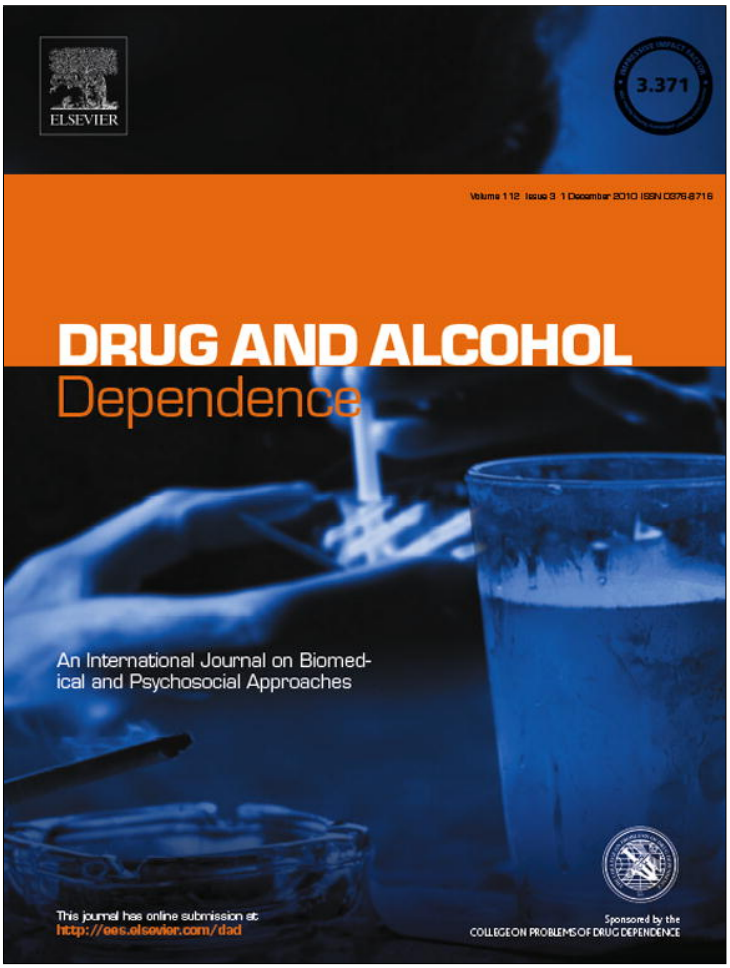

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Effect of the threat of a disulfiram–ethanol reaction on cue reactivity in alcoholics☆,☆☆

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ABSTRACT

Rationale: Little is known about the effect of disulfiram on subjective and autonomic nervous system cue reactivity in the laboratory. The dissuasive psychological effect manifested as a threat would seem to prevail over the pharmacological effect.
Objectives: The primary objective was to determine whether there was a difference in cue reactivity responses during a threat condition compared to a neutral condition during alcohol cue exposure.
Methods: In a crossover randomized study, participants received threat and neutral messages during two cue exposure sessions. The threat condition consisted of leading the patients to believe they had ingested 500 mg of disulfiram and the neutral condition of informing them that they had ingested a placebo, while in both condition they received the same placebo.
Results: Physiological cue reactivity was demonstrated by a decrease in diastolic blood pressure during the threat compared to the neutral condition ($p = 0.04$). Heart rate and subjective cue reactivity measures remained unchanged. There was a negative affect (assessed by the Positive and Negative Affect Scale) by condition by exposure interaction.
Conclusions: The threat of a disulfiram–ethanol reaction appears to affect cue reactivity physiologically rather than subjectively. While the data does not show changes in subjective ratings, it is possible that there are alternative beneficial effects arising from other cognitive processes that are not captivated by self-reported craving scales, reflected by decreases in negative affect and blood pressure. From this perspective, disulfiram might be recast to be more acceptable to patients.

1. Introduction

One of the major challenges in addiction treatment is how to prevent relapse when a patient desiring abstinence is thrown off balance by a reaction to alcohol or an alcohol related stimulus (Skinner and Aubin, 2010). This phenomenon may or may not be identified as "craving" as it may occur without awareness (Robinson and Berridge, 2008), but it nonetheless affects behavior that may lead to relapse. One method to reinforce abstinence has been to increase aversion to alcohol. Disulfiram appears to help increase the duration of abstinence in patients who observe their treatment schedule (Chick et al., 1992; Fuller and Gordis, 2004; Diehl et al., 2010; Mutschler et al., 2010). Furthermore, there is some evidence that disulfiram decreases craving (De Sousa, 2004, 2005; Petrakis et al., 2005; De Sousa et al., 2008), but its mechanism of action on craving is unclear.

Three studies evaluated subjective craving in order to compare the effectiveness of disulfiram to acamprosate (De Sousa, 2005), naltrexone (De Sousa, 2004), and topiramate (De Sousa et al., 2008). Disulfiram was found to reduce craving in alcoholics post-treatment as measured by the OCDS (Obsessive Compulsive Drinking Scale) (Anton et al., 1995), but not to the same extent as the other medications. Disulfiram was found superior, however, in

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reducing the number of drinking days. This may have been due to the strong psychological effect of the prohibition of drinking on craving but also due to the association between disulfiram and reduced anxiety as Petrakis et al. (2005) have shown. On the other hand, it is still not clear if other cognitive or physiological processes were responsible for the superiority of disulfiram.

In a large, randomized trial with alcohol dependent patients with a comorbid DSM-IV, Axis 1 psychiatric disorder, the effectiveness of four different treatment conditions was compared over a 12-week period: a placebo alone, disulfiram + (blinded) naltrexone, naltrexone alone, and disulfiram + (blinded) placebo (Petrakis et al., 2005). The medication-alone groups had fewer drinking days compared to the placebo group; the combination treatment, however, did not have superior results in reduced drinking days or craving than either medication alone. Interestingly, the disulfiram patients reported less craving based on the OCDS and fewer anxiety-like symptoms than the naltrexone patients. Both groups also had similar compliance rates, probably because they were highly motivated (Petrakis et al., 2005).

In another study, disulfiram was shown superior to acamprosate and naltrexone in reducing drinking and probably craving because patients were told to target use of the medications to craving situations during the unsupervised phase of the study (Laaksonen et al., 2008). No physiological measures were taken, raising questions as to how disulfiram functions.

The present study was conducted to address some of the gaps in knowledge about the effect of a threat of a disulfiram–ethanol reaction vs. a neutral condition on subjective and autonomic nervous system (hereafter referred to as physiological) cue reactivity. The study used a placebo in both experimental conditions in order to avoid confounding the pharmacological effect of disulfiram with the psychological effect of the threat. We evaluated subjective and physiological cue reactivity in relation to the threat of a disulfiram–ethanol reaction.

We also tested possible associations between subjective and physiological measures. Findings are contradictory with some studies showing associations (Ludwig and Wikler, 1974; Ludwig et al., 1977; Stormark et al., 1995), while others showed dissociations, suggesting that during physiological cue reactivity (e.g., salivation) patients may not be aware of their urges (Monti et al., 1993a; Rohsenow and Monti, 1999; Reid et al., 2006). The independence of the two dimensions could influence how cue reactivity is evaluated and interpreted.

Craving and aversion were evaluated on separate scales to further understand their relationship to each other. Little evidence exists for their independence with alcohol dependent patients contrary to other substance users where independence was demonstrated (Avants et al., 1995; Breiner et al., 1997; McEvoy et al., 2004; Stritzke et al., 2004). This question is important for future cue reactivity studies because if found independent, the two dimensions would best be evaluated on separate scales to avoid the underreporting of the approach dimension. This is particularly relevant for patients who are ambivalent, that is both high in approach and avoidance inclinations.

Also evaluated were measures of levels of dependence and positive and negative affect as possible modulators of responses. Physiological cue reactivity measures seem to be related to levels of alcohol dependence (Kaplan et al., 1985; McCusker and Brown, 1991; Monti et al., 1993a), while the relationship of desire to drink and dependence levels is inconsistent (Kaplan et al., 1985; Dolinsky et al., 1987; Corty et al., 1988; Zilberman et al., 2003). Regarding affect, studies have shown that negative affect has been associated with craving (McCusker and Brown, 1991; Rohsenow et al., 1992; Baker et al., 2004; Fox et al., 2007). This study extends the research into another domain by asking how the threat of a disulfiram–ethanol reaction compared to a no threat condition would interact with negative affect and cue reactivity. Demonstrating differences could impact the way physicians present disulfiram to potential patients.

We hypothesized that cue reactivity to alcohol would be affected as follows: (1) the threat of a disulfiram–ethanol reaction would reduce the subjective desire to drink, and (2) heart rate and blood pressure would be higher in the neutral condition than in the threat condition because of the increased risk of consuming in the neutral condition.

Secondary exploratory hypotheses were: (1) subjective craving and physiological responses would not be correlated, (2) desire and aversion would vary independently in both threat and neutral conditions, (3) compared to the less dependent participants, the more dependent would have higher craving as well as higher heart rate and blood pressure, and (4) negative affect would be associated with craving in both threat and neutral conditions.

2. Methods

2.1. Participants

Participants were recruited from inpatients in a French detoxification program at Emile Roux Hospital, Limeil-Brévannes between November 2006 and September 2008. Inclusion criteria were: (a) age 18 or older; (b) current diagnosis of alcohol dependence according to DSM-IV criteria (American Psychiatric Association, 1994); (c) abstinence goal of at least 6 months post-treatment; (d) intellectual, social, or educational level sufficient to respond to the questionnaires; (e) no prior use of disulfiram; (f) no contraindication to disulfiram; (g) no use of antidepressants or neuroleptics during the past 6 days; (h) no treatment by naltrexone, acamprosate, beta-blockers, or clonidine during the past 7 days; (i) no use of benzodiazepines during the past 3 days except diazepam, maximum 30 mg per day, (j) no change in treatment that could affect the desire to drink between the two cue exposure sessions, (k) no hearing impairment, and (l) no anosmia or rhinitis. Participants were not allowed to consume any alcohol during enrollment in the study. If drinking occurred, a delay of 6 days of abstinence was required before resuming participation.

2.2. Design and procedure

The study was a crossover design, initially inspired by the cue reactivity assessment developed by Monti and colleagues (Monti et al., 1987, 1993b; Rohsenow et al., 2000) and modified for the study objectives. Each participant was seen three times. An inclusion visit occurred six or more days after consuming the last drink. During this visit, the procedures and objectives of the experiment were explained and written informed consent obtained; the experimenter collected socio demographic data, administered the Mini International Psychiatric Interview (Sheehan et al., 1998) for alcohol dependence, and collected data on alcohol consumption over the past 6 months. Once written informed consent was obtained, participants completed the Alcohol Dependence Scale (ADS) (Skinner and Allen, 1982). The alcoholic drink that would most likely provoke a craving was selected by the participant who also described how it should be served. Patient identity was protected as per French law on biomedical research by unlinking the data file for analysis from all identifiers. All procedures received institutional review board approval by the French board for protection of participants in biomedical research (CPP—Comité de protection des personnes, Hôpital Pitié-Salpêtrière, Paris, France).

The two experimental beverage trials took place over the next 2 weeks (see Fig. 1). Each was associated with a *neutral* or *threat* message regarding the contents of a placebo which was swallowed by the participants. The first trial occurred from 1 to 7 days after the inclusion visit and the second after a wash out period of 4–8 days. To counterbalance the message order, participants were randomized by blocks of 6 into two groups. On the first beverage trial, half of the patients received a neutral message in French: *This morning you have taken a tablet without any effect on a possible consumption of alcohol. If you had a drink, the alcohol would have the usual effect*. On the second beverage trial, the same group received a threat message: *This morning you have taken a tablet that would rapidly provoke a strong, unpleasant reaction if you consumed any alcohol – nausea, vomiting, an intense feeling of heat, very rapid heartbeat. But this tablet will have no effect if you do not consume any alcohol*. The remaining half received the same messages but in the reverse order.

Each message was accompanied by the ingestion of a tablet at 8:10 a.m. for each beverage trial. In both the threat and neutral conditions, the participants received an identical placebo. The aim was to test only the psychological threat and not the pharmacological effect of disulfiram.

Each participant reported to the assessment room at 1:30 p.m. on the experimental day. The experimenter explained and demonstrated the procedure (~30 mn), but afterwards remained hidden from view behind a one-way mirror during most of the experiment. Talking was not allowed. Participants sat at a table adjacent to the mirror. The materials needed during the beverage trials were behind the mirror: the Colin monitor model no. BX-10Ma (used to evaluate blood pressure and heart

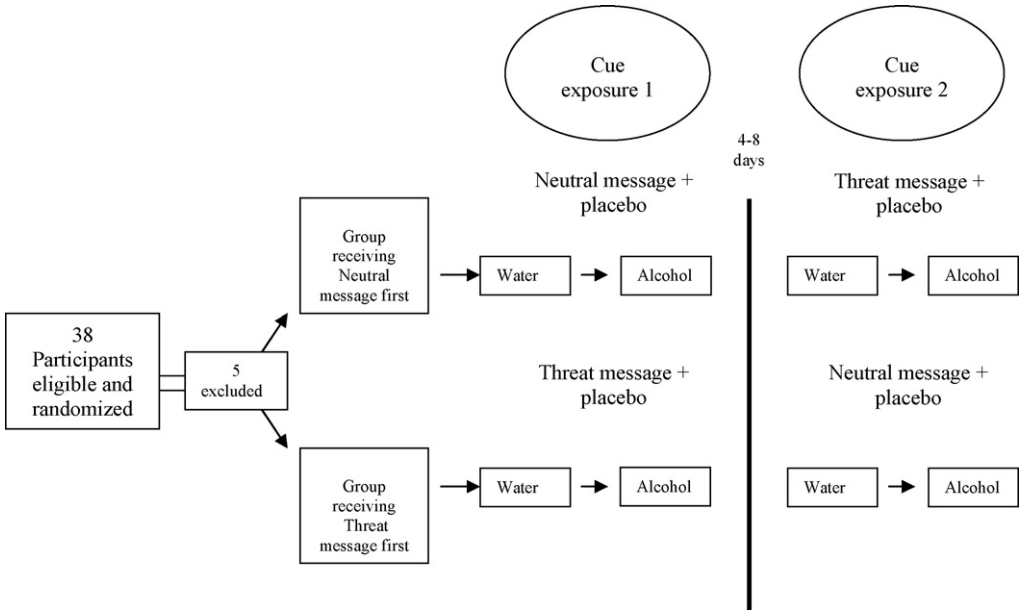

Fig. 1. Cue exposure procedure.

rate), the alcoholic beverage and its commercial container, drinking related items, bottled mineral water, glasses, tray, opaque cover, and a CD player. All instructions were recorded and played step by step. The Colin monitor blood pressure cuff was attached to the participant's non-dominant arm during the entire session, but only turned on during the three relaxation periods and two beverage trials.

The steps involved in each beverage trial were: a 3 min relaxation period, a 3 min water exposure, a time for completing the questionnaires, a 3 min relaxation period, a 3 min alcohol exposure, a time for completing the questionnaires, and a 3 min relaxation period with debriefing after the final trial. The experimenter filled the glass half full with either water or alcohol in front of the patient and then remained behind the one-way mirror for the remainder of the session. Participants were signalled to smell the drinks by 13 pairs of recorded high and low tones per 3 min trial. The interval between the pairs was varied to prevent temporal conditioning. Instructions were given to hold the drink from 2 to 5 cm from the mouth and to not drink the contents. The questionnaires referred to the desire for alcohol, even during the water trial. As a reminder, the message given the morning of the trial was repeated immediately before each alcohol trial. At the end of the session, the participant remained with the experimenter until there was no further desire for alcohol. At the end of the final session, the experimenter asked the participants about how they perceived the experiment, possible coping strategies, and the experiment's effect on their confidence level. At the conclusion of the experiment, participants were informed by letter of the results of the study and that they had received a placebo in both conditions.

2.3. Cue reactivity measures

2.3.1. Arterial blood pressure and heart rate. The Colin monitor, set to continuous mode, collected and calculated mean heart rate and arterial blood pressure every 30 s during relaxation periods and during beverage trials. The results were stocked in the Colin's microprocessor and printed based on each 15 s sampling period.

2.3.2. Subjective measures. Immediately after each beverage trial, the participant filled out questionnaires consisting of five visual analogue scales of 100 mm long: (1) How much do you want a drink right now? (*craving now*) (2) How much does the idea of drinking turn you off right now? (*aversion now*) (3) If you were not at the hospital but rather in a situation where you habitually drank in the past, how much would you want a drink right now? (*craving imaginary*) (4) If you were not at the hospital but rather in a situation where you habitually drank in the past, how much would the idea of drinking turn you off right now? (*aversion imaginary*) (5) Are you nauseated now? (*nausea*).

After completing the above questionnaire, the participant filled out the PANAS (Positive and Negative Affect Scale) (Watson et al., 1988), an evaluation of affect from the moment the beverage was poured into the glass.

Primary outcome measures were the change scores of cue reactivity during alcohol and water exposures between the threat and neutral conditions.

2.4. Statistical analyses

2.4.1. Calculation of the sample size. The main analysis consisted of calculating interaction exposure by condition effects on subjective cue reactivity (*craving now*). This analysis was performed using a Mann–Whitney test comparing differences in change scores (alcohol minus water exposure scores) of *craving now* between both randomisation order groups. A correlation of 0.7 between 2 craving measures of the same subject during the same visit was assumed. Moreover, measures from the literature (Monti et al., 1993b) of mean ± SD craving scores of water exposure followed by alcohol exposure were 2.7 ± 2.8 and 5.6 ± 3.3, respectively. Thus, baseline change scores of craving between alcohol and water exposure were estimated at 2.9 ± 2.4. We also hypothesized that with the threat of an aversive reaction, change score would be reduced by half, being equal to 1.45, with the same standard deviation of 2.4, and that the correlation between 2 change scores of craving in the same subject would be 0.5. Consequently, the differences in change scores were expected to be −1.45 ± 2.4 for the off-on (neutral-threat) sequence group and 1.45 ± 2.4 for the on-off (threat-neutral) sequence group. With alpha risk of 0.05 and beta risk of 0.2, 28 patients were necessary for a non-parametric test. In order to take into account losses during the study, 38 patients were included.

2.4.2. Data analysis. The effects of alcohol exposure, threat, period, and interactions on cue reactivity measures were analyzed using multivariate linear modelling. The triple interaction alcohol-threat-period was tested as well as the carryover effect. There was no significant alcohol by threat by period interaction and at a 10% significance level, no carryover effect was found; the analyses were pursued to determine the effects of the threat and alcohol exposure on cue reactivity. The crossover design allowed each parameter estimate derived from the model to be analyzed using the Mann-Whitney test which was used to compare both randomisation order groups (neutral followed by threat condition and threat followed by neutral condition). A test of carryover effect was thus performed by calculating the sums of the change scores (alcohol exposure scores minus water exposure scores) for each participant and then comparing the two randomisation order groups. The comparison of differences between second and first cue exposure visits for the change scores in each measure allowed for an analysis of the threat by alcohol exposure interaction. Likewise, the comparison of differences between second and first cue exposure visits of the sum of water and alcohol exposure scores for each variable allowed for an analysis of the threat effect. Computational details are given in Supplementary material available online and were based on the theory of non-parametric comparison tests for a crossover design (Hills and Armitage, 1979).[1] Unlike cue reactivity measures, heart rate, systolic, and diastolic blood pressure were analyzed using a repeated measures ANOVA since these data were assumed to be normally distributed.

Secondary analyses consisted of correlations between cue reactivity measures, alcohol dependence scores, and affect and were analyzed using Spearman's rank order tests. These analyses were stratified according to threat and neutral conditions and adjusted for the period using a partial correlation coefficient. Data were described as means (SD) if the distribution was normal or by median (range) if not normal. According to the definition of Baron and Kenny (1986), a moderator analysis was performed testing the interaction effect between the moderator (PANAS) and

[1] Additional materials are available with the online version of this article at doi:10.1016/j.drugalcdep.2010.06.011.

Table 1
Demographics, drinking history, and alcohol dependence score (ADS).

Variable	Total ($n = 33$)
Demographic characteristics	
Age, mean (SD), years	43.24 (8.55)
Female, no. (%)	7 (21.21)
Race, no. (%)	
African origin	2 (6.06)
White	31 (93.94)
Married or cohabiting, no. (%)	18 (54.55)
Unemployed, no. (%)	15 (45.45)
High school or greater, no. (%)	15 (45.45)
Drinking history	
Abstinence days over the past 6 months, median (range)	21 (0–106)
Average weekly consumption g, median (range)	780 (140–2700)
ADS, median (range)	17 (7–31)

the conditions (threat or neutral and water or alcohol) on cue reactivity measures in a mixed linear model. All statistical tests were two-tailed at a 5% significance level. The analyses were performed using SAS/STAT software, Version 8.2 (SAS Institute, Cary, NC).

3. Results

3.1. Sample description

Of entering patients screened between November 2006 and September 2008 ($n = 538$), 38 were selected based on inclusion criteria, provided consent, and were randomized to the order of threat and neutral conditions. Of these, 33 were analyzed. Demographic and clinical characteristics are presented in Table 1. Five participants were excluded. The exclusions occurred regardless of the randomisation order (see Fig. 2). Two patients did not participate in the second beverage trial. After the first beverage trial, one consumed alcohol and the other ingested acamprosate. We obtained and analyzed data only from the first exposure for these two patients, bringing the total of completed studies to 31.

3.2. Effect of alcohol on cue reactivity

The alcohol cue significantly increased the scales *craving now*. ($p < 0.0001$), *craving imaginary* ($p = 0.0027$) and PANAS negative affect scores ($p = 0.028$). It had no effect on the other variables.

3.3. Effect of the threat condition on cue reactivity

There was a significant condition by alcohol interaction on diastolic blood pressure ($p = 0.044$) such that it decreased in response to the alcohol cue in the threat condition and remained the same in the neutral condition. The interaction term showed a trend ($p = 0.071$) for systolic blood pressure. No condition by alcohol interaction occurred for the other measures, specifically, there was no significant condition by alcohol interaction for *craving now*, *craving imaginary* (see Table 2 and Fig. 3), or the PANAS.

3.4. Secondary analyses

A period effect on cue reactivity was found for the scales *craving now*, ($p = 0.039$), *craving imaginary* ($p = 0.048$), diastolic blood pressure ($p = 0.002$), and systolic blood pressure ($p = 0.007$). All decreased during the second exposure compared to the first. There was no condition by alcohol interaction for the scale *nausea*. There was no correlation between subjective and physiological measures. Regarding the relationship between desire (*craving now*) and aversion (*aversion now*), in both the neutral and threat conditions, there was a significant and inverse correlation (Spearman's $\rho = -0.42$, $p = 0.02$ and Spearman's $\rho = -0.39$, $p = 0.03$, respectively). Alcohol dependence scores were not related to threat minus neutral change scores (alcohol minus water scores) of the subjective measures for *craving now*, *aversion now*, and *craving imaginary*, nor for the physiological measures. Dependence was, however, related to *aversion imaginary*, (Spearman's $\rho = 0.43$, $p = 0.02$). This result indicated that the more severely dependent participants were less turned off by drinking alcohol in an imaginary situation. Further exploration showed that this correlation occurred during the neutral condition (Spearman's $\rho = -0.46$, $p = 0.01$). When the threat was present, the participants reacted the same way regardless of the level of dependence. PANAS negative affect increased during the alcohol exposure ($p = 0.028$) in both neutral and threat conditions (see Fig. 4).

3.5. Moderator analysis

Because PANAS negative affect was correlated with alcohol exposure, we tested the hypothesis that negative affect moderated the effect of a threat on alcohol cue reactivity (*craving now*). Inclusion of PANAS negative affect as a covariate in the condition by alcohol interaction model reduced the model's p-value from 0.41 (NS) to 0.1. The relationship between negative affect and craving was stronger during the threat condition or during alcohol exposure (in threat and neutral conditions) than during water exposure in the neutral condition, which resulted in a significant triple interaction effect (PANAS negative affect by cue exposure by condition; $F = 6.08$, $p = 0.0034$) on *craving now* (see Fig. 4).

We also tested the hypothesis that PANAS negative affect moderated the effect of a threat on diastolic blood pressure. The linear mixed model showed that diastolic blood pressure in response to cue exposure or threat was modulated by PANAS negative affect (triple interaction negative affect by cue exposure by condition; $F = 11.94$, $p < 0.0001$) (see Fig. 4).

Because there was no effect of alcohol dependence (ADS) on *craving now*, *craving imaginary*, and the physiological variables, its moderator effect was not tested.

Table 2
Cue exposure responses in the neutral and threat conditions.

Change scores[a]	Neutral then threat message		Threat then neutral message		p
	Cue exposure 1	Cue exposure 2	Cue exposure 1	Cue exposure 2	
Craving now[b]	12 (0 to 74)	1.5 (−3 to 51)	8 (0 to 90)	2 (−5 to 71)	0.41
Aversion now[b]	−0.5 (−46 to 48)	0 (−44 to 76)	−2 (−73 to 56)	0 (−52 to 26)	0.89
Craving imaginary[b]	10.5 (−20 to 84)	0 (−28 to 45)	8 (−32 to 72)	0 (−26 to 71)	0.89
Aversion imaginary[b]	0 (−47 to 61)	0 (−46 to 19)	2 (−26 to 61)	0 (−50 to 20)	0.77
Nausea[b]	0 (−4 to 71)	0 (−16 to 30)	0 (−1 to 23)	0 (−1 to 50)	0.95
Heart rate (beats/min)[c]	0.38 (3.22)	−1.21 (7.36)	0.35 (2.60)	−1.29 (2.87)	0.91
Diastolic blood pressure (mm Hg)[c]	1.50 (3.60)	−4.43 (8.52)	0.53 (2.74)	−1.00 (2.85)	0.04
Systolic blood pressure (mm Hg)[c]	3.63 (5.61)	−5.93 (14.82)	−0.24 (5.76)	−2.47 (3.89)	0.07

[a] Change scores consist of the difference between the alcohol exposure score and the water exposure score.
[b] Numbers are medians and (range).
[c] Numbers are means and (SD).

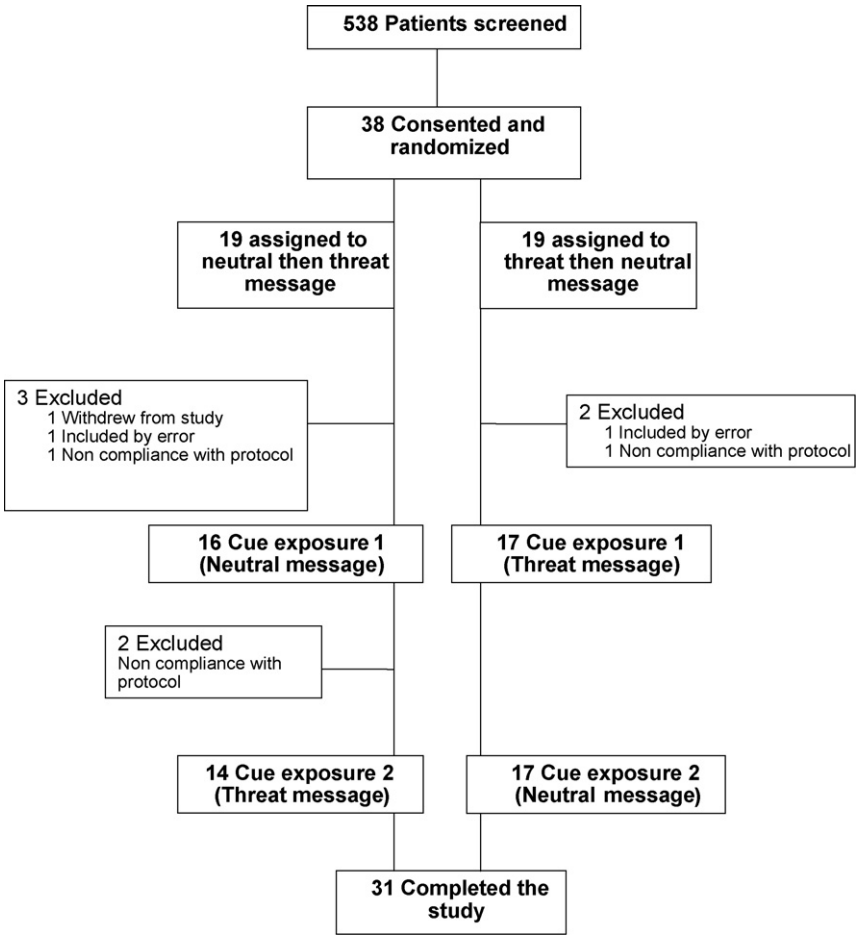

Fig. 2. Flow chart of participant recruitment and retention.

4. Discussion

The primary purpose of this study was to determine whether there was a difference in cue reactivity responses during a threat condition compared to a neutral condition during alcohol cue exposure. First we established that our participants responded with increased desire to the alcohol cue. This was accompanied by an increase in negative affect. Then we tested the effect of the threat of a disulfiram–ethanol reaction condition compared to a neutral condition on cue reactivity. To summarize our findings, no effect of a threat was found on craving. Regarding autonomic nervous system measures, we observed a decrease in diastolic blood pressure during the threat compared to the neutral condition. Systolic blood pressure showed a trend, while heart rate remained unchanged.

Inclusion of negative affect in the model strengthened the relationship between alcohol cue exposure and craving for alcohol and decreased the diastolic blood pressure in response to cue exposure in the threat condition. The threat of an aversive reaction during alcohol exposure was not associated with an increase in negative affect, probably because temptation and risk were reduced, which is reflected in the decrease in blood pressure.

Petrakis et al. (2005) have shown that alcohol dependent outpatients treated with disulfiram had fewer anxiety related symptoms compared to those treated with naltrexone or placebo. In addition, it is probable that taking disulfiram facilitated a sense of control to abstain from alcohol as suggested by an efficacy study of disulfiram and acamprosate (Besson et al., 1998).

Some authors who have measured both subjective and physiological measures have suggested that heart rate and blood pressure were the most consistent and valid measures of cue reactivity (Rohsenow et al., 1990; Monti et al., 1999). This could be because physiological measures are less likely to be under volitional control (Reid et al., 2006) and are not dependent upon self-report. In addition, several studies have shown that a physiological measure (salivation) predicted more drinking at follow up compared to urge (Rohsenow et al., 1989, 1994). Few studies evaluated blood pressure, however, compared to heart rate, salivation and temperature (Niaura et al., 1988). In one study, blood pressure decreased in response to cues interpreted as an orienting, attentional response to alcohol cues (Monti et al., 1999). It is possible that the decrease in blood pressure in the present study was associated with increased attention during the threat condition as the threat was repeated just before the alcohol cue exposure, drawing the participant's attention to the consequences of a possible consumption. Future studies specifically evaluating attention would be necessary to confirm this. A blood pressure decrease, which signifies a decrease in sympathetic cardiovascular arousal (Critchley, 2005), could also arise from a reduced need for cognitive effort and any accompanying anxiety because the participants had less difficulty resisting temptation because of the support of believing they had ingested disulfiram.

Regarding secondary hypotheses, as we expected, subjective and physiological responses varied independently. A similar dissociation was found by other investigators (Ooteman et al., 2006; Carter and Tiffany, 1999; Niaura et al., 1988). Salivation was not associated with urge (Cooney et al., 1984; Rohsenow et al., 1990; Monti et al., 1993b). The dissociation is not surprising if we consider physiological processes to be multidetermined. Physiological

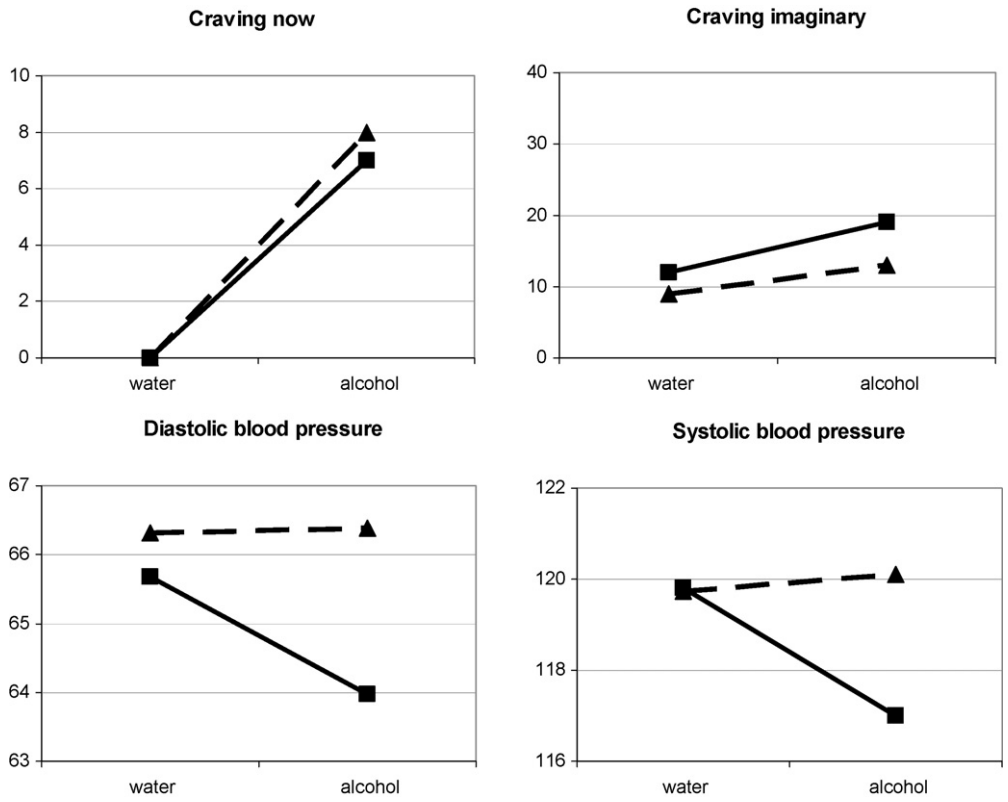

Fig. 3. Variations of craving now (median), craving imaginary (median), diastolic blood pressure (mean), and systolic blood pressure (mean) by threat vs. neutral conditions when exposed to water or alcohol. Continuous lines with square points represent the threat condition. Dotted lines with triangular points represent the neutral condition.

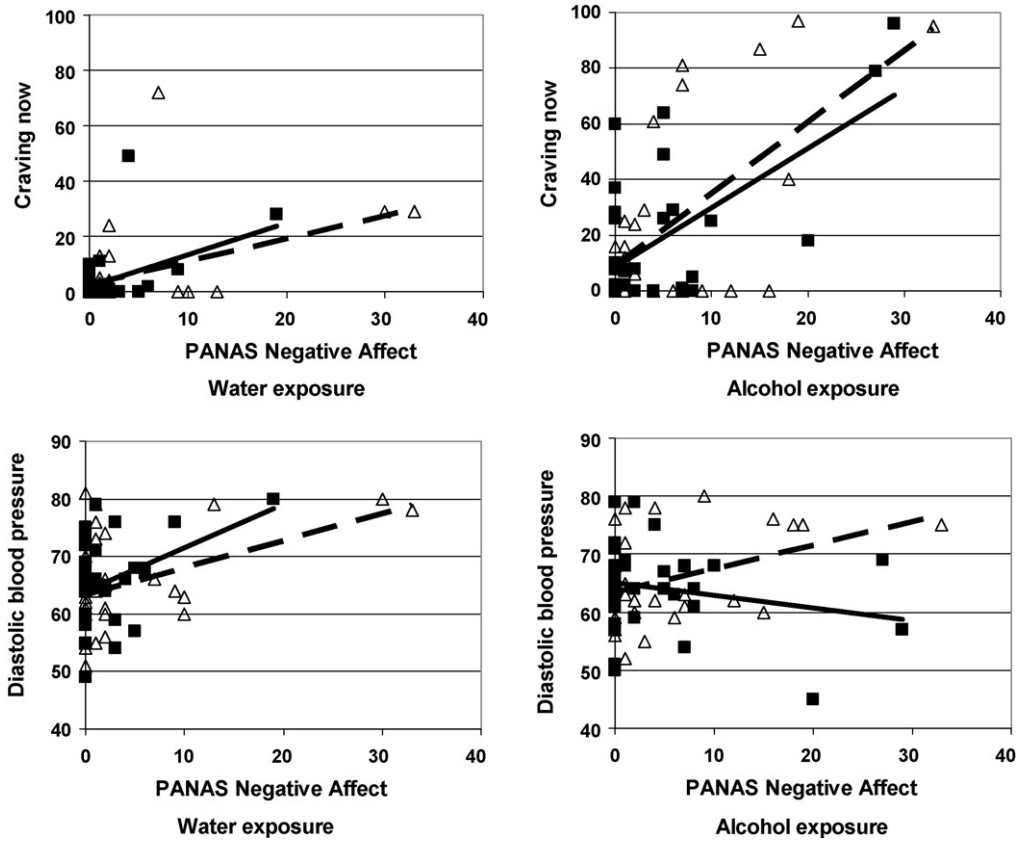

Fig. 4. Relationships between negative affect (PANAS), craving now, and diastolic blood pressure by exposure and threat vs. neutral conditions. Lines represent linear regressions. Squares and continuous lines represent the threat condition. Triangles and dotted lines represent the neutral condition.

processes are probably engaged in many functions unrelated to the cue manipulation (Rohsenow et al., 1990; Carter and Tiffany, 1999). Patients were found unaware of their urges while salivating (Monti et al., 1993b; Rohsenow and Monti, 1999) and unaware of their physiological reactions during cue exposure (Ooteman et al., 2006), indicating that a substantial number of alcohol dependent patients are unable to detect bodily sensations of craving. These findings do not support conditioning models in which the physiological measures as well as the subjective measures should correlate (Ludwig and Wikler, 1974; Baker et al., 1986).

Contrary to our hypothesis, subjective craving and aversion were negatively correlated. As described in the multidimensional ambivalence model (Breiner et al., 1999), craving and aversion were thought to be two independent dimensions. Support for their independence has been shown (Avants et al., 1995; Breiner et al., 1997), but has yet to be validated among alcoholics. Because our participants confirmed that they were committed to a goal of abstinence, they may have been less ambivalent, at least while hospitalized, thus accounting for the correlation.

High levels of dependence have been shown to be associated with greater craving (Kaplan et al., 1985; Rohsenow et al., 1992; Monti et al., 1993b; Rohsenow and Monti, 1999; Drummond and Phillips, 2002). Our participants did not report a difference in craving according to the severity of dependence perhaps because of social desirability bias. On the other hand, more severely dependent patients were not *turned off* by the idea of alcohol in an imaginary situation as long as there was no threat. In the threat condition, however, they reacted in the same way as the less dependent. Disulfiram treatment might thus be targeted to the most severely dependent patients to increase the aversion. There was no relationship between dependence and the physiological cue reactivity measures.

Several studies have shown negative affect to be associated with craving although not specifically measured by the PANAS (McCusker and Brown, 1991; Rohsenow et al., 1992; Baker et al., 2004; Fox et al., 2007). This study was no exception. In the threat condition or during alcohol exposure (in threat or neutral conditions), the relationship between negative affect and *craving now* was stronger than in the neutral condition during water exposure, indicating that negative affect modulated subjective craving.

Physiologically, as expected, participants with higher negative affect also had higher blood pressure. An interaction was found between diastolic blood pressure, threat, exposure, and negative affect. The linear relationship between negative affect and diastolic blood pressure was stronger in all of the conditions and exposures except during the alcohol exposure in the threat condition. Even though negative affect prevailed for those participants who thought they had taken disulfiram, blood pressure was not affected. Perhaps those participants were less perturbed and had a stronger sense of control over alcohol intake than in the neutral condition where they were less stable.

The present study has several limitations that need to be taken into consideration. One limit is that physiological cue reactivity is commonly viewed as multidetermined, that is, it could be activated by a number of different factors such as appetitive or aversive reactions (Glautier, 1999). Misinterpretation is possible, although it is reduced when the research questions are specific and the context well defined as in the present study. We might have included more various types of physiological measures that are less difficult to interpret than blood pressure such as skin conductance and salivation. Finally, there is the possibility of social desirability bias by our participants in order to convince the researchers or themselves of their capacity to cope with a craving. They were also enrolled in group cognitive behavioral therapy for relapse prevention during part of the study which may have altered their responses to cues.

Further research is necessary to understand the relationship between disulfiram and the physiological as well as the psychological responses to cues. Many questions remain unanswered regarding the effect of a potential disulfiram–ethanol reaction on decision-making, self-control, self-efficacy, commitment, attention, affect, and cognitive dissonance.

In summary, physiological measures continue to be of value precisely because they lie outside of conscious control, are salient, and replicable. The effect of the threat condition on diastolic blood pressure may reflect a psychophysiological mechanism involving reductions in negative affect and increases in a sense of control, attention, and commitment. Patients treated with disulfiram, if they want to avoid a disulfiram–ethanol reaction, need to remind themselves of the potential negative consequences that could arise if they consume. The effort involved in being vigilant, despite craving, may divert them from their inclination to approach alcohol and decrease negative affect. This could explain why disulfiram significantly reduces the number of drinking days with many patients. In addition, it provides evidence to reframe disulfiram's image from punitive to beneficial because of the relief it could provide from the effortful, internal conflict inherent in deciding whether or not to drink. This could help reverse the problem of treatment compliance, the principle obstacle to the success of disulfiram.

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Contributors

Authors Skinner, Aubin, and Berlin designed the study and Skinner and Aubin wrote the protocol. Author Skinner managed the literature searches, summaries of previous related work, and wrote the first draft of the manuscript. Authors Coudert and Berlin undertook the statistical analyses. Author Passeri assisted in the data collection and methodology of the protocol. Author Michel provided clinical research assistance. All authors contributed to and have approved the final manuscript.

Conflict of interest

Dr. Berlin is an employee of Université P. and M. Curie and Assistance Publique-Hôpitaux de Paris and reported having received consulting fees from Pfizer Ltd. and Sanofi-Aventis. Dr. Aubin has received sponsorship to attend scientific meetings, speaker honorariums, and consultancy fees from Pfizer, McNeil, Glaxo-SmithKline, Pierre-Fabre Sante, Sanofi-Aventis, and Merck-Lipha. All other authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.drugalcdep.2010.06.011.

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