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Alcohol-cue exposure decreases response inhibition towards alcohol-related stimuli in detoxified alcohol-dependent patients

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ABSTRACT

The induction of alcohol craving and the cognitive processing of alcohol-related stimuli in alcohol-dependent patients have been reported to compete with inhibitory control and contribute to alcohol relapse. The aim of the present study is to investigate whether the induction of a craving state, using an alcohol cue exposure paradigm, influences response inhibition towards both neutral stimuli and alcohol-related stimuli in alcohol-dependent patients. Thirty-one detoxified alcohol-dependent patients were exposed to either their preferred alcoholic beverage or to a glass of water. They then performed a modified stop signal task, which used alcohol-related words, neutral words and non-words, and a lexical decision as the Go response. The alcohol-cue exposure group reported significantly higher alcohol craving and showed higher percentages of commission errors towards alcohol-related words than the control group. All participants, but especially those of the alcohol-cue exposure group, showed also shorter reaction times when alcohol words were used as targets in go trials. The induction of alcohol craving in detoxified alcohol-dependent patients increases the motivational salience value of alcohol stimuli, leading them to automatically approach alcohol-related cues and therefore impairing response inhibition towards those stimuli.

1. Introduction

Numerous models of addictive disorders state that cues associated with alcohol consumption are automatically processed by alcohol abusers (Robinson and Berridge, 1993; Tiffany, 1990; Wiers et al., 2007). In heavy drinkers and alcoholic patients, it was observed that alcohol-related stimuli capture the attention (Johnsen et al., 1994; Jones et al., 2006; Noël et al., 2006). This alcohol-cue reactivity has been widely documented as predicting alcohol craving. Indeed, several authors suggest that the automatic processing of alcohol-related cues fosters the occurrence of craving episodes and thereby facilitates the compulsive consumption of alcohol (Field and Cox, 2008; Franken, 2003). For example, it has been demonstrated, in alcohol-dependent patients, that remembering a recent contextual situation associated with alcohol consumption or being exposed to alcohol odor is sufficient to trigger alcohol craving (Fox et al., 2007; Mason et al., 2008). Recent findings also indicate that the level of cue-reactivity for alcohol-related stimuli can predict relapse in treated alcohol-dependent patients (Garland et al., 2012). However, it is noteworthy that a number of other studies failed to show significant relationships between alcohol-related cue reactivity, craving and relapse (Tiffany and Conklin, 2000).

Beyond the incentive motivational properties of alcohol-related cues, it has been proposed that an impairment of inhibitory control, also reflected by a higher neural recruitment to perform inhibition tasks (Petit et al., 2014), contributes to alcohol relapse in addicted subjects (e.g. Fillmore, 2003). Actually, an increased salience of substance-related cues combined with a weak regulatory executive system have been suggested to explain the development and the maintenance of addictive behaviors (Goldstein and Volkow, 2002; Noël et al., 2010; Robinson and Berridge, 1993; Wiers et al., 2007). Indeed, high attentional biases for alcohol cues together with a reduced efficacy of control mechanisms have been documented in previous studies (e.g. Weafer and Fillmore, 2012). Such a reduced efficacy of control mechanisms might be preexistent to alcohol abuse and dependence (Finn, 2002) or might be a consequence of the chronic consumption of alcohol, as alcohol abuse has been reported to impair executive functions due to the neurotoxic effects of alcohol (Noël et al., 2001; also see Luijten et al., 2014, for a review of the neural deficits in alcohol and substance dependence).

Several theories also postulate that alcohol craving further weakens

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inhibitory performances, especially in alcohol-dependent patients attempting to stop drinking. According to the resource depletion model (Muraven et al., 1998; Muraven and Baumeister, 2000), trying to resist drinking when experiencing alcohol craving requires a high amount of cognitive resources, which decreases the cognitive resources available for other concurrent tasks like exerting self-control. To support this hypothesis, a reduced ability of self-control has been shown in social drinkers and in detoxified alcohol-dependent patients exposed to the odor of their favorite alcohol beverage (Gauggel et al., 2010; Muraven and Shmueli, 2006). Interestingly, this effect is much larger in the clinical sample than in social drinkers, suggesting that alcohol cue exposure leads to higher inhibitory deficits in alcoholic patients. In line with the resource depletion hypothesis, the elaborated intrusion theory (Kavanagh et al., 2005) postulates that craving episodes are characterized by elaborated cognitive imagery and affective reactions, which compete with concurrent cognitive tasks. More broadly, these theories are in agreement with the idea that emotional and motivational processes compete with attentional and effortful control, particularly when the emotional content is high, e.g. threatening stimuli (Pessoa, 2009). For example, the prior presentation of positive and negative emotional pictures has been shown to increase the stopping latencies to a subsequent neutral stimulus in a stop signal task (Verbruggen and De Houwer, 2007). Moreover, this interruption of active inhibition is more pronounced when high-arousing pictures are presented, irrespective of the valence of the picture. A common explanation of this interference effect is that the automatic capture of attention by high arousal stimuli reduces the available resources to exert active self-control (Schimmack, 2005; Verbruggen and De Houwer, 2007). In alcohol dependent patients, alcohol-related cues are highly arousing (Billieux et al., 2011) and should therefore interrupt ongoing cognitive activity and reduce the efficacy of inhibitory control (Mainz et al., 2012). This effect should be even more pronounced in alcohol-dependent patients with an already impaired inhibitory control (Fillmore, 2003; Noël et al., 2001), although it might be offset by a stronger neural recruitment to perform inhibition tasks (Luijten et al., 2014; Petit et al., 2014).

Whereas both the resource depletion model and the elaborated intrusion theory postulate that alcohol cues impair the performances in inhibition tasks involving any kind of stimuli, recent studies suggest that alcohol dependent patients specifically show an impairment of response inhibition when the target of the response is an alcohol-related cue. For example, Noël and colleagues (Noël and colleagues (2007)) have used a variant of the Go/No-go paradigm in which participants have to produce a motor response to a target while ignoring distracters (target and distracters are either alcohol-related words or neutral words). The results of the study show a higher number of commission errors (i.e., responding while a distracter is presented) in alcoholics relative to control participants when the distracter is an alcohol-related word. Data from studies in non-clinical heavy drinkers from the community however failed to replicate this result in a modified Go/No-go or a stop signal task (Kreusch et al., 2013; Nederkoorn et al., 2009). These inconsistent findings may be due to the studied sample (heavy drinkers vs. alcohol dependent patients) as a poor response inhibition towards alcohol-related cues may only characterize people with a clinical alcohol problem. Nevertheless, the deficit observed in alcohol-dependent patients relative to control participants (Noël et al., 2007) could also be due to a global impairment in cognitive functioning (Field and Cole, 2007; Field and Cox, 2008). Reduced inhibition performances in tasks requiring to refrain a response towards alcohol-related cues might be the consequence of high approach biases for such highly salient and motivational stimuli in alcohol-dependent patients. Furthermore, if this specific impairment in response inhibition towards alcohol cues is the consequence of an approach bias, experimental manipulations aimed at increasing alcohol craving, e.g. a priming dose of alcohol (see review in Field et al., 2010) or an alcohol-related context (Cox et al., 2003), might be expected to further increase such response inhibition impairment.

A few studies have tested whether a priming dose of alcohol (usually 0.6 g/kg) impacts upon response inhibition towards alcohol-related cues in several populations of non-dependent drinkers (Adams et al., 2013; Rose and Duka, 2008). Results tend to indicate that the administration of a priming dose of alcohol can influence, but only in some circumstances, response inhibition performances towards alcohol-related stimuli. It is noteworthy that these experiments were performed on non-dependent drinkers, who are expected to be less affected by alcohol cognitive biases and inhibition deficits (Robinson and Berridge, 2003). As it is difficult to use a priming dose of alcohol in detoxified alcohol-dependent patients for obvious ethical reasons, other experimental strategies should be considered to manipulate alcohol craving in such a population. One possibility is the use of an alcohol odor exposure paradigm (Gauggel et al., 2010). Furthermore, using the odor of alcohol rather than its administration removes the pharmacological effects of alcohol and should be closer to the conditions of relapse which is often triggered by contextual drinking cues (Rohsenow et al., 1991). Previous studies have also shown that alcohol odor exposition is able to increase both alcohol craving and attentional biases for alcohol cues in non-problem student drinkers (Ramirez et al., 2015a, 2015b).

The aim of the present study is to investigate whether alcohol cue-exposure affects the performances in an inhibition task involving alcohol-related cues. The rationale behind our study is that this procedure allows mimicking the capacity to resist alcohol consumption when confronted with alcohol-related cues (which is actually not the case when participants are primed with a dose of alcohol). Detoxified alcohol dependent patients were randomly divided into two groups: an alcohol-cue exposure and a control-cue exposure group. Similarly to Gauggel et al. (2010), participants were exposed to the odor of their preferred alcoholic beverage (or a glass of water for the control group). They then performed an adapted stop signal task using non-words, neutral words and alcohol-related words to test their capacity to refrain responding to alcohol cues (Zack et al., 2011). We expect the alcohol odor to increase alcohol craving, which was checked using craving visual analog scales. Based on the depletion resources model (Muraven and Baumeister, 2000) and the elaborated intrusion theory (Kavanagh et al., 2005), we hypothesize that participants exposed to the odor of alcohol will be impaired in their general inhibition performances (to both neutral and alcohol-related stimuli). Second, on the basis of previous studies showing that alcohol dependent patients are impaired in response inhibition towards alcohol cues (Noël et al., 2007), we expect weaker performances in alcohol dependent patients from both groups when trying to inhibit a response towards alcohol-related words relative to neutral words. Third, we hypothesize that alcohol odor exposure will specifically decrease the ability to inhibit a response for alcohol-related cues. We therefore expect that the alcohol odor exposure will more strongly impair response inhibition for alcohol words than for neutral words. Indeed, alcohol odor exposure is expected to increase alcohol craving and therefore to enhance approach biases for alcohol-related cues. In relation with this third hypothesis, we also expect a significant correlation between the levels of induced craving and the performances in response inhibition towards alcohol cues.

2. Method

2.1. Participants and procedure

Participants were alcohol-dependent patients screened in psychiatric hospitals against initial inclusion/exclusion criteria. Participants fulfilled DSM-IV diagnostic criteria for alcohol dependence (American Psychiatric Association, 1994) and had no history of other types of substance dependence (except tobacco). None of the participants displayed diagnosis of schizophrenia or schizophreniform disorders nor presented neurologic injury (head injury, coma, epilepsy,

Wernicke's encephalopathy) that might have altered their cognitive functioning. All participants have been detoxified and were abstinent for at least two weeks (mean days of abstinence=66.22; range 15–300). Most of them were also under psychological therapy for alcohol dependence. In addition, we selected only participants who did not receive any pharmacological treatment altering alcohol craving, such as acamprosate, aripiprazole, quetiapine, baclofen or nalmefene. Only neuroleptics, antidepressants and sleeping pills were allowed as psychotropic medication in order to be included in the study. Additionally, one participant was treated with disulfiram. If the participants met the selection criteria, their preferred alcoholic drink was recorded and they were informed that they would be randomly assigned to one of two groups (alcohol or water odor exposure). At that stage, they were already informed that the study might involve alcohol odor exposure such that they might immediately refuse participation with full knowledge of implications. Two patients refused participation and an additional patient asked to stop the testing at the time of alcohol odor exposure. The final sample included 31 alcohol-dependent patients (10 women; mean age=46.1 years; range 26–61 years).

The day of the experiment, participants were tested in a quiet room. They were given an information sheet and a written informed consent was obtained. The experimenters ensured that all participants understood the information note, such that they were able to provide an informed consent before inclusion in the study. A semi-structural anamnesis was then directed by the psychologist researcher (F.K.) to collect demographic data (age, education level) and alcohol-related information data (abstinence duration, alcoholism duration, number of previous detoxifications, and type of alcoholism). Then, the alcohol or water cue exposure and the stop signal task modified for alcohol were administered. The craving measure (VAS) was administered before and after cue exposure. Impulsivity traits (UPPS-P; Billieux et al., 2012), state-anxiety (STAI form Y; Spielberger, 1983) and depressive symptoms (BDI-II; Beck et al., 1996)) were assessed after the stop signal task and did not significantly differ among the two groups (see Table 1). No differences between groups were identified regarding the above mentioned questionnaires, which is of importance as some studies emphasized relationships between inhibitory control and impulsivity traits and negative affect states (Gay et al., 2008; Kaiser et al., 2003). Demographic data and alcoholism variables (abstinence and alcoholism duration; and number of previous detoxifications) were also collected and were not statistically different between the alcohol-cue exposure and the control-cue exposure groups (see Table 1). Moreover, Pearson Chi^2 tests revealed that the number of men/women (χ^2=1.37; p=0.24), the number of alcoholic patients of type 1/2 (Cloninger et al., 1996) (defined during the anamnesis) (χ^2=1.10; p=0.29) and the number of nonsmokers/smokers (χ^2=0.52; p=0.47) were not statistically different between the two groups. In view of the ethical implications of the present study (i.e. alcohol odor exposure in withdrawn alcohol dependent patients), a comprehensive debriefing was performed with each participant at the end of the experiment. The debriefing included an explanation of the experiment purpose and a psychoeducational session about inhibition deficits and attentional biases in alcohol dependence. Individualized contexts in which these biases usually occur were discussed and coping strategies were investigated for each participant. The experimenter ensured that the patient felt well before closing the interview. In addition, participants were offer the opportunity to contact again the experimenter or a member of the medical team of the hospital for a follow-up to further discuss the alcohol cue exposure experience. The study conformed to the principles of the Helsinky Declaration (1999) and was approved by the ethics committee of the hospital (ISOSL-Liège).

2.2. Alcohol or water cue exposure

A standard cue-exposure paradigm was employed (Gauggel et al., 2010; Monti et al., 1993). In the alcohol-cue exposure group, a glass filled with a small quantity of the participant's preferred alcoholic beverage (identified prior to the experiment in the screening procedure) was placed in front of their dominant hand. In the control-cue exposure group, participants were exposed to a glass filled with water. An audio recording delivered the instructions, which were exactly the same in the two groups. Participants were required to take the glass in their hand, to lift up under their noses and to smell the drink during 15 s. Then, they replaced the glass on the table and repeated the procedure ten times (total exposure time: 3′40). A voiceover guided the subjects during the procedure. The participants were asked to think about and monitor their temptation to drink. Moreover, guidelines insisted on the capacity that the participants had to resist and to control their urge to drink. Participants were not allowed to consume the drink (neither alcohol nor water). All participants were able to resist the urge to drink.

2.3. Measures

2.3.1. Craving for alcohol

Alcohol craving was assessed before and after the cue exposure procedure. It consisted of four individual 15 cm Visual Analog Scale items (VAS) from 0 (no craving) to 20 (severe craving) (Mason et al., 2008); adapted from Alcohol Craving Questionnaire (ACQ; Singleton et al., 1994). The four VAS were expectancy for positive reinforcement (*"Having a drink would make things just perfect"*), strength of craving (*"How strong is your craving to drink alcohol"*), intent (*"If I could drink alcohol now, I would drink it"*), and lack of control (*"It would be hard to turn down a drink right now"*). A global craving score was calculated as the average of the four items.

Table 1
Mean (standard deviation) for each demographic and psychological characteristics in the alcohol cue exposure group and the control-cue exposure group, t value of the student test comparison between groups and the associated probability.

	Alcohol-cue exposure group (n=17)	Control-cue exposure group (n=14)	t	*p*
Age	48.3 (9.7)	43.5 (9.8)	1.36	0.18
Educational level	11.6 (2.5)	11.3 (4)	0.19	0.84
BDI	16.1 (8.9)	19.1 (10.8)	−0.85	0.39
STAI-A	33.5 (11)	37.3 (11.2)	−0.95	0.35
STAI-B	50.2 (12.1)	51 (10)	−0.18	0.85
UPPS-Negative urgency	10.6 (2.6)	10.5 (3.4)	0.08	0.93
UPPS-Positive urgency	11.9 (1.8)	10.8 (3.1)	1.14	0.26
UPPS-Lack of premeditation	8.6 (2.8)	9.1 (2.6)	−0.57	0.57
UPPS-Lack of perseverance	8.4 (2.7)	9.3 (2.8)	−0.94	0.35
UPPS-Sensation seeking	11.6 (3.1)	10.3 (3.2)	1.20	0.24
Abstinence duration (days)	62 (47.2)	71.3 (75)	−0.42	0.67
Alcoholism duration (years)	16.5 (13)	18.2 (11.4)	−0.39	0.69
Number of previous detoxifications	3.6 (3.6)	3.6 (3.9)	0.05	0.95

2.3.2. Stop signal task

The modified stop signal task was adapted from the classical stop signal paradigm (Logan, 1994; Logan et al., 1997). The task consisted in a lexical decision in which the participants had to determine if the visual target presented in the center of the screen was a non-word or a word. Words were either alcohol-related words (32, e.g.,"pub") or neutral words (32, e.g.,"house"). Stimulus category was matched on length and familiarity. All words were taken from a previous study (Noël et al., 2007). In the non-word category, we found pronounceable pseudo-words (64, e.g.,"typar") matched to words on length and frequency of occurrence of bigrams and trigrams in print (www.lexique.org). Before starting the test phase, participants were trained during two blocks using only neutral words (one block of 20 trials of classification only and one block of 20 trials in which 5 stop trials were inserted). Four test blocks of 64 trials were then administered. Participants had to respond as quickly and accurately as possible upon the occurrence of the target by pressing with their index finger the "C" key on the keyboard when a word appeared on the screen or the "N" key when this was a non-word (Go trials). In 25% of the trials (16 trials per block), a computer-generated sound (1000 Hz, 100 ms) was emitted instructing the participant to withhold his response (Stop trials). Among the Stop trials, 8 involved pseudo-words, 4 involved alcohol-related words and 4 involved neutral words. Among the Go trials, 24 involved pseudo-words, 12 involved alcohol-related words and 12 involved neutral words. Since there were four blocks, each word was presented twice during the procedure (Fig. 1). The order of the blocks was counterbalanced across participants and conditions (alcohol or water cue exposure). Instructions were reminded on the screen between each block. Participants also received a feedback at the end of each block with their mean reaction time for the block in comparison to the training block. This reminded participants that they had to respond as quickly as possible. This was done to reduce the tendency of the participants to slow down their responses to wait for the stop signal. Moreover, they were instructed not to delay responding in anticipation of the stop signal but to try to withhold responding if they heard the stop signal. After the presentation of a fixation point (500 ms), words remained on the screen until subjects responded, or until 1250 ms elapsed. An inter-stimulus blank screen (ISI, 1000 ms) was displayed between each trial. The Stop Signal Delay (SSD) varied between 200, 250, 300 and 350 ms and the order of trials for each delay and words type was randomly defined. The entire task lasted about 10 min.

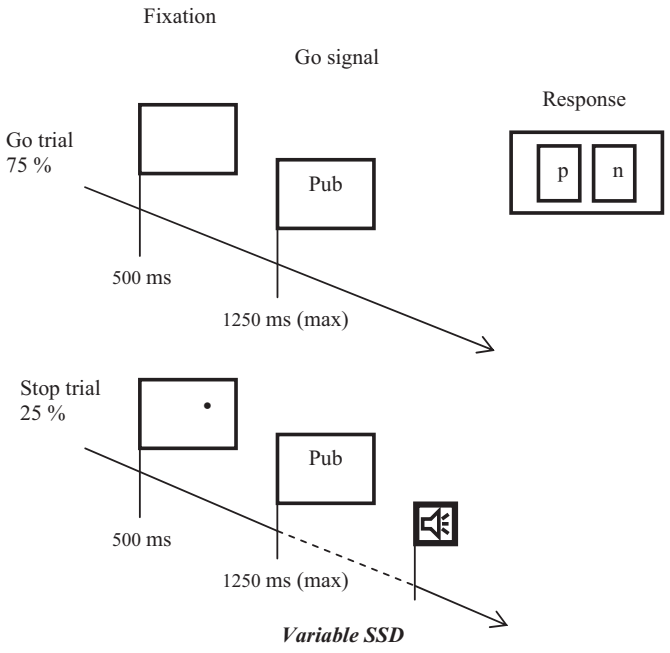

Fig. 1. Stop signal paradigm. In "go" trials (75%) participants responded to the go signal by determining if the visual target presented in the center of the screen was a non-word or a word. Words presented on the screen can be alcohol-related (e.g. pub) or neutral (e.g. house). In the "stop" trials (25%) participants had to withhold the response when they heard a sound (1000 Hz, 100 ms). In both trials, the go signal occurred 500 ms after the fixation point. The go signal disappeared at the time of button press or when 1250 ms had elapsed. In stop trials, the stop signal occurred following a variable stop signal delay (SSD) of 200, 250, 300 or 350 ms.

Two variables were recorded. First, the mean reaction time (RT) in correct Go trials for each participant and for each type of words (neutral words and alcohol-related words) was collected. Secondly, the percentage of errors in Stop trials was calculated for each participant and for each type of words. The Stop Signal Reaction Time proposed by the horse-race model (SSRT (Logan, 1994)) was not computed because there were too few observations to reliably estimate the latency of the stop process (Verbruggen and Logan, 2009).

2.4. Statistical analysis

A composite score of craving difference was calculated as the average of the four items of the VAS before the cue exposure subtracted from the average of the four items after the cue exposure. As the variable was not normally distributed according to the Kolmogorov–Smirnov test, we used a non-parametric Mann–Whitney *U*-test to test whether craving increase was different between the exposure groups (alcohol-cue or control-cue). Mann–Whitney *U*-tests were also used to test for differences on each craving item.

RT in Go trials (ms) and inhibition errors in Stop trials (%) were analyzed with repeated measures ANOVAs with group (alcohol-cue exposure and neutral cue exposure) as a between subject factor and word type (neutral words or alcohol-related words; following Zack et al., 2011) as a within participant factor. To limit the impact of late responses, every go trial that was longer than the mean for go trials plus 2.5 standard deviations was deleted on a subject-by-subject and word type basis (Billieux et al., 2010; Verbruggen and De Houwer, 2007). Effect sizes were reported as partial eta squared (η^2). Newman-Keuls post hoc tests were computed to clarify mean differences.

In order to test for the relationships between alcohol craving and the performances on the stop signal task, Spearman correlations were computed between the averages of the four items of craving (global score of craving) after the exposure procedure and the RT on Go trials and the percentage of errors for alcohol-related words and for neutral words in both groups separately. Statistical analyses were computed with Statistica (version 10) for Windows.

3. Results

3.1. Manipulation check of alcohol craving

Table 2 shows the mean scores for each craving item and for the global craving score before and after cue exposure in both groups. The Mann–Whitney *U*-test computed on the composite scores of craving differences revealed that participants in the alcohol-cue exposure group showed significantly higher increase in craving scores after the cue exposure (mean difference =1.42, SD =3.7) compared to the control-cue exposure group (mean difference=−0.47, SD=0.77) (Z=2.64, p=0.008). The Mann–Whitney *U*-tests computed on each craving item emphasized a significantly higher increase specifically for the strength of alcohol craving in the alcohol-cue exposure group compared to the control-cue group (Z=2.34, p=0.02), while no statistically significant differences between the two groups were observed for the items relative to positive reinforcement (Z=0.81, p=0.41), intention to drink (Z=0.74, p=0.45), or lack of control (Z=0.49, p=0.62). These results confirm that the experimental manipulation was successful in increasing the global average score of alcohol craving.

Table 2
Mean (standard deviation) for the scores on the four items of craving and the global score of craving before and after exposure in both the alcohol and water cue exposure groups.

Alcohol-cue group	**Before alcohol exposure Mean (SD)**	**After alcohol exposure Mean (SD)**
Global craving score	2.94 (4.56)	4.37 (5.99)
Positive reinforcement	2.65 (4.33)	2.65 (4.95)
Strength of craving	3.76 (5.37)	5.41 (6.74)
Intent	2.53 (5.35)	4.47 (7.53)
Lack of control	2.82 (6.45)	4.94 (6.89)
Control-cue group	**Before water exposure Mean (SD)**	**After water exposure Mean (SD)**
Global craving score	2.87 (4.01)	2.39 (3.93)
Positive reinforcement	3.04 (5.71)	2.18 (5.47)
Strength of craving	4.57 (4.90)	3.46 (4.63)
Intent	1.96 (5.37)	1.93 (5.37)
Lack of control	1.89 (4.46)	2.00 (4.58)

3.2. Stop signal task performances

The ANOVA performed on mean RT in Go trials revealed a significant main effect of word types ($F(1,29)=4.80$, $\eta^2=0.14$, $p=0.037$) indicating faster responses for alcohol-related words compared to neutral words. There were no significant main effect for the experimental group ($F(1,29)=2.11$, $\eta^2=0.07$, $p=0.16$) nor for the interaction between the two factors ($F(1,29)=1.22$, $\eta^2=0.04$, $p=0.27$) (Fig. 2). The Newman Keuls post-hoc test revealed a significantly shorter mean RT for alcohol-related words compared to the neutral words in the alcohol-cue exposure group ($p=0.03$) but not in the control-cue exposure group ($p=0.44$) (Table 3).

The ANOVA performed on the percentage errors in Stop trials revealed no significant main effect for word type ($F(1,29)=0.02$, $\eta^2=0.00$, $p=0.90$) and for the experimental group ($F(1,29)=0.68$, $\eta^2=0.02$, $p=0.42$). However, there was a statistically significant interaction between these two factors ($F(1,29)=8.10$, $\eta^2=0.22$, $p=0.008$) (Fig. 2). The Newman Keuls post-hoc test revealed a significantly higher percentage of errors for alcohol-related words compared to neutral words in the alcohol-cue exposure group ($p=0.04$).

Table 3
Means, standard deviations and ranges for reaction times (RT) in Go trials (ms) and inhibition errors in Stop trials for each type of words and non-words in the alcohol-cue exposure group and the control-cue exposure group.

	Alcohol-cue exposure group (n=17)			**Control-cue exposure group (n=14)**		
	Mean	**SD**	**Range**	**Mean**	**SD**	**Range**
RT alcohol	776	86	609–932	834	112	620–973
RT neutral	794	85	634–955	840	118	627–1001
RT non-words	882	86	676–1026	864	104	655–1013
Inhibit alcohol (%)	33	17	6–56	22	16	0–56
Inhibit neutral (%)	27	24	0–75	27	21	0–69
Inhibit non-words (%)	20	16	6–56	21	15	0–47

Table 4
Spearman correlations between the global score of craving and the reaction times (RT) and percentages of errors for alcohol and neutral words in the alcohol-cue exposure group and the control-cue exposure group.

	Alcohol-cue exposure group (n=17)		Control-cue exposure group (n=14)	
	r	p	r	p
RT alcohol	−0.49	0.044	0.16	0.59
RT neutral	−0.36	0.15	0.20	0.48
Inhibit alcohol (%)	0.61	0.009	0.36	0.21
Inhibit neutral (%)	0.57	0.016	0.43	0.13

3.3. Correlations between alcohol craving and stop signal task performances

Table 4 shows the correlations between the global score of craving

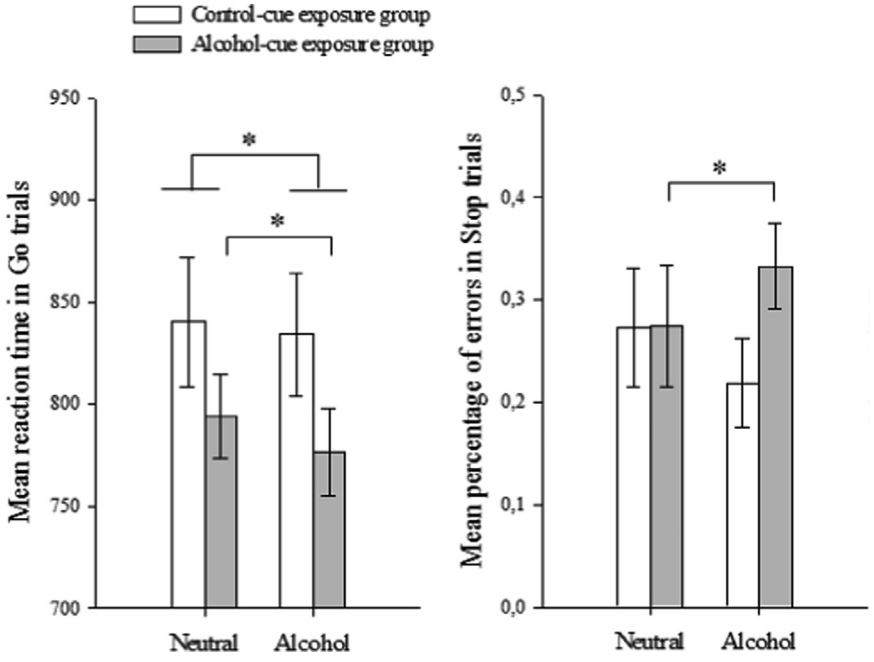

Fig. 2. Mean reaction time (SEM) in Go trials (left) and mean percentage (SEM) of errors in Stop trials (right) in the alcohol-cue exposure group and the control-cue exposure group for neutral words and alcohol-related words. *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$.

after cue exposure and the stop signal performances in both groups. In the alcohol-cue exposure group, there was a significant negative correlation between the craving score and the reaction time for alcohol-related words. Participants with higher craving scores responded faster to alcohol-related words in go trials. Positive and statistically significant correlations were also observed in the alcohol-cue exposure group between the score of craving and the mean percentages of errors for both alcohol-related words and neutral words.

In the control-cue exposure group, none of the correlations were statistically significant, either for reaction times in go trials or for percentages of errors in stop trials.

4. Discussion

This is the first study in detoxified alcohol dependent patients testing the impact of alcohol cue exposure on prepotent response inhibition towards alcohol-related cues. This experiment aimed to model an alcohol relapse context by investigating how the exposure to the smell of alcohol can increase alcohol craving and impair subsequent inhibitory control towards both alcohol-related stimuli and neutral stimuli. The manipulation check indicates that the alcohol-cue exposure effectively increased alcohol craving. The results of the current study first show that the alcohol dependent patients exposed to an alcohol odor showed weaker inhibitory control towards alcohol-related cues than patients that were not exposed to alcohol odor, as reflected by a higher percentage of commission errors in the stop signal task for alcohol-related words compared to neutral words. Furthermore there was a significant correlation between the levels of alcohol craving and the impairment of inhibitory control.

As only participants exposed to alcohol cues displayed higher rates of errors for alcohol-related words compared to neutral words, the results of the present study are consistent with our third hypothesis which stated that alcohol odor exposure would specifically decrease the ability to inhibit a response for alcohol-related cues. We further suggest that this effect is due to an increased approach bias for alcohol cues induced by the enhanced state of alcohol craving after the alcohol odor exposure. Two observations support such an idea. First, the higher rates of errors for alcohol-related words are combined with faster reaction times for alcohol-related cues. Second, in the alcohol-cue exposure group, there were significant correlations between the levels of alcohol craving and both the number of commission errors in stop trials and the reaction times for alcohol-related words in go trials. In a previous study, a strong desire for alcohol was also correlated with faster reaction times for alcohol-related stimuli in alcohol dependent young women, which indicates that alcoholics experiencing craving respond faster to alcohol-related stimuli (Tapert et al., 2004).

According to the results of Noël et al. (2007), we hypothesized that alcohol dependent patients from both groups would show a higher percentage of errors for alcohol-related words than for neutral words. This would have been indicative of a poor response inhibition towards alcohol-related cues, probably related to an approach bias for those cues. Although both groups of alcohol dependent patients showed faster reaction times when the target was an alcohol word, suggestive of an approach bias for alcohol cues, lower inhibitory performances for alcohol related-cues (a higher percentage of commission error) were only observed in the alcohol cue exposure group. Furthermore, there was a significant correlation between the levels of alcohol craving and the percentages of commission errors for alcohol words only in the alcohol-cue exposure group. It is not surprising that the ability to inhibit a response towards a specific class of stimuli is related to an internal state such as the level of alcohol craving. This idea is included in several theories of motivation and addiction. For example, Pessoa (2009) argued that the motivational state directly interacts with executive functions to enhance or impair behavioral performances according to the circumstances. The incentive-salience theory of addiction also states that the motivational value of a specific reward stimulus may be dynamically increased in a targeted fashion by relevant physiological states involving mesolimbic activation (Berridge, 2007; Robinson and Berridge, 2003). For example, the cue-triggered motivational processes for caloric foods can be either increased or decreased by physiological hunger-satiety states. Such a motivational state would determine brain calculation of the hedonic value of particular sensory goals (Zhang et al., 2012). Following this assumption, the induction of a craving state by alcohol odor exposure in detoxified alcohol dependent patients could increase the motivational salience value of alcohol-related stimuli. An automatic tendency to approach alcohol-related cue and a difficulty to refrain this response for alcohol would then occur based on such a physiological state. The results of the present study suggest that inhibition deficits for alcohol-related words may not be permanent in detoxified alcohol-dependent patients, as it was proposed by the second hypothesis, but might be dependent upon the context-dependent induction of a specific motivational state. In agreement with this idea, Ramirez et al. (2015a) recently showed in college-student drinkers that alcohol-cue exposure increased both alcohol craving and attentional biases for alcohol stimuli. Another study recently demonstrated a significant relationship between alcohol craving and attentional biases for alcohol cues in abstinent alcoholics (Field et al., 2013). Future studies should therefore take into account the internal motivational state when investigating cognitive biases for alcohol-related cues in alcohol-dependent patients. The alcohol odor exposure paradigm is one way to control the motivational state for alcohol, while studying the interaction with other factors, like stress for example (Zack et al., 2011). It is noteworthy, however, that the discrepancies with previous studies, which showed poor response inhibition towards alcohol-related cues in all alcohol dependent patients without any specific procedure to induce alcohol craving, might be due to the features of the present sample of alcohol dependent patients. Indeed, the participants in the present study were abstinent alcohol dependent patients under treatment (mean of 66 days of abstinence) with low basal levels of alcohol craving (mean of 2.9 on a 20-point scale) before alcohol cue exposure. It is likely that alcohol dependent patients with higher levels of basal alcohol craving would show similar effects without alcohol cue exposure. Finally, it remains possible that the reduced performances in our participants were offset by a higher neuronal recruitment during the inhibition task as suggested by recent event-related potential and functional magnetic resonance imaging studies (Luijten et al., 2014; Petit et al., 2014).

Based on the depletion resources model (Muraven et al., 1998; Muraven and Baumeister, 2000) and the elaborated intrusion theory (Kavanagh et al., 2005), we also hypothesized that participants exposed to the odor of alcohol would exhibit less available self-control for the execution of an inhibition response. We therefore expected impaired general capacity of inhibition evidenced by a higher percentage of commission errors for both neutral and alcohol-related words in the alcohol cue exposure group. However, inconsistent with several studies, the mean percentage of commission errors for neutral words was not affected by alcohol odor exposure (Gauggel et al., 2010; Muraven and Shmueli, 2006). Similar results were obtained by Mainz et al. (2012), who did not show significant differences in inhibition performances between patients exposed to the odor of alcohol and patients exposed to a control odor. These authors suggested two possible explanations for their results. First, it is possible that alcohol craving has no influence on general inhibition performances, in contradiction to the claims of the depletion resources model and the elaborated intrusion theory. On the other hand, it is possible that alcohol odor exposure in a controlled laboratory setting and in patients under treatment does not induce a sufficiently high alcohol craving to have a significant impact on general inhibition performances. In support of this hypothesis, the present results show that alcohol craving was significantly correlated with the percentage of errors for both alcohol-related and neutral words in the alcohol-cue exposure

group. This suggests that general inhibition performances (for neutral words) are to some extent related to the levels of craving even if they are not significantly increased by alcohol-cue exposure. Alcohol-cue exposure in a more natural environment as tested in previous studies (e.g. Papachristou et al., 2013) might induce higher levels of craving and therefore significantly impact general inhibitions performances. It is noteworthy that the increase in alcohol craving in the present study was of a moderate magnitude (4.4 of 20) relative to other studies that have reported general impairments in inhibition performances (for example 15.6 of 32 in the study from Gauggel et al. (2010)). It is therefore possible that the increased alcohol craving in the present study was high enough to potentiate alcohol approach biases and therefore to impair the inhibition of a response involving highly salient alcohol stimuli, but not to affect general inhibitory processes.

Several limitations of the present study remain to be addressed in future researches. A first limitation is the absence of a non alcohol-dependent control group. While the present study failed to show a general inhibition deficit for neutral stimuli after exposure to the odor of alcohol, such an impairment might have been observed if the performances of the alcohol-dependent patients had been compared with a group of non-problem drinkers. This might be tested in further studies investigating the effect of alcohol odor exposure in participants with different levels of alcohol consumption. Although it is likely that the reported effects of the induction of alcohol craving are specific to alcohol dependent patients, it would be interesting to compare low or heavy social alcohol drinkers. Secondly, as alcohol craving is a core element of alcohol dependence and relapse, it would be interesting to add some physiological responses to the alcohol cue exposure (e.g., salivation, heart rate variability) to independently confirm the effects of the alcohol odor exposure on craving.

Future studies could further investigate the relationship between craving for alcohol, inhibition capacity towards alcohol-related cues and relapse by using a paradigm of alcohol odor exposure in alcohol-dependent patients. A better understanding of the interactions between the motivational state and the automatic processes of alcohol cue in relapse might be particularly interesting at the clinical level. As new therapeutic approaches have recently been developed involving the retraining of self-control functions and the reduction of automatic responses towards alcohol-related cues (Houben et al., 2011; Wiers et al., 2010), these techniques should also take into account the internal motivational state of consumers, i.e. alcohol craving, as it could impact the reported effects.

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