

Research report

Reduced processing of alcohol cues predicts abstinence in recently detoxified alcoholic patients in a three-month follow up period: An ERP study



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HIGHLIGHTS

- Early alcohol abstiners show different electrophysiological features compared to relapsers.
- Abstainers show decreased P3 amplitude for alcohol compared to non-alcohol related pictures.
- The decreased P3 could express a reduction of the motivational significance of alcohol pictures.
- The difference in amplitude between alcohol and non-alcohol cues is the best predictor of relapse.
- Reaction times do not allow differentiating between abstainers and relapsers.

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ABSTRACT

One of the major challenges in alcohol dependence is relapse prevention, as rates of relapse following detoxification are high. Drug-related motivational processes may represent key mechanisms in alcoholic relapse. In the present study, event-related potentials (ERPs) were recorded during a visual oddball task administered to 29 controls (11 females) and 39 patients (9 females). Deviant stimuli were related or unrelated to alcohol. For patients, the task was administered following a 3-week detoxification course. Of these, 19 relapsed during the three months follow-up period. The P3, an ERP component associated with activation of arousal systems in the brain and motivational engagement, was examined with the aim to link the fluctuation of its amplitude in response to alcohol versus non-alcohol cues to the observed relapse rate. Results showed that compared to relapsers, abstainers presented with a decreased P3 amplitude for alcohol related compared to non-alcohol related pictures ($p = .009$). Microstate analysis and sLORETA topography showed that activation for both types of deviant cues in abstainers originated from the inferior and medial temporal gyrus and the uncus, regions implicated in detection of target stimuli in oddball tasks and of biologically relevant stimuli. Through hierarchical regression, it was found that the P3 amplitude difference between alcohol and non-alcohol related cues was the best predictor of relapse vulnerability ($p = .013$). Therefore, it seems that a devaluation of the motivational significance of stimuli related to alcohol, measurable through electrophysiology, could protect from a relapse within three months following detoxification in alcohol-dependent patients.

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1. Introduction

Although the first step in the treatment of alcohol dependence (detoxification) is straightforward, a major challenge is the prevention of relapse. Typically, around 50% of patients drop out of treatment and resume alcohol use within three months of the end of detoxification [1]. From a clinical point of view, it is essential to identify factors influencing treatment outcome and relapse that

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may be modulated by therapeutic intervention [2]. A potential key element is that of attentional bias [3,4]. Theoretical accounts underlying attentional bias rely on the incentive sensitization theory of Robinson and Berridge [5]. The theory assumes that drugs of abuse can induce neuroadaptations in incentive motivation and reward systems, causing these systems to become hypersensitive to both drugs and drug-related stimuli. The incentive salience attributed to drug-related stimuli is responsible for the attention to be automatically oriented toward these stimuli: this is called an attentional bias. Many studies have indeed demonstrated the presence of a cognitive processing bias for alcohol-related stimuli in alcohol dependence. Historically, authors used behavioral assessment techniques through modified neuropsychological tasks (such as Stroop Task or Dot Probe Detection Task) in which they showed altered reaction times in response to alcohol-related stimuli [6–12] or difficulty shifting attention away from them [13–17] in alcohol abusers. Today, these behavioral techniques are used as training instruments dedicated to overcoming these biases. This relatively new area of investigation has yielded promising results (see [18] for a review) and is very relevant given that the phenomenon of cue reactivity is believed to play a central role in the maintenance of drug consumption disorders [19,20] and relapse [3,21–25]. Indeed, attentional biases are believed to elicit conditioned responses such as drug craving and consumption (e.g. [26]). Moreover, Robinson and Berridge proposed that an important characteristic of the phenomenon of sensitization underlying attentional bias is that it survives long after taking the drug has stopped [5]. It has been shown in animal, as well as human studies, that sensitization could still be present years after the subject has stopped using drugs [27,28]. This characteristic of conditioned associations and attentional bias could explain the phenomenon of relapse after a long period of abstinence (e.g. [3,29]).

Many researchers have examined the association between bias toward alcohol-related stimuli and craving (e.g. [30]). However, very few have evaluated the critical clinical question of the extent to which the presence (or absence) of attentional bias can predict the likelihood of relapse (or remaining abstinent) in people trying to abstain. To our knowledge, only two studies based on behavioral investigations of attentional bias related a link between their presence and alcohol relapse [11,31]. Concerning dependencies on other substances, a link between bias and treatment outcomes has been found in some studies [32–34], but the predictive value could not be confirmed in the same amount of work [34–36]. New developments in cognitive neuroscience provide an opportunity to investigate additional aspects of relapse predictors as processing bias in a way that go beyond observable behavioral measures [37,38]. Neurosciences techniques, such as event-related potentials (ERPs) of the electroencephalogram (EEG), have shown their potential to highlight some brain abnormalities not detectable based on behavioral data only (e.g. [39]). These techniques are able to reveal the neural underpinnings of the cognitive configuration and processing response to stimuli linked to substance use [40,41]. The use of the ERP technique has objectified that the cerebral activity recorded during processing of alcohol-related pictures is heightened in alcoholics patients compared to controls. Specifically, researchers have shown that the P300 component (also called P3) in response to alcohol-related stimuli is heightened in alcohol abusers compared to controls [42,43]. The P3 component is a large, positive deflection of the ERP, arising about 300–800 ms after stimulus presentation, typically maximal at the medial central and parietal electrode sites (e.g. [44,45]). It is believed to reflect the mental processes underlying the deployment of attentional resources to task-relevant stimuli (e.g. [44,46]). Additionally, research has repeatedly shown that the amplitude of the P3 is enhanced in response to stimuli that are necessary for survival of the individual and that tend to automatically attract attention,

i.e., stimuli that signal threat or danger or that signal the availability of sex and food or reward (for a review, see [47]). Increased P3 amplitude has thus been correlated with motivational engagement, motivated attention, and the activation of arousal systems in the brain [48,49]. Therefore, the P3 enhancement in alcohol abusers compared to controls could indicate high “motivational” value of alcohol-related stimuli and reflect the allocation of attentional resources to stimuli corresponding to alcohol-dependent subjects’ motivational states. Such P3 amplitude enhancement in response to motivationally relevant stimuli are classical in substance use disorders (see [50] for a review), as increased P3 has (as compared to neutral stimuli) also been shown for instance for food targets in obese individuals [51] as well as for drug cues in opiate addiction [52]. However, no study to date has investigated whether an increased (or reduced) P3 found in substance-dependent subjects may be a predictor of relapse (or abstinence). The main goal of this study is to examine whether an electrophysiological index of alcohol cue reactivity, the modulation of the amplitude of the P3 component, is predictive of alcohol relapse or abstinence in alcohol-dependent patients three months after the end of a detoxification course. Specifically, we hypothesized that a decreased reactivity to alcohol cues, indexed by a lower P3 in response to these cues measured at the end of the detoxification cure would reflect a decrease in motivation for alcohol and would therefore be associated with subsequent alcohol abstinence in the next three months follow-up period. The scalp topography of the P3 elicited by both alcohol and non-alcohol related cues in abstainers was further assessed by means of the brain electrical microstates technique and its cortical sources were evaluated by standardized low resolution brain electromagnetic tomography (sLORETA).

2. Methods and materials

2.1. Participants

Inpatients diagnosed with alcohol dependence according to Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [53] criteria were recruited as volunteers during the third week of their treatment from the Alcohol Detoxification Program of the Institute of Psychiatry, Brugmann Hospital (Brussels, Belgium). Healthy controls, gender- and age-matched to alcohol-dependent patients were also recruited. Healthy individuals whose alcohol consumption exceeded 14 standard drinks/week (7 for women) or 4 drinks/day (3 for women) were excluded because their consumption pattern placed them ‘at risk’ for alcohol-related problems according to the National Institute on Alcohol Abuse and Alcoholism [54]. Exclusion criteria for both groups included: current DSM-IV diagnosis of axis I disorders (other than alcohol dependence for patients); significant previous or current medical problems; visual impairment; head injury affecting the central nervous system; and current medical treatment that could interfere and/or reduce the cognitive ability to perform the task. In our study, patients ($n = 39$, 11 females) were 20–68 years-old, and controls ($n = 29$, 9 females) were 24–72 years old. Control participants abstained from alcohol consumption for at least 24 h before testing. Participants in the patient group were tested prior to discharge, approximately 3 weeks after admission in detoxification. These three weeks of detoxification typically takes place as follows. Patients are accommodated in single rooms. Exits are prohibited during the first week and limited to the garden of the hospital. They are then limited to the surrounding park in the second week. Visits are allowed every day. The purpose of the detoxification course is physical and psychological alcohol withdrawal. Psychiatric, medical, family, and social assessments are obtained. Benzodiazepines (Diazepam®) are given in regressive doses. An anti-craving

medication is also proposed. The patient is supplemented with B vitamins and receives 1.5 l of juice per day during the first week.

2.2. Oddball task

The task consisted of a visual oddball paradigm in which participants were confronted with one regularly repeated standard stimulus and deviant target ones. Deviant stimuli consisted of pictures of a man drinking different beverages. Three out of these beverages were alcohol-related (A) and three others were not (NA). Alcohol related beverages were beer, whiskey and wine, and non-alcohol ones were Sprite, Coca-Cola and Fanta. The frequent stimulus was the same man drinking water. These pictures were repeated in four blocks. In each block, 144 stimuli were presented: the frequent stimulus appeared 114 times (79%), and the three deviant pictures for each condition (A and NA) each appeared five times (21%), for a total of 15 deviant A and 15 deviant NA stimuli in each block (i.e. and a total of 60 deviant of each category (A and NA) for the whole task). Each picture was presented for 800 ms. A black screen was displayed between pictures for a random duration of 600–1000 ms (see Fig. 1). The participants had 1200 ms to answer from the onset of the stimulus. They were instructed to indicate as quickly as possible (but not at the cost of accuracy) the occurrence of any deviant stimulus with a right finger tap. The response times and percentages of correct answers were recorded.

2.3. Procedure

Informed written consent was first obtained from each participant. They received an explanation of the nature and duration of the study and were informed of what was expected from them. They were told that they were free to participate or not, as well as leave the study at any time without having to justify their decision and, for patients, without this influencing in any way the medical care they receive. Patients agreed to submit details and contact information of their regular doctor and a close relative in order to be contacted again in the months following hospitalization. The experiment then started. Participants were first instructed to rate their urge to drink alcohol at the commencement of the study using a 100-mm Visual Analog Scale [55]. Next, participants sat in a darkened room on a chair approximately 1 m from a computer screen. The oddball task was administered after a practice block. Following the task, participants were asked to assess their craving scale and complete the following questionnaires: the Alcohol Use Disorder Identification Test (AUDIT, Saunders, [56]); the State-Trait Anxiety Inventory (STAI [57]); the Beck Depression Inventory (BDI [58]); and a questionnaire about alcohol and other drug consumption (history, characteristics and degree of family history of alcoholism [FHA], if any). The local ethics committee at the Brugmann Hospital ("Comité d'Éthique Hospitalier OM 026") approved our study.

2.4. Relapse evaluation

For alcohol-dependent individuals, a three-month follow-up was conducted to gather information about drinking behavior once the detoxification program had ceased. Relapse was defined as the reinstallation of a state of alcohol dependence according to DSM-IV criteria, and treated as a binary outcome variable [59,60]. According to Wiers et al. [59], unique re-consumption that did not exceed three days and after which the patient recovered control without further negative consequences, was not defined as proper relapse. Information was obtained by telephone, supplied directly by patients and confirmed by family members, or the patient's regular doctor.

2.5. EEG recording and analysis

During the testing phase, EEG activity was recorded with 32 electrodes mounted on a Quik-Cap and placed in standard (based on the 10–20 system) and intermediate positions [61]. Recordings were made with a linked mastoid physical reference but re-referenced offline using a common average, based on the principle that the integral surface of the potential on a surface that completely encompasses all the active sources should be zero [62]. The EEG was amplified with battery-operated ANT[®] amplifiers with a gain of 30,000 and a bandpass of 0.01–100 Hz. The impedance of all electrodes was maintained below 5 k Ω . EEG was recorded continuously at a sampling rate of 1024 Hz with ANT Eeprobe software. 98.19% of the participants' responses were correct (i.e., a finger tap given for deviant stimuli). Only correct answers were considered for analysis of reaction times and EEG activity. The trials contaminated by eye movements or muscular artifacts were manually eliminated offline. Epochs starting 200 ms before the onset of the stimulus and lasting for 800 ms were created. The data were filtered with a 30 Hz lowpass filter. To compute averages of P3 to target stimuli for each subject, two parameters were coded for each stimulus: (i) the type of stimulus (A; NA); and (ii) the type of response (key press for deviant stimulus, no key press for frequent stimulus). A general time window was first determined globally for the identification of the component of interest (the P3) based on the literature (e.g. [63,64]). The measurement window was then tailored for each participant: for each subject, the P3 was investigated by gathering individual values of maximum peak amplitudes and peak latencies for each stimulus type in a 350–650 ms time range. These data were obtained from the following electrodes: Pz, P3, P4, POz, Cz, and Fz.

2.6. ERP statistical analysis

We analyzed ERP and behavioral data using analysis of variance (ANOVA) and covariance (ANCOVA). Our aims were to investigate whether the group belonging (Patients vs. Controls or Relapsers vs. Non-relapsers) affected behavioral and electrophysiological responses to both stimuli types. To investigate whether the group variable affected reaction times in response to both stimuli types, a Type (A vs. NA) vs. Group (Relapsers, Non-Relapsers, and Controls), ANOVA was performed on reaction times for correct answers. To investigate whether the group variable affects the P3 parameters in response to both stimuli types, $2 \times 3 \times 6$ ANOVAs were performed separately for P3 latencies and amplitudes, imputing type of stimulus (A vs. NA) and electrodes (Pz, P3, P4, CP1, CP2 and POz) as within-subject variables and group (Relapsers, Non-Relapsers, and Controls) as the between-subject variable. Simple effects were explored and interaction sources were systematically examined using Student's independent or paired *t*-tests. Moreover, analyses were systematically redone to control for a possible influence of demographic variables that differed between groups and that are known to either influence cue reactivity and/or P3 component parameters i.e., family history of alcoholism [65,66], anti-craving medication (e.g. [67,68]), tobacco smoking (e.g. [69]) and education level. Greenhouse–Geisser correction was applied to all ANOVAs and ANCOVAs when necessary. Hierarchical multiple regression analysis was used to examine predictors of abstinence within the follow-up period. All analyses were conducted with SPSS 17.02H, with the level of significance at 0.05.

2.7. Microstate analysis

In order to explore brain sources of the ERP effects observed, scalp ERP data were analyzed with the microstate analysis method introduced by Lehman et al. [70]. Briefly, it consists of calculating the global field power (GFP) corresponding to the standard

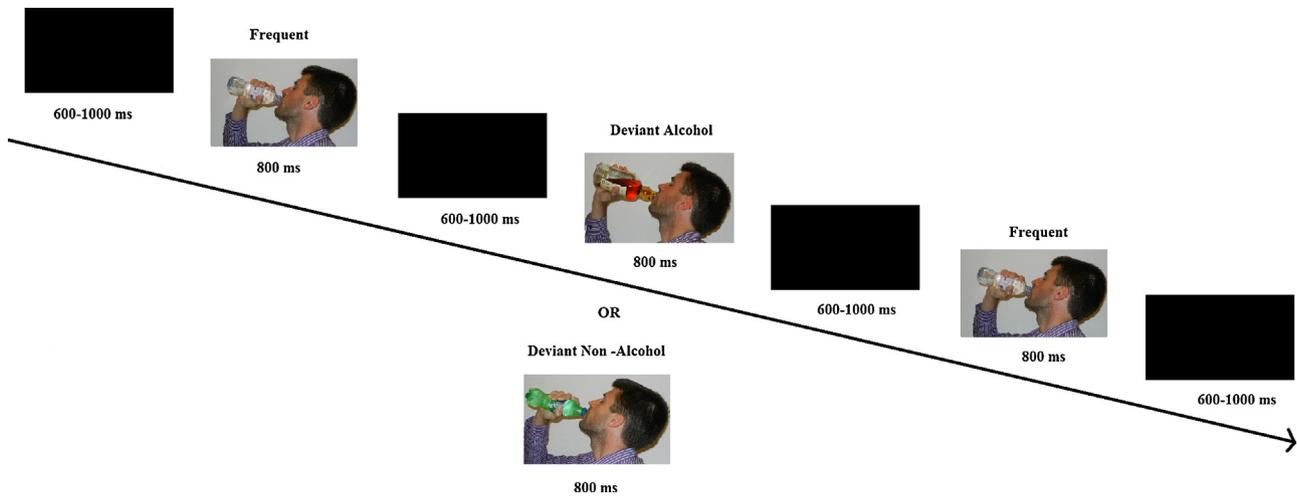


Fig. 1. The oddball task. Schematic of the task course, illustrating the frequent stimulus and one example of each category of deviant stimuli (whiskey for alcohol-related and Sprite for non-alcohol-related stimuli).

deviation of the averaged signals of all 32 electrodes recorded at each time point. For this we used publicly available CARTOOL software [71] dedicated for EEG microstate analysis on averaged pre-processed data. Then, a subroutine of CARTOOL (TAAHC) validated by Tibshirani and Walther [72] was used in order to perform a topographic atomize and agglomerate hierarchical clustering (TAAHC) to segment the data into microstates. This analysis was made on grand mean ERP across deviant cues (alcohol and non-alcohol) in the Non-relapsers' group.

2.8. sLORETA analysis

We performed source analysis on the defined microstates using sLORETA software. This method calculates a particular solution of the non-unique EEG inverse solution [73]. The sLORETA algorithm is based on the assumption that neighboring voxels tend to activate synchronously with each other [74]. This distributed inverse solution method is an interesting tool for modeling spatially distinct sources without prior knowledge about the anatomical location of the generators. In order to map the generators of P3 for deviant cues, we computed the sLORETA solution for the microstate containing the P3 activity. The sLORETA solution was computed using a 3D grid of points (or voxels) that represent possible sources of the signal, which are restricted to the gray matter based on the probabilistic brain tissue maps available from the Montreal Neurological Institute (MNI) [75]. Finally, the equally spaced grid points (5.00-mm grid spacing) and the recording array (32 electrodes) were placed in registration with the Collins 27 MRI produced by the MNI [76]. The final coordinates (x, y, z , Talairach coordinates) were used for labeling the corresponding brain areas [77].

3. Results

3.1. Demographic and alcohol consumption characteristics

Within the three-month follow-up period, 49% (19/39) of patients relapsed. The clinical and demographic characteristics of Controls (C), Relapsers (R) and Non-relapsers (NR) are summarized in Table 1. As described in Table 1, no group differences were found for gender ($\chi^2 = .128$; $p = .938$) and age ($F(2,67) = 2.967$; $p = .058$).

Nevertheless, the groups differed concerning a few variables: education level ($F(2,67) = 11.794$; $p < .001$), for which both patients groups were lower than controls (R: $t(33.596) = -4.748$; $p < .001$; NR: $t(31.401) = -3.327$; $p = .002$); AUDIT score ($F(2,67) = 198.377$;

$p < .001$), for which both patient groups scored higher than Controls as expected (R: $t(25.498) = 20.05$; $p < .001$; NR: $t(22.614) = 14.436$; $p < .001$); craving score before experiment ($F(2,67) = 5.101$; $p = .009$) for which Relapsers showed higher craving than Controls ($t(19.091) = 2.279$; $p = .034$) whereas Non-relapsers did not differ from Controls; craving score after experiment ($F(2,67) = 3.681$; $p = .031$), for which Relapsers showed higher craving than Controls ($t(18.99) = 2.191$; $p = .041$) whereas Non-relapsers did not differ from Controls; global craving score ($F(2,67) = 5.256$; $p = .008$), for which Relapsers showed higher craving than Controls ($t(19.07) = 2.385$; $p = .028$) whereas Non-relapsers did not differ from Controls; alcohol intake prior detoxification ($F(2,67) = 30.249$; $p < .001$), for which both patient groups were higher than Controls as expected (R: $t(18.033) = 6.991$; $p < .001$; NR: $t(19.025) = 5.922$; $p < .001$); tobacco smoking, for which both patients groups had a greater number of smokers compared to Controls (R: $\chi^2 = 26.716$; $p < .001$; NR: $\chi^2 = 24.507$; $p < .001$); depression score ($F(2,67) = 15.144$; $p < .001$), for which both patients scored higher than Controls (R: $t(40.126) = 5.12$; $p < .001$; NR: $t(35.369) = 4.2$; $p < .001$); trait anxiety ($F(2,67) = 6.598$; $p = .002$), for which both patient groups scored higher than Controls (R: $t(44.747) = 3.118$; $p = .003$; NR: $t(39.310) = 2.998$; $p = .005$); state anxiety ($F(2,67) = 9.148$; $p < .001$), for which both patients scored higher than Controls (R: $t(40.941) = 3.396$; $p = .002$; NR: $t(41.435) = 3.738$; $p = .001$); and family history of alcoholism (FHA) for which both patients groups had a greater number of individuals with FHA compared to Controls (R: $\chi^2 = 4.907$; $p = .027$; NR: $\chi^2 = 9.462$; $p = .002$).

As far as both patients groups (Relapsers and Non-relapsers) are concerned, no significant difference was found for age of onset of alcohol misuse ($t(36.834) = 1.302$; $p = .201$), duration of dependence ($t(36.619) = 1.243$; $p = .222$), number of prior detoxifications ($t(30.899) = 1.504$; $p = .143$), and benzodiazepine use ($t(34.823) = .111$; $p = .912$). However, the groups differed for anti-craving medication use ($\chi^2 = 5.132$; $p = .023$): the Relapsers group had a greater number of patients taking anti-craving medication compared to the Non-relapsers.

3.2. Reaction times

The analysis showed a significant effect for the type of stimulus [$F(1,65) = 43.528$, $p < .001$, $\eta^2 = .401$, observed Power = 1.000], suggesting that all participants had faster reaction times in response to A compared to NA stimuli (493 ± 80 ms vs. 511 ms ± 82) (see Table 2). A Type vs. group interaction was also found [$F(2,65) = 5.299$, $p = .007$, $\eta^2 = .140$, observed Power = .820].

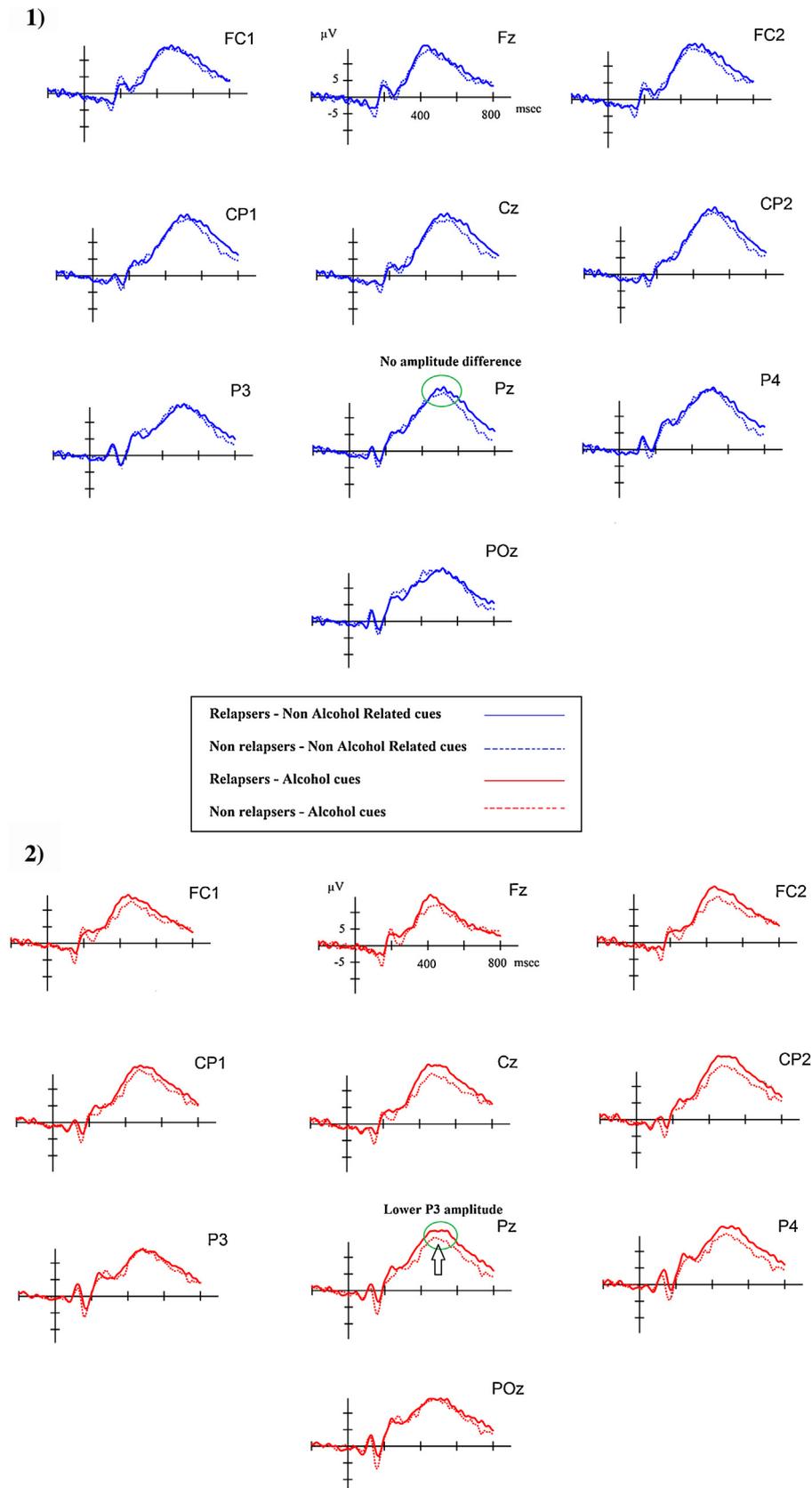


Fig. 2. Illustration of the mean P3 component wave on ten electrodes (FC1, FC2, Fz, CP1, CP2, Cz, P3, P4, Pz, and POz): (1) for non-alcohol-related cues for both groups on the top panel (Relapsers represented by the solid blue line and Non-relapsers by the dotted blue line) (2) for alcohol-related cues on the bottom panel (Relapsers represented by the solid red line and Non-relapsers by the dotted red line). The y-axis represents components' amplitudes, expressed in microvolts (μV) and the x-axis represents time, expressed in milliseconds (ms).

Table 1
Clinical characteristics of Relapsers, Non-relapsers and Controls in our study presented as means (standard deviations).

	Relapsers (n = 19)	Non-relapsers (n = 20)	Controls (n = 29)
Females	5	6	9
Age (years)	43 (11)	51 (12)	44 (12)
Education level ^a	12 (3)	13 (3)	16 (2)
Alcohol problems (AUDIT)	31 (4)	32 (9)	4 (2)
Alcohol intake prior detoxification (U/day)	21 (12)	21 (16)	0.5 (0.4)
Age of onset of alcohol misuse ^b	31 (10)	35 (12)	NA
Duration of current treatment (days)	18.7 (2.4)	19.2 (1.7)	NA
Duration of dependence ^c (years)	12 (10)	16 (9)	NA
Number of prior detoxifications	1.4 (3.0)	3.4 (5.1)	NA
Smoking (% with nicotine dependence)	89	85	14
Depression (BDI score)	22 (9)	21 (12)	7 (9)
Anxiety Trait (STAI-B)	47 (7)	51 (9)	38 (9)
Anxiety State (STAI-A)	47 (8)	48 (9)	40 (9)
Craving before experiment	18 (31)	5 (10)	1 (6)
Craving after experiment	17 (31)	7 (18)	1 (6)
Global craving score	18 (30)	6 (11)	1 (6)
Family history of alcoholism ^d (% with FHA)	42	55	13
Anticraving medication (% receiving treatment)	84	50	NA
Benzodiazepine (% of users)	31	33	NA

^a Number of years of education since completing primary school.

^b Age at which drinking first began to have an effect on the subjects' life of which he/she did not approve [99].

^c Number of years that the subject fulfilled dependence criteria before assessment.

^d Presence of at least one first- (father and/or mother) and/or second-degree (grandfather and/or grandmother) relative with alcohol dependence.

AUDIT, Alcohol Use Disorders Identification Test.

One unit (U) represents 10 g of alcohol.

BDI, Beck Depression Inventory; STAI A-B, State and Trait Anxiety Inventory; UPPS, The Impulsive Behavior Scale; ACVAS, Alcohol craving on the Alcohol Craving Visual Analog Scales.

Independent *t*-tests showed that all groups differed in their reaction times between A and NA stimuli: reactions times to A stimuli were shorter than that of NA stimuli (Rs: $t(18) = -2.993$; $p = .008$; NRs: $t(19) = -5.577$; $p < .001$; C: $t(28) = -2.216$; $p = .035$). Thus, to clarify the interaction, we performed a univariate ANOVA on the score of difference between reaction times to A vs. NA stimuli. It showed that while this score of difference did not differ between Controls and Relapsers (7.8 vs. 18.6; $p = .345$) and Relapsers and Non-relapsers (18.6 vs. 29.4; $p = .441$), it significantly differed between Non-relapsers and Controls (29.4 vs. 7.8; $p = .006$). Controls had a smaller difference in their reaction times between A and NA stimuli compared to Non-relapsers. However, when we secondarily controlled for the influence of the variables cited above using a Type (A vs. NA) vs. Group (Relapsers, Non-Relapsers, Controls) vs. medication (taking medication vs. not taking medication) vs. tobacco smoking (smoking vs. non-smoking) ANCOVA with education level as covariate, this effect was no longer significant ($p = .475$).

3.3. P3

3.3.1. Amplitudes

The analysis of P3 amplitudes did not show any main group effects, but it produced a significant group vs. type interaction [$F(1,65) = 4.421$, $p = .016$, $\eta^2 = .120$, observed Power = .742]. Paired *t*-test suggested that while in the Controls and the Relapsers' groups, no significant difference in response to the two types of stimuli was noted [R: $t(18) = 1.184$: 11.3 (3.7) vs. 10.5 (4.1); $p = .252$;

C: $t(19) = -2.908$; $p = .143$: 11.7 (5.1) vs. 12.2 (4.8)], in the Non-relapsers group, A cues tended to elicit lower amplitudes than NA cues [$t(28) = -1.366$; $p = .009$: 9.6 (5.7) vs. 11.3 (5.1)] (see Table 2 and Fig. 2). The additional analysis using a type (A vs. NA) vs. group (Relapsers, Non-relapsers, and Controls) vs. medication (taking medication vs. not taking medication) vs. tobacco smoking (smoking vs. non-smoking) ANCOVA with education level as covariate did not change these results ($p = .023$).

3.3.2. Latencies

P3 latencies analyses did not show any group or interaction effect ($p > .085$).

3.4. Regression

In order to examine the unique contribution of the difference between P3 amplitude for A stimuli and P3 amplitude to NA stimuli on abstinence beyond and above other variables, hierarchical regression was conducted with FHA, the craving, depression, and anxiety state scores, and the use of anti-craving medication entered as predictors in the first step. Together these variables could not significantly predict abstinence ($F(1,33) = 1.554$, $p = .2$). In a second step, we entered the difference between P3 amplitude for A stimuli and P3 amplitude to NA stimuli. The addition of this variable significantly contributed to the prediction of abstinence ($F(1,32) = 6.869$, $p = .013$). Thirty-three percent of the variance of the abstinence outcome was explained by the model and by this variable

Table 2
The means (standard deviations) of reaction times, amplitudes (μV) and P3 latencies (ms) for deviant stimuli as a function of group (Relapsers, Non-relapsers, and Controls) and type (Alcohol and Non-alcohol-related).

		Relapsers	Non-relapsers	Controls
Reaction Times	Alcohol-related pictures	488 (92)	502 (86)	491 (71)
	Non-alcohol related pictures	506 (86)	531 (91)	499 (72)
P3 Amplitudes	Alcohol-related pictures	11.3 (3.7)	9.6 (5.7)	11.7 (5.1)
	Non-alcohol related pictures	10.5 (4.1)	11.3 (5.1)	12.2 (4.8)
P3 Latencies	Alcohol-related pictures	428 (33)	403 (68)	428 (33)
	Non-alcohol related pictures	418 (68)	411 (66)	430 (41)

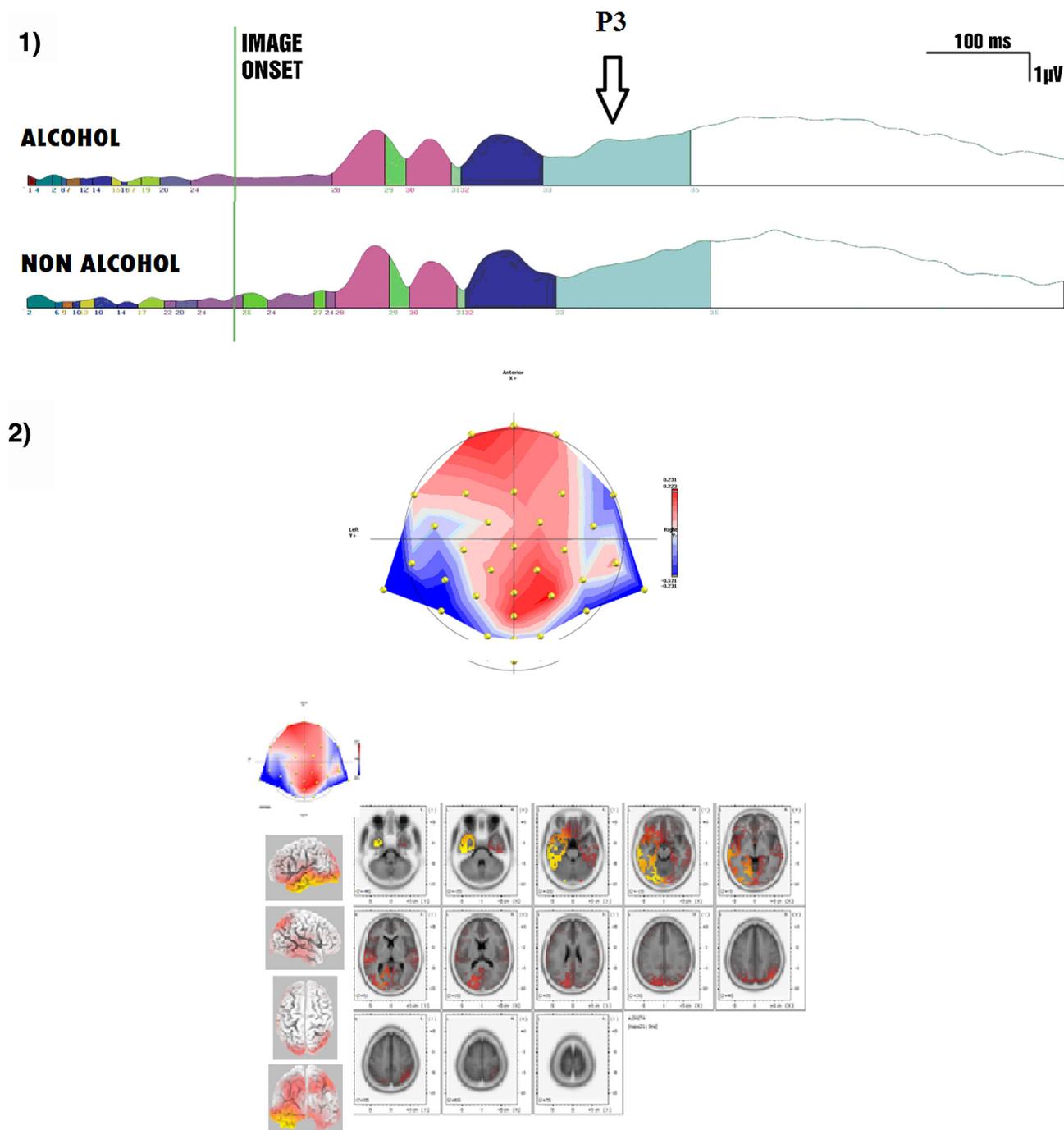


Fig. 3. Microstates and sLORETA analysis for alcohol- and non-alcohol-related stimuli in the Non-relapser group.

(1) Microstates for the two different stimuli condition during 1 s of display including 200 ms of baseline and 800 ms after the onset of the image presentation. The envelope is represented by the Global Field power (GFP) of all electrodes. Each color represents a stable topographic state in time labeled by a number at the bottom of each microstate (from 1 to 34). (2) Illustration of the P300 source in 3D and transversal views (sections from Collins 27 MRI, MNI [76]). Significantly active structures are marked in yellow to red on each section. The maximum is obtained for Talairach coordinated ($x = -30$, $y = -5$, and $z = -45$). This corresponds to a radius of 0–12 mm at BA 20 of the inferior temporal gyrus, BA 36 of the uncus, BA 38 and BA 21 of the middle temporal gyrus and BA 28 of the uncus, respectively.

on its own. Odds of abstinence increased by a factor of 0.412 for each additional microvolt included in the difference between P3 amplitude for A stimuli and P3 amplitude to NA stimuli. [Table 3](#) depicts the logistic regression results.

3.5. Microstate analysis and sLORETA topography

CARTOOL analysis performed on the averaged data demonstrated a series of microstates ($n = 34$), the duration of these microstates ranging from 5 to 300 ms ([Fig. 3\(1\)](#)). After the

presentation of the deviant pictures, the microstates timing organization corresponding to cortical activation (since the microstate 28 relates to the P1 component) was similar for alcohol and non-alcohol related cues. We then focused our analysis on the time of interest, i.e., around the P3 (peaking at 403 ms and 411 ms for alcohol and non-alcohol cues, respectively) which was represented by the same microstate 33. The localizations of the microstate 33 generators were found to be in the inferior and medial temporal gyrus (BA 20, BA 21, and BA 38) and the uncus (BA 28 and BA 36) ([Fig. 3\(2\)](#)).

Table 3
Multiple hierarchical regression analysis examining predictors of abstinence after the three-month follow-up period.

Variable	β	S.E.	OR (95% CI)
Step 1			
FHA	0.166	0.158	0.166 (–0.155 to 0.488)
Medication	–0.341	0.172	–0.321 (–0.690 to 0.009)
Craving	–0.004	0.004	–0.210 (–0.012 to 0.003)
Depression	0.003	0.008	0.068 (–0.013 to 0.019)
Anxiety	0.001	0.010	0.017 (–0.019 to 0.021)
Step 2			
FHA	0.220	0.147	0.220 (–0.080 to 0.519)
Medication	–0.304	0.159	–0.287 (–0.628 to 0.019)
Craving	–0.002	0.004	–0.105 (–0.009 to 0.005)
Depression	–0.003	0.008	–0.680 (–0.019 to 0.012)
Anxiety	0.002	0.009	0.035 (–0.16 to 0.20)
Amplitude	0.067	0.260	0.412 (0.15–.119)
NA–Amplitude A			

β , slope of the regression line; S.E., standard error; OR, odds ratio; CI, confidence interval.

4. Discussion

The present results confirm that patients who remained abstinent during a three-month follow-up period can be differentiated from those who relapsed by a decrease of the P3 component amplitude in response to alcohol-related relative to neutral images. Most interestingly, this wave of difference between alcohol and non-alcohol pictures predicts abstinence during the follow-up period, above and beyond other relevant predictors such as family history of alcoholism, alcohol craving, depression and anxiety state scores, and the use of anti-craving medication. That is to say, a decrease in motivation for alcohol-related stimuli, which becomes not equal to that of neutral stimuli but still below the threshold thereof, could predict success in stopping alcohol consumption after detoxification.

Importantly, electrophysiological difference between relapsers and abstainers is observed while behavioral data (reaction times) do not allow differentiating between the groups. It thus seems that the use of electrophysiology allows circumventing the difficulty of behavioral measures to identify a link between relapse and attentional bias/cue reactivity phenomena. To our knowledge, no study to date has addressed the relationship between indices of electrophysiological response to stimuli associated with an abused substance and relapse in addictions. However, recent data from studies on the electrophysiological response to substance-related pictures in ex-addicted are interesting in light of our results. In the study of Littel et al. [78] alcohol-dependent patients in the sample were not just out of treatment at the time of the evaluation; however, they had an average of 5.3 months of abstinence, which makes them quite close to our group of Non-relapsers. And yet, data from Littel and colleagues suggest, identically to ours, that pictures associated with alcohol generate a decrease in the amplitude of the P3 component in these abstinent patients compared to controls. Two other studies have shown that ex-smokers, exhibited significantly lower P3 and LPP (late positive potential) wave amplitudes in response to images related to cigarette smoking compared to those of current smokers [79,80], which also suggest that former (abstinent) smokers do not find cigarette-related cues to be as motivationally salient as present smokers.

Taken together, these data first seem to show that processing biases may not be a permanent feature of addiction. This is in contrast with a characteristic of the incentive-sensitization theory of Robinson and Berridge [5], which predicts that the neuro-adaptations underlying the bias for addiction cues are more or less permanent, and that addiction cues keep their

incentive-motivational properties even after drug cessation. The reality appears to be more optimistic and the reverse plasticity phenomenon seems to be possible in some individuals. The incentive sensitization theory [5] suggests that addiction cue reactivity is due to the disturbance of a sensitized neural system (mesocorticolimbic dopamine and related systems) that normally works to attribute incentive salience to reward cues through dopamine release. Via this dopamine liberation, the system converts cues associated with rewards into incentive stimuli, which renders them attractive and able to provoke an irrepressible need to obtain their reward. Repeated drug use produces a massive release of dopamine, inducing the sensitization of this brain system, leading to an increased drug wanting, in turn inducing excessive control of behavior by drug-related incentive stimuli. We could make the hypothesis that the decreased salience of addiction-related stimuli in ex-addicted found in the studies cited above [78–80], and in alcohol-abstainers patients in the present study could indicate a normalization or a decrease of the attribution of incentive salience through the resumption of normal or diminished dopamine release in response to addiction cues. The occurrence of this phenomenon in some patients would protect them from a return to the addicted state. This remains, of course, hypothetical and should be properly tested by neurochemical studies.

In the meantime, our results secondly suggest that brain activity that processes alcohol-related stimuli might serve as a biomarker helping to identify patients vulnerable to relapse after detoxification, i.e., patients in whom this decreased salience of alcohol-related stimuli does not occur. The use of EEG as a screening instrument for relapse has gained much interest in recent years (e.g. [81–85]). Aside from new evidence indicating an advantage of its sensitivity compared to behavioral measures, the EEG is a relatively low-cost, non-invasive, and easily accessible biomarker. Therefore, its use in clinical settings to predict treatment issues in terms of alcohol consumption would be very profitable and achievable. However, it will require some time before we can use the marker identified in this study in clinical practice. Our results will have to be replicated on a larger scale to confirm that the factor we identified is associated with maintaining abstinence. Obviously, one of the biggest challenges will be the ability to translate associations between group characteristics and abstinence to individual predictions following treatment. If the results hold after replication and it is demonstrated that our tool can accurately forecast at the individual level, they could help identify dependent patients who are or are not prone to relapse. The systematic screening of the protective marker and its absence in some patients could then lead to offering these patients some cognitive approaches (e.g. [86,87]) and drug treatment (e.g. [67,88,89]) aimed to decrease responsiveness to stimuli associated with alcohol in addition to the usual psychological therapy. The microstate analysis allowed for the identification of stable topographic states during the presentation of deviant stimuli in the Non-relapsers' group. The timing was similar for both alcohol and non-alcohol related cues, which indicates highly conserved topography activation. The localization of the P3 generators of the microstate 33 was found to be in the inferior and medial temporal gyrus (BA 20, BA 21, and BA 38) as well as in the uncus (BA 28 and BA 36). These regions have been associated with visual recognition and high-level visual processing (BA 20), emotional treatment (BA 21) [90], judgment process of visual stimuli (BA 28) [91] and face recognition (BA 36) [92]. Interestingly, temporal gyrus and uncus have been found to be activated by target stimuli in oddball tasks (e.g. [93,94]), by biologically relevant stimuli [95] and by addiction-related cues in alcohol-dependent populations [96]. The absence of differences in scalp topography and cortical sources between both alcohol and non-alcohol deviant cues suggests that the two types of stimuli activate the same neural processes in abstainers and only

differ by the power of their activation, as indexed by the decreased amplitude of the P3 for alcohol-related cues.

The present study suffers from several limitations that should be taken into account in further studies. First, the dichotomous characteristic of the relapse variable did not allow us to more precisely investigate the frequency and quantity of relapsers' alcohol reconsumption during follow-up. Predictors of relapse as dichotomous measures could vary from predictors of the frequency and quantity of alcohol reconsumption. We also limited our investigation of reactivity toward information related to the visual aspect of alcohol. However, contact with information related to addictive substances is a fully sensory experience, which may also include auditory, olfactory, tactile, etc. components. Some drinkers may be more sensitive to certain types of stimulatory channels than others and concurrent presentation of different types of stimulatory channels could also potentiate the observable effects. It seems that multi-sensory stimuli induce more robust brain responses than visual stimuli commonly used, and correlations between neuronal reactivity and clinical variables such as craving have been reported more frequently when using multi-sensory visual clues alone [97]. It is therefore possible that the lack of varietal stimuli channels used in our study could have led to an underestimation of the effects of alcohol-related stimuli. Finally, while the ERP analysis is a highly valuable, time-resolved, brain-imaging technique given its millisecond time-resolution and direct relationship to neuronal activity, it does not allow for making statements on localization. Although we used sLORETA to estimate the sources of scalp-recorded electric activity, the technique still presents some limitations (see [73] for a review), and especially in this work since we only based our analysis on 32 channels. Future studies utilizing simultaneous fMRI/EEG techniques would be able to provide both high spatial and time resolution and therefore more insight into specific neural generators of alcohol-cue elicited electrophysiological responses (e.g. [98]).

5. Conclusion

In conclusion, this study highlighted a neurophysiological protective marker of relapse, which consists of a reduction in the amplitude of the P3 component originating from the temporal gyrus and the uncus in response to the alcohol-related relative to non-alcohol related pictures, reflecting a decrease in motivation for alcohol related stimuli. In the future, it would therefore be advantageous to routinely assess the P3 amplitude in response to alcohol-related pictures compared to non-alcohol-related pictures in alcohol-dependent patients at the end of detoxification treatment. Ultimately, treatment programs could be tailored to individual patients to maximize their chances of success in abstinence.

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