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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 abstainers 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.

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