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Title: REDUCED ANTERIOR PREFRONTAL CORTEX ACTIVATION IN YOUNG BINGE DRINKERS DURING A VISUAL WORKING MEMORY TASK

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Abstract: Working memory (WM) is a major cognitive function that is altered by chronic alcohol consumption. This impairment has been linked to alterations in the hippocampus and prefrontal cortex (PFC). Animal and human studies have shown that the adolescent brain is more sensitive to the neurotoxic effects of alcohol than the adult brain, particularly those structures that mature late on in development, such as the hippocampus and prefrontal brain. The aim of the present study was to assess visual working memory and its neural correlates in young university students who partake in intermittent consumption of large amounts of alcohol (binge drinkers).

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The results revealed that, despite adequate performance, binge drinkers showed a smaller late positive component (LPC) associated with hypoactivation of the right anterior prefrontal cortex (aPFC) for matching stimuli, in comparison with control subjects.

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Contributors

All authors contributed to and have approved the final manuscript.

Authors Montserrat Corral, Socorro Rodríguez-Holguín and Fernando Cadaveira designed the study and wrote the protocol. Author Alberto Crego managed the literature searches and summaries of previous related work. Authors Nayara Mota, María Parada and Alberto Crego collected data. Author Alberto Crego undertook the statistical analysis, and wrote the first draft of the manuscript. Authors Socorro Rodríguez-Holguín and Fernando Cadaveira reviewed the final manuscript.

Conflict of Interest

All other authors declare that they have no conflicts of interest.

**REDUCED ANTERIOR PREFRONTAL CORTEX ACTIVATION IN YOUNG
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Abstract

Working memory (WM) is a major cognitive function that is altered by chronic alcohol consumption. This impairment has been linked to alterations in the hippocampus and prefrontal cortex (PFC). Animal and human studies have shown that the adolescent brain is more sensitive to the neurotoxic effects of alcohol than the adult brain, particularly those structures that mature late on in development, such as the hippocampus and prefrontal brain. The aim of the present study was to assess visual working memory and its neural correlates in young university students who partake in intermittent consumption of large amounts of alcohol (binge drinkers).

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1. Introduction

Alcohol abuse is probably the most common type of drug abuse in Western countries. The effects of alcohol on the central nervous system (CNS) have been widely studied in animals, and the neurocognitive, neuroanatomical and neurofunctional consequences of alcoholism in humans is well-known (for a review see Oscar-Berman and Marinkovic, 2007). In recent decades, there has been increasing concern regarding the neurocognitive effects of alcohol in adolescents and young people because of the high prevalence of alcohol abuse among this population.

Epidemiological studies across the USA and UK indicate that around 40% of university students are binge drinkers (Gill, 2002; Weschler et al., 2000, 2002). In a recent study by our research group in Spain (Caamaño et al, 2008), 37% of first-year university students (N= 2700) were found to consume large amounts of alcohol ("risky consumption") and 12.2 % were classified as binge drinkers. Binge drinking (BD) is characterized by the consumption of large amounts of alcohol in a short time, followed by a period of abstinence, as opposed to regular drinking in which a person may consume similar amounts of alcohol weekly but without the extremes of alcohol intoxication, and is common among young people, especially university students, and particularly on Thursdays and weekend days (Beets et al., 2009).

A standardized conceptual definition of BD was proposed by the US National Institute on Alcohol Abuse and Alcoholism (NIAAA, 2004): "a binge is a pattern of drinking alcohol that brings blood alcohol concentration to 0.08 gram percent or above. For the typical adult, this pattern corresponds to consuming five or more drinks (four or more for females), in about two hours". This definition of BD is similar to that used in most epidemiological studies, however, it does not specify the time period or number of

binge events that would describe a long-term BD pattern. The inclusion of a minimum criterion for frequency of BD episodes is necessary to define a BD pattern (for a review, see Courtney and Polich, 2009). This temporal aspect of a BD pattern has been variably defined, mainly as at least once in the previous two weeks (Keller et al., 2007; Presley and Pimentel, 2006; Syre et al., 1997; Wechsler et al., 1994, Weschler and Austin, 1998; Wechsler et al., 2000; White et al., 2006) or in the previous month (Griffiths et al., 2006; Jenninson, 2004; McNally and Palfai, 2001; Xing et al., 2006). In the USA, one standard alcoholic drink equals 14 g of alcohol. However, in Europe (except Portugal and UK) and Australia, one standard alcoholic drink equals about 10 g of alcohol, which obviously affects the definition of BD. Thus, most widely accepted and used definition of BD pattern includes two criteria for minimum consumption: a quantity/frequency criterion (consumption of five or more standard alcoholic drinks -six in Europe and Australia- on the same occasion one or more times per month) and a speed of consumption criterion (five or more standard alcoholic drinks in two hours, i.e., three or more per hour) (Ministerio de Sanidad y Consumo de España, 2008; NIAAA, 2004; World Health Organization, 2004).

Animal studies demonstrate that the intermittent consumption of high doses of alcohol causes major alterations in the CNS (Hunt, 1993; Jaatinen et al., 2003; Roberto et al., 2002; Tokunaga et al., 2006) and that the adolescent brain is more sensitive to the neurotoxic effects of alcohol and BD than the adult brain (Crews et al., 2000, 2006; Silvers et al., 2003; White et al., 2000). Alcohol particularly affects those structures of the brain that mature late on in development, such as the hippocampus and the prefrontal cortex (PFC) (Monti et al., 2005; White and Swartzwelder, 2004).

Human studies have also revealed the presence of neurostructural and neurocognitive anomalies in adolescents with alcohol use disorders (AUDs). According

to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV: American Psychiatric Association, 1994), AUDs include both alcohol abuse, which is characterized by a “maladaptive pattern of alcohol use manifested by recurrent and significant adverse consequences related to the repeated use of alcohol”, and alcohol dependence, which is defined as “a cluster of cognitive, behavioral, and physiological symptoms (such as tolerance for alcohol and withdrawal symptoms) indicating that the individual continues to use alcohol despite significant alcohol-related problems”. These studies have reported significant reductions in the volume of hippocampus and PFC (De Bellis et al., 2000, 2005; Medina et al., 2008; Nagel et al., 2005), and at the neurocognitive level, deficits in functions related to these areas, such as visospatial attention, and particularly working memory (WM) (Brown and Tapert, 2004; Tapert and Brown, 1999; Tapert et al, 2002), in adolescents with AUD in comparison with paired controls. As regards BD, although few studies have investigated the neurobiological and neurocognitive effects of this pattern of alcohol consumption in non-clinical samples of adolescents and young people, it has been shown that young people who indulge in BD experience difficulty in carrying out tasks involving prefrontal cortex functions, such as WM, planning, attention and decision making (García-Moreno et al., 2008; Goudriaan et al., 2007; Hartley et al., 2004; Johnson et al., 2008; Townshend and Duka, 2005; Weissenborn and Duka, 2003). Weissenborn and Duka (2003) compared BD and non-BD students and found that the performance of the binge drinkers in a spatial working memory test was significantly poorer than that of the non-binge drinkers. Similarly, Townshend and Duka (2005) found that female binge drinkers performed worse in a spatial working memory task than non-binge drinkers.

Working memory is therefore one of the cognitive functions most affected by AUDs. Impairment of this cognitive function is probably related to the effects of

alcohol on brain structures such as the hippocampus and the PFC. Studies with young binge drinkers, although still scarce, also indicate a possible deficit in this function. Therefore, the aim of the present study was to explore visual working memory function and its neural correlates in young binge drinkers.

One of the most useful tasks in exploring the neural correlates of WM is the continuous performance task (CPT) (Baddeley, 2001; Borgaro et al., 2003; Riccio et al., 2001). A typical CPT requires attention to a continuous stream of data demonstrated by response to specific target stimuli. In this task, subjects are typically asked to monitor a long series of visually presented digits, letters or other characters appearing at regular intervals, and to respond when they observe a pre-designated target (Rosvold et al., 1956). A specific variant of this task, the identical-pairs continuous performance task (IP-CPT) is a high processing load version in which subjects have to identify the consecutive repetition of any item in a sequence (Cornblatt et al., 1988; Keilp et al., 1997). This task has been used to assess psychiatric diseases, such as schizophrenia and attentional-deficit hyperactivity disorder, and has proved to be useful in characterizing neural processes associated with impaired attention and WM in such diseases (Perlstein et al., 2003; Salgado-Pineda et al., 2003, 2004). Although it is difficult to reach general conclusions because of the variability among studies as regards the design of specific tasks, the analytical techniques and the outcomes measured, it can be concluded that IP-CPT involves activation of frontal, limbic, subcortical and posterior brain structures responsible for sensorial integration (Keilp et al., 1997). Adler et al (2001) used fMRI to explore cerebral activity in subjects executing an IP-CPT with a random stream of four-digit numerals, in which the subjects had to respond by pressing a button when the same four-digit numeral appeared twice in succession during the sequence. The authors found that this task was associated with significantly larger activation of prefrontal

cortex, bilateral posterior temporal cortex, bilateral putamen and thalamus than occurred in a simple CPT. The authors attributed this increase in activation to increased memory processing demands by the IP-CPT.

In the present study we recorded event-related potentials (ERPs) in order to explore the neural correlates of visual WM during IP-CPT. The IP-CPT elicits an ERP component, named the late positive complex (LPC), which has been closely related to WM processes and PFC activation (Düzel et al., 2001; Schendan and Maher, 2009) and consists of a broad positive waveform with centro-parietal maximum amplitude and peak latency at about 500-700 ms post-stimulus. It is known that ERP studies enable investigation of the electrical brain responses associated with cognitive processes with high temporal resolution, and ERPs (especially the P3 family components) have been widely used to assess the neurocognitive effects of alcohol in different populations (chronic alcoholics, abstinent chronic alcoholics, children of alcoholics) (Cadaveira et al., 1991; Cohen et al., 1997; Cristini et al., 2003; Kamarajan et al., 2005; Miyazato and Ogura, 1993; Rodríguez Holguín et al., 1999). However, to our knowledge only two studies have used ERPs to explore BD in young people. Ehlers et al. (2007) used a facial emotional expression recognition task and evaluated ERPs in young adults with a history of BD during adolescence. They reported that young adults participating in BD during adolescence displayed a lower amplitude in a late subcomponent of P3 (P450) than subjects who did not partake in BD during adolescence. The authors suggested that these anomalies may be associated with a loss or delay in the development of inhibitory brain systems in binge drinkers. Recently, Maurage et al. (2009) used a test-retest paradigm and reported that short-term BD can produce marked cerebral dysfunction undetectable by behavioral measures alone. The results of the study revealed that, after nine months of BD, subjects presented significantly delayed latencies for P1, N2 and P3

components elicited by emotional auditory stimuli compared with controls, with no behavioral differences.

In the present study, the LPC elicited in response to a visual identical-pairs continuous performance task and its neural sources were analyzed in order to assess the effects of binge drinking on working memory processes in healthy young university students (without AUDs). Exact low resolution electromagnetic tomography (eLORETA) was used to estimate the cerebral sources of LPC. This software enables examination of specific sources of neural activation during the activity measured at the scalp. The main objectives of the present study were: (i) to establish any differences in LPCs between binge drinkers and control university students, and (ii) to examine possible BD-related differences in the pattern of neural activation associated with the LPC, which may reveal any alteration in working memory processes.

2. Methods

2.1. Participants

Ninety-five first-year university students (age range 18-20 years) participated in the study. Forty-two of the participants (21 females) were classified as binge drinkers (BD) and 53 (26 females) as controls (see Table 1).

Insert Table 1 about here

For sample selection, first-year students at the University of Santiago de Compostela (Spain) (N=2700) were asked to complete a questionnaire during class. The

initial sample used in the present study is the same as that used in an epidemiological study carried out by our research group (Caamaño et al., 2008). The questionnaire included the Galician validated version of the Alcohol Use Disorder Identification Test (AUDIT) (Varela et al., 2005), items 10, 11 and 12 of the Alcohol Use Questionnaire (AUQ, Townshend and Duka, 2002), i.e. speed of drinking (average number of drinks consumed per hour), number of times the subject became drunk in the previous six months and percentage (average) number of times the subject became drunk when drinking, as well as other items regarding alcohol use –frequency of BD episodes in the previous two weeks and the previous month, number of drinks per occasion, number of drinks consumed on each day of the last week, age of onset of use, etc.), and other drug use (type of drug use, frequency of consumption, etc.).

According to the quantitative definition of BD used in European countries such as Spain, where a standard alcoholic drink equals about 10 g of alcohol, this study established the criterion for consumption, of six or more standard alcoholic drinks on the same occasion, one or more times per month. This data was obtained from the subject's response to question 3 of the AUDIT (“How often do you have six or more drinks on one occasion? Never / Less than monthly / Monthly / Weekly / Daily or almost daily”). In addition to this quantity/frequency criterion, speed of alcohol consumption was also considered. To be classified as binge drinkers, subjects had to drink at least three drinks per hour during BD episodes. This data was obtained from the subject's response to question 11 of AUQ, which refers to the speed of drinking (average number of drinks consumed per hour).

Therefore, subjects who (1) drank six or more standard alcoholic drinks on the same occasion, one or more times per month and, during these episodes, (2) drank at a speed of consumption of at least three drinks per hour, were classified as binge drinkers.

Those who (1) drank six standard alcoholic drinks on the same occasion less than once per month and (2) drank at a maximum speed of consumption of two drinks per hour, were classified as non-BD (see Fig. 1). Non-BD alcohol consumers were used as the comparison (control) group, rather than abstainers, because the latter are scarce amongst young university students (at least in the study population). Thus, the low level of alcohol consumption of the subjects in the control group was representative of most of the students surveyed, and the amounts, frequency and speed at which they drank guaranteed the absence of a BD pattern or any other type of alcohol-related problems.

Insert Figure 1 about here

The initially selected subjects were interviewed about their personal and family history of alcoholism and medical or psychopathological disorders. The interview comprised a translated and adapted version of the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA), Individual Assessment Module (IAM) and Family History Assessment Module (FHAM), designed by the Collaborative Study on the Genetics of Alcoholism (COGA) (Bucholz et al., 1994). Questions about individual and familiar psychopathological problems were based on DSM-IV criteria and at least one other diagnostic classification system. The Symptom Checklist-90-Revised questionnaire (SCL-90-R, Derogatis, 2002) was also applied in order to detect any psychopathological symptoms. Alcohol abuse/dependence was assessed in all subjects, both controls and binge drinkers, by use of the AUDIT. The original AUDIT has been validated to assess alcohol-related problems or disorders (Allen et al., 1997; Babor et al., 2001; Conigrave et al., 1995), and specifically in university students (Aertgeerts et al., 2000; Fleming et al., 1991). AUDIT scores in the range of 8-19 reveal “risky”

consumption, while scores of 20 or above warrant further diagnostic evaluation for alcohol dependence. Information on tobacco, cannabis and other drugs use was obtained from the subjects' responses to items about drugs use included in the questionnaire.

The exclusionary criteria were non-corrected sensory deficits, any episode of loss of consciousness for more than 20 minutes, history of traumatic brain injury or neurological disorder, personal history of psychopathological disorders (DSM-IV Axis I and Axis II disorders), family history of major psychopathological disorders (major depressive disorder, schizophrenia or anxiety disorders according to DSM-IV criteria) in first-degree relatives, regular cannabis consumption (at least once a week), personal history of regular or occasional use of other drugs (opiates, hallucinogens, cocaine, amphetamine compounds or medically prescribed psychoactive substances) and percentile scores > 90 for the global severity index (GSI) or at least two symptomatic dimensions of the SCL-90-R. As regards alcohol consumption, subjects with AUDs (AUDIT scores ≥ 20) and subjects with complete absence of consumption (abstainers) were excluded from the study. Family history of alcohol was also assessed. This was not an exclusionary criterion because of the general purposes of the research. Nonetheless, there were no cases of high density familiar history of alcoholism (defined as the presence of one first-degree and at least another two first- or second-degree relatives) in the subjects selected for this study; three BD and two control subjects had one alcoholic first-degree relative.

There were no significant differences between BD and Control groups in the sociodemographical and psychological variables considered (age, gender, ethnicity -all were Caucasian-, handedness, occasional use of cannabis, family history of alcohol dependence or substance abuse disorder, any SCL-90-R score scale) other than those related to alcohol consumption.

The experiment was undertaken in compliance with Spanish legislation and the code of ethical principles for medical research involving human subjects outlined by the World Medical Association (Declaration of Helsinki: see Williams, 2008). Participants signed an informed consent form and were paid 15 euros for participating in the entire experiment.

2.2. Procedure

Participants were asked to abstain from consuming drugs and alcohol for 12 hours before the experiment. In addition, they were instructed not to smoke or drink tea or coffee for at least three hours prior to the experiment. Compliance with these restrictions was self-reported by the subjects. Each subject was seated in a comfortable armchair located in a light- and sound-attenuated electrically shielded room, and a brain cap and electrodes (see below) were fitted to the subject's head. General instructions were given to avoid movements during the test and the task was explained.

A visual IP-CPT, originally developed by Cornblatt et al. (1988), was used. In comparison with other CPT tasks, this test is considered to demand high attention and WM (Cornblatt et al., 1988). Participants have to respond when the same stimulus appears in two consecutive trials (an identical pair), ensuring that subjects will decode each stimulus carefully, to determine whether the next item is a match.

Two hundred stimuli, size $2.6 \times 2.6^\circ$ visual angle, were presented at random in the centre of a computer monitor placed 100 cm in front of the subject's eyes. The stimulus duration was 50 ms and the interstimulus interval (ISI) varied between 2500 and 2800 ms. The stimuli consisted of 60 different abstract figures, which were difficult to verbalize. Participants were instructed to press a button with the preferred hand when

two consecutive identical stimuli appeared (probability = 0.2) and not to respond in the other cases (probability = 0.8). They had therefore to maintain each figure present in the WM during the ISI, and had to respond if the next figure was the same (see Fig. 2).

Insert Figure 2 about here

2.3. ERP Recording

The Electroencephalogram (EEG) was recorded with Brain Vision Recorder system using a Braincap with 32 synerized Ag-AgCl electrodes placed at AF3, AFz, AF4, F7, F3, Fz, F4, F8, FC3, FCz, FC4, C3, Cz, C4, CP3, CPz, CP4, T7, T8, P7, P3, Pz, P4, P8, PO7, PO3, POz, PO4, PO8, O1, Oz and O2 (according to the extended 10-20 International System). All active electrodes were referred to the nose tip and grounded with an electrode placed at FPz. Vertical electrooculogram (EOG) activity was recorded bipolarly from above and below the left eye to control eye movements and blinks. Electrode impedances were kept below 5 K Ω . EEG signals were continuously amplified and digitized at a rate of 500 Hz, and filtered on-line with a 0.01-100 Hz band pass filter.

2.4. Data Analysis

2.4.1. Behavioral analysis. Only Reaction Times (RTs) occurring between 100 and 1200 ms after the onset of a matching stimulus were considered as correct responses. Responses to the non-matching stimuli were scored as false alarms, and failures to respond to matching stimuli were defined as omissions. The RTs and the percentage of

correct responses, false alarms and omissions were analyzed by ANOVA, with two between-subjects factors: Group (BD and control) and Gender (male and female).

2.4.2. ERP analysis. All EEG data were analyzed with Brain Vision Analyzer software (Version 1.05). The EEG was corrected for ocular artifacts by the procedure developed by Gratton et al. (1983). It was then digitally filtered off-line with a 0.1-30 Hz bandpass filter and segmented into epochs of 1000 ms from 100 ms pre-stimulus to 900 ms post-stimulus. Baseline correction was applied, epochs exceeding $\pm 80 \mu\text{V}$ at any scalp electrode were rejected (this criterion resulted in less than 4% of rejected epochs) and EEG epochs corresponding to incorrect responses (omissions or false alarms) were excluded. Average ERPs time-locked to matching and non-matching stimuli were computed separately for each participant.

The ERP data were examined by temporal Principal Components Analysis (tPCA) to ensure correct identification of LPC. This analysis is recommended for identifying and quantifying ERP components independently of the influences of adjacent or subjacent components (Chapman and McCrary, 1995; Dien, 1998). It also enables identification of hidden ERP components and prevents possible misinterpretations that occur with traditional visual inspection of grand averages. The tPCA provides two matrices, one for factor loadings and another for factor scores. The first shows the load of each factor over time, and the second provides information about the extent to which each factor is present in the averaged ERPs at each electrode site. The factor scores are transformed values of the original voltages, which may be considered as “clean amplitudes” and thus can be used as a measure of the amplitude.

A covariance-matrix-based tPCA was applied for both conditions (matching and non-matching stimuli). The decision regarding selection of the number of components

(or factors) was based on the results of the scree test (Cattell, 1966). The number of data points (factors) above the “break” in the scree test was tested by running multiple factor analyses and manually setting the number of factors to be retained. Nine factors, which accounted for 94.8% of the total variance, were finally selected. Extracted factors were then submitted to Promax rotation. Promax rotation was used because it minimizes miscalculations due to, e.g., misallocation of variance (Dien, 1988). The temporal and spatial characteristics of the components indicated that factor 1 (explained variance: 59%; latency: 625ms) corresponded to the LPC. The nine temporal factors extracted are shown in Fig. 3.

Insert Figure 3 about here

The factor scores corresponding to LPC from both matching and non-matching stimuli were organized into three regions, each with six electrodes: frontal (F3, Fz, F4, FC3, FCz, FC4), central (C3, Cz, C4, CP3, CPz, CP4) and parietal (P3, Pz, P4, PO3, POz, PO4). Preliminary statistical analyses were performed with the Gender factor included, and once it was verified that there were no major gender effects or interactions, this factor was not considered in the design. A mixed model ANOVA with four factors was used for the statistical analysis, with one between-subjects factor and three within-subject factors. The between-subjects factor was Group (BD and control) and the within-subject factors were Match Condition (matching and non-matching stimuli), Region (frontal, central and parietal) and Electrode (six channels).

An experiment-wise alpha level of 0.05 was used. Whenever appropriate, degrees of freedom were corrected by the conservative Greenhouse-Geisser estimate.

All post-hoc pair comparisons were performed with the Bonferroni adjustment for multiple comparisons, also with an alpha level of 0.05.

2.4.3. eLORETA analysis. On the basis of the scalp-recorded electric potential distribution, the exact low resolution brain electromagnetic tomography (eLORETA) software (publicly available free academic software, at <http://www.uzh.ch/keyinst/loreta.htm>) was used to compute the cortical three-dimensional distribution of current density at LPC for matching trials in both groups. The eLORETA method is a distributed, linear weighted minimum norm inverse solution. The weights endow the tomography with the property of exact localization to test point sources, yielding images of current density with exact localization, albeit with low spatial resolution (i.e. neighboring neuronal sources will be highly correlated). The method and the proof of its exact zero-error localization property are described in Pascual-Marqui, 2007 and 2009.

It is also important to emphasize that eLORETA has no localization bias even in the presence of structured noise. In this sense, eLORETA is an improvement over previously developed tomographies (LORETA: Pascual-Marqui et al., 1994), and over the standardized version, sLORETA (Greenblatt et al., 2005; Pascual-Marqui, 2002; Sekihara et al., 2005).

The previously developed related tomographies LORETA and sLORETA (Pascual-Marqui et al., 1994, 2002) have been validated in several studies combining LORETA with other more established localization methods such as functional Magnetic Resonance Imaging (fMRI, Mulert et al., 2004; Vitacco et al., 2002), structural MRI (Worrell et al., 2000), Positron Emission Tomography (PET, Dierks et al., 2000; Pizzagalli et al., 2004; Zumsteg et al., 2005), and invasive implanted electrodes

recordings (Zumsteg et al., 2006). The results of these studies also validate eLORETA, owing to its improved localization properties. It is worth emphasizing that deep structures such as the anterior cingulate cortex (ACC, Pizzagalli et al., 2004) and mesial temporal lobes (Zumsteg et al., 2006) can be correctly localized with this method.

Computations were made in a realistic head model (Fuchs et al., 2002), with the MNI152 template (Mazziotta et al., 2001), and with the three-dimensional solution space restricted to cortical gray matter. The intracerebral volume is partitioned in 6239 voxels at 5 mm spatial resolution. Thus, eLORETA images represent the electric activity at each voxel in neuroanatomic Montreal Neurological Institute (MNI) space as the exact magnitude of the estimated current density. Anatomical labels such as Brodmann areas are also reported using MNI space.

The grand mean LPC eLORETA images were computed by first calculating the eLORETA solution for each subject in the matching condition, and then averaging the current density values across all subjects for each group (BD and control).

The eLORETA software was then used to perform voxel-by-voxel between-group comparisons of the LPC current density distribution. Specifically, in order to identify possible differences in the brain electrical activity in matching trials between groups (BD and control), nonparametric statistical analyses of functional eLORETA images (Statistical non-Parametric Mapping; SnPM) were performed with a log-F-ratio statistic for independent groups. The results correspond to maps of log-F-ratio statistics for each voxel, for corrected $P < 0.05$. As explained in the review by Nichols and Holmes (2002), the SnPM methodology corrects for all multiple comparisons, and at the same time does not require any assumption of Gaussianity.

3. Results

3.1. Behavioral results

The behavioral data for each group are summarized in Table 2. No significant differences between the control and BD groups were observed for RTs, percentage of correct responses, false alarms or omissions.

Insert Table 2 about here

3.2. Electrophysiological results

The grand averages of the ERPs recorded in the control and BD groups are shown in Figs. 4 and 5 respectively. The LPC was identified by PCA, for both matching and non-matching conditions. The latency was approximately 625 ms, and maximum factor scores were obtained at central and parietal locations.

Insert Figures 4 and 5 about here

Analysis of the LPC revealed that Match Condition (matching or non-matching stimuli) had a significant effect [$F(1,91) = 4.02, P < 0.05$]. The LPC factor scores were significantly larger in the matching than in the non-matching condition. The analysis also revealed that Region had a significant effect [$F(2,182) = 116.19, P < 0.001$], with higher factor scores in posterior than anterior regions: Parietal > Frontal ($P < 0.001$) and Central > Frontal ($P < 0.001$). The Match Condition x Group interaction showed significant effects [$F(1,91) = 4.85, P < 0.05$] with larger LPC factor scores in the Control

than in the BD group in matching condition (see Fig. 6). Although there were no significant interactions involving Region, separate analyses were performed for each region, and showed that the difference between the two groups was only significant at the Frontal [$F(1,91) = 5.48, P > 0.05$] and Central [$F(1,91) = 4.57, P > 0.05$] regions.

Insert Figure 6 about here

3.3. *eLORETA results*

The eLORETA brain maps representing cortical regions where BD and control subjects showed maximal activation at LPC for the matching condition are shown in Fig. 7.

Insert Figure 7 about here

In the comparisons between the two groups, significant differences were found in matching trials. Significantly less activation was observed in the BD group than in the control group for matching stimuli in the right anterior prefrontal cortex (aPFC) (Brodmann area 10) (Log-F-ratio = -2.85, corrected $P < 0.05$). The eLORETA statistical nonparametric maps comparing electrical neuronal activity of BD and control subjects for matching stimuli at LPC are shown in Fig.8. Those brain regions where the SnPM Log-F-ratio statistic for independent groups was statistically significant are listed, along with the MNI coordinates, in Table 3.

Insert Figure 8 and Table 3 about here

4. Discussion

Little is known about the neurocognitive effects of repeated and intermittent excessive consumption of alcohol over short periods of time (BD) in human adolescents and young adults. In the present study, ERPs were recorded in a group of young BD and control university students during the execution of a visual working memory task, and the LPC was analyzed. The cortical sources of the LPC were modeled and analyzed by eLORETA software. The specific aims were to establish whether the LPC differs between binge drinkers and control university students and to examine possible BD-related differences in LPC neural activation during processing in a visual working memory task.

The results revealed a reduction in the LPC and hypoactivation of the aPFC in the BD group in matching trials during the execution of the working memory task, although no behavioral differences between BD and control groups were observed.

Very few ERPs studies have been carried out in relation to BD. Ehlers et al. (2007) assessed ERPs during the execution of a facial emotional expression discrimination task in three groups of Southwest California Indians: Adults with no regular BD during adolescence (mean intake per occasion before 18 was < five drinks - of 14 g of alcohol- per occasion) and no diagnosed drug dependence; adults with history of BD during adolescence (mean intake per occasion before 18 was > five drinks per occasion) with no diagnosed life-time drug dependence, and adults with history of BD during adolescence and diagnosed drug dependence comorbidity. The results revealed that adults with history of BD adolescence with no diagnosed life-time drug dependence showed a lower amplitude of a later subcomponent of P3 (P450) than adults with no

regular BD during adolescence and no drug dependence. However, the decrease in the amplitude cannot be attributed exclusively to BD during adolescence, because family history of alcohol and conduct disorder or antisocial personality disorder were not excluded and were significant covariates in the analysis. Recently, Maurage et al. (2009) compared young adult binge drinkers (more than 10 drinks of 10 g of alcohol at least 2 times a week) with matched paired controls (both were first-year university student), in a test-retest paradigm over a nine month period. In this study, the potentially biasing variables were controlled and the subjects included in the study had to meet strict selection criteria: no positive history of alcoholism, total absence of past or current drug consumption (including tobacco and medication), no history of psychiatric disorder and no moderate or high depression-anxiety scores. The results revealed that although the two groups did not differ in any psychological, behavioral or electrophysiological measures in the first session (before the subjects started binge drinking habits), nine months later, the binge drinkers displayed significantly delayed latency in the P1, N2 and P3 components elicited by emotional auditory stimuli in a discrimination task, relative to controls, still with no behavioral differences between the two groups.

These studies have revealed that young binge drinkers show electrophysiological anomalies in the processing of emotional stimuli, and the results of the present study suggest that electrophysiological anomalies also occur during WM processes. In fact, anomalous electrophysiological patterns associated with binge drinking during the execution of this WM task do not only affect LPC. In a previous report by our research group (Crego et al., 2009) with the same subjects and task as in the present study, binge drinkers showed anomalies in the N2 and P3 components. The N2 component elicited by matching stimuli in central and parietal regions was significantly larger in the BD

than in the control group; the P3 component, which was larger in the matching than in the non-matching condition in the frontal, central and parietal regions in the control group, did not differ significantly between conditions in the BD group. Thus, although ERPs studies on BD are still scarce, and despite the different nature of the tasks used, the results of the study by Maurage et al. (2009), our previous study (Crego et al., 2009) and the present study appear to confirm that healthy binge drinkers (with no psychopathological comorbidities, AUDs, abuse or dependence on other illegal drug, or family history of alcoholism) may display anomalies in the electrophysiological responses when processing information, even in the absence of behavioral impairment.

Although it is not entirely clear which cognitive processes are associated with the LPC, this component is mainly related to the categorical response, possibly associated with executive functions in the prefrontal cortex (Kirino et al., 2000). In fact, to evoke LPC, it appears necessary to use high load processing tasks in which the subjects have to do more than detect a given stimulus and, for example, must use WM or carry out a task with a sub-goal task. This component appears to be particularly closely related to WM and any synchronized operation immediately following target or match detection (García-Larrea and Cézanne-Bert, 1998), such as selection of a response category and evaluation of the success of a category-related decision or memory match (Schendan and Maher, 2009).

The results of the present study revealed that the LPC was larger in matching than in non-matching trials, suggesting that, in this task, the LPC may indicate WM recognition and the detection of memory match. Therefore, the significant reduction in the factor scores of the LPC in matching trials found in the BD group in comparison with the control group may reveal anomalies in the electrophysiological processing

underlying working memory and memory match processes in young binge drinking university students.

Neuropsychological studies have revealed that adolescents and young people with AUD perform worse in working memory tasks (Brown et al., 2000; Tapert et al., 2002; Brown and Tapert, 2004). However, studies with healthy youths and adolescents with a BD pattern are scarce and the behavioral effects in working memory tasks are not clear. Weissenborn and Duka (2003) compared BD and non-BD students and found that the performance of the binge drinkers in a spatial working memory test was significantly poorer than that of the non-binge drinkers. Similarly, Townshend and Duka (2005) also found that female binge drinkers performed worse in a spatial working memory task than the corresponding control subjects. In contrast, Hartley et al. (2004) did not find any behavioral differences between binge and non-binge drinkers with the same spatial working memory task. It is important to note that the subjects in the first two studies were between 18 and 30 years old and the binge drinkers consumed large quantity quantities of alcohol every week, whereas subjects in the latter study were younger students (aged 18-23 years) who consumed smaller amounts of alcohol per week, and perhaps their drinking may not have reached the threshold or duration needed to show behavioral impairments.

As regards the neuroanatomical basis of the electrophysiological dysfunction found in the present study, between-group comparisons of eLORETA data revealed BD-related hypoactivation of the right aPFC in the matching trials. Although alcoholism-related cortical changes have been documented throughout the brain, most studies have consistently found the frontal lobes, especially PFC, to be more vulnerable to alcohol-related brain damage than other cerebral regions (Chen et al., 2007; Demir et al., 2002; Gansler et al., 2000; Pfefferbaum et al., 2001; Volkow et al, 1992, 1994).

To our knowledge, no functional neuroimaging studies have been carried out with BD young people without AUDs. However, recent studies have revealed that adolescents and young people with AUD display a smaller volume of PFC (De Bellis et al., 2005; Medina et al., 2008) and functional abnormalities in this area (Akine et al., 2007; Caldwell et al., 2005; Tapert et al., 2001; 2004). For example, Tapert et al. (2004) reported that, despite similar performance during a spatial working memory task, adolescents with AUD displayed less PFC and cerebellar activation in completing the task in comparison with controls. Recently, Akine et al. (2007) also reported, for a long-term memory retrieval task, that although young abstinent patients with alcohol dependence did not differ from controls in behavioral measures of task performance, they showed less activation in the PFC. The authors suggested that the lower PFC activations may be considered a latent lesion and a subclinical alcoholic brain pathology.

The results of the present study are therefore consistent with the structural and functional anomalies reported for alcohol-related disorders, especially in young people. Although the low resolution of eLORETA does not guarantee the involvement of a specific area such as the aPFC, it is worth discussing this possibility in relation to reports that link this area with WM, since a WM task was used in the present study and WM is one of the cognitive functions most affected by alcohol.

The aPFC area corresponds to a subdivision of the cytoarchitecturally defined prefrontal region of cerebral cortex also known as the frontopolar cortex, and incorporates the most anterior parts of the three frontal gyri. Traditionally it has been suggested that this area plays a unique role in retrieval of episodic memory (Düzel et al., 2001; Lepage et al., 2000; Tulving et al., 1994). However, aPFC activation has been observed in both WM and long-term memory tasks in several recent studies (Braver et

al., 2001; Nyberg et al., 2003; Ranganath et al., 2003). For example, activation in the bilateral aPFC has been observed during face recognition in working memory and in the left aPFC during face recognition in episodic memory, with parallel designs for both memory tasks (Ranganath et al., 2003). Leung et al. (2005) used a spatial working memory task and also found that, although the aPFC was active during other critical events in WM such as encoding and maintenance, activation was greater in the recognition phase.

Considering findings from studies on both working memory and long-term memory, it appears that the aPFC may support recognition in both types of memory in a similar way. Besides, the retrieval or reactivation of target or matched items in episodic memory has been considered to require working memory (Baddeley, 2000). Perhaps the main function of aPFC is to compare the target or matched item with the on-line information maintained in WM or with the information retrieved from long-term memory. What does appear to be clear is that aPFC is involved in working memory and particularly in processes that distinguish matching and non-matching stimuli during recognition. Hypoactivation of right aPFC associated with LPC for matching stimuli found in the BD group in comparison with control group in this study may therefore reveal BD-related alteration of working memory processes involved in recognition.

The observed right lateralization of the hypoactivation was not surprising. Memory retrieval studies, with both episodic and working memory tasks, have reported right lateralized (Braver and Bongiolatti, 2002; Düzel et al., 2001; Grady et al., 2001; Nyberg et al., 2000; MacLeod et al., 1998; Tulving et al., 1994) and also bilateral aPFC activation (Andreasen et al., 1995; Leung et al., 2005; Ranganath et al., 2003; Rugg et al., 1996). The right or bilateral effect may depend on the characteristics of the tasks used. The IP-CPT has been demonstrated to be sensitive to the characteristics of the

stimuli. Studies involving words or numbers have revealed left lateralization in brain activity (Keilp et al., 1997), related to increased subvocalization strategies required to retain phonological information (Gruber et al., 2000; Rypma et al., 1999). Conversely, the IP-CPT with shapes reveals a slight right lateralization and an increase in bilateral occipital activation, perhaps because these stimuli demand more prolonged visual processing and do not require semantic or phonological processing (Keilp et al., 1997). In the present study, the right lateralization effect may be related to the nature of the stimuli used. The stimuli were abstract figures, which were difficult to verbalize, and it is possible that greater activation was required in the right hemisphere than in the left because such stimuli demand more prolonged visual processing and do not require semantic or phonological processing.

Therefore, in the present study, the BD young university students retained the ability to perform the visual working memory task correctly at a behavioral level, but responded abnormally at the neural level. This inconsistency between behavioral (no group differences) and neurofunctional (deficit in binge drinkers) results may be explained by either (or both) of the following possibilities: (1) that the subjects' lifetime alcohol consumption had not yet reached the threshold or duration required to cause behavioral performance deficit, and therefore, for now, they only show cerebral alteration at the electrophysiological level, or (2) that the task employed was not sensitive enough to detect any possible behavioral deficit, thus producing a ceiling effect in both groups (the percentage of correct answers was around 85%, and there were very few false alarms or omissions in both groups). Further neuropsychological studies, in which more sensitive tests are used to assess WM, and longitudinal studies are required to elucidate whether or not impairment of behavioral performance occurs in more demanding tasks or when the subjects continue binge drinking. Moreover, new

studies with neuroimaging techniques are also needed to establish whether or not this dysfunction is associated with any structural brain damage.

Finally, it must be noted that the possible influence of gender was initially assessed in the present study. However, although several neuroimaging and neurofunctional studies on alcohol consumption have reported that women with AUD are more sensitive to the neurotoxic effects of alcohol than men (Caldwell et al., 2005; Hommer et al., 2001; Mann et al., 2005; Medina et al., 2008; Schweinsburg et al., 2003), this factor was not considered because we did not observe any significant gender-related effects or interactions with other factors.

Conclusions

Although there were no behavioral differences between BD and control groups, the reduction in the LPC in the BD group in matching trials and the associated hypoactivation of the right aPFC suggest that there are functional alterations in the prefrontal cortex related to processes of visual working memory in young university binge drinkers.

The results suggest that impaired prefrontal cortex function may occur at an early age in binge drinkers, even in young university students without AUD or psychopathological comorbidities. However, further research is needed to clarify the effects of BD on WM. Future research should be aimed at: i) understanding the effects of different degrees of BD, ii) understanding, through longitudinal studies, the evolution of the BD pattern and of associated neurofunctional and behavioral abnormalities, and iii) determining whether or not the functional alterations are associated with structural brain damage.

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Figure legends

Figure 1. Mean number of drinks that the BD and Control subjects consumed on each day of the last week.

Figure 2. Description of the task: an example of the sequence of stimuli used and timing of stimuli presentation.

Figure 3. PCA: Factor loadings of the nine temporal factors (tf) after promax rotation. Factor 1, associated with LPC, is shown with a thick line.

Figure 4. Grand averages of event-related potentials from the Control group in response to the non-matching stimuli (solid lines) and matching stimuli (dashed lines). Averages are presented for 32 electrode locations.

Figure 5. Grand averages of event-related potentials from the BD group in response to the non-matching stimuli (solid lines) and matching stimuli (dashed lines). Averages are presented for 32 electrode locations.

Figure 6. Factor loadings of the LPC from the Control group (solid line) and the BD group (dashed line) in response to the matching stimuli.

Figure 7. Grand averages LPC eLORETA images showing exact current density maxima of binge drinkers (n=42) and controls (n=53) for the matching stimuli. Each

map consists of axial, sagittal and coronal planes showing the same activation areas. Maxima are indicated in yellow. L-left, R-right, A-anterior, P-posterior.

Figure 8. eLORETA-based statistical nonparametric maps (SnPM) comparing the exact current density values between binge drinkers and control subjects for matching stimuli at LPC. Significantly reduced activation (corrected $P < 0.05$) in binge drinkers relative to controls is shown in blue color. L-left, R-right, A-anterior, P-posterior.

Table 1. Demographic and drinking characteristics of the Control and BD groups (mean \pm SD)

	Control	BD
N (females)	53 (26)	42 (21)
Age (range)	18.7 \pm 0.5 (18-20)	18.9 \pm 0.5 (18-20)
Handedness (right/left)	49 / 4	41 / 1
Caucasian ethnicity (%)	100	100
Family history of alcohol dependence ^a	2	3
Family history of substance abuse disorder ^a	1	1
Tobacco smokers	8	17
Occasional use of cannabis ^b	12	17
Age of onset on alcohol consumption	15.3 \pm 2.9	14.4 \pm 1.3
Quantity of consumption: drinks per occasion ^c **	1.0 \pm 0.9	5.1 \pm 2.1
Drinks in the last week self-reported **	2.79 \pm 0.3	18.69 \pm 2.7
Speed of consumption: drinks per hour **	0.6 \pm 0.5	3.8 \pm 0.7
BD episodes in the last two weeks **	0.2 \pm 0.6	1.9 \pm 1.8
Times drunk in the last 6 months **	1.37 \pm 3.4	14.02 \pm 16.1
Percentage of times became drunk when drinking **	7.02 \pm 13.6	47.62 \pm 32.77
Total AUDIT score (range)**	2.3 \pm 2.1 (0-8)	12.8 \pm 4.8 (5-18)
SCL-90-R: GSI percentile scores	61.82 \pm 16.30	53.15 \pm 31.41

* $t < 0.05$ significant group differences (Control vs BD)

** $t < 0.001$ significant group differences (Control vs BD)

^a first-degree family history

^b less than 10 occasions per year

^c 1 standard alcoholic drink equals 10 g of alcohol

Table 2. Behavioral data from the Control and BD groups (mean \pm SD)

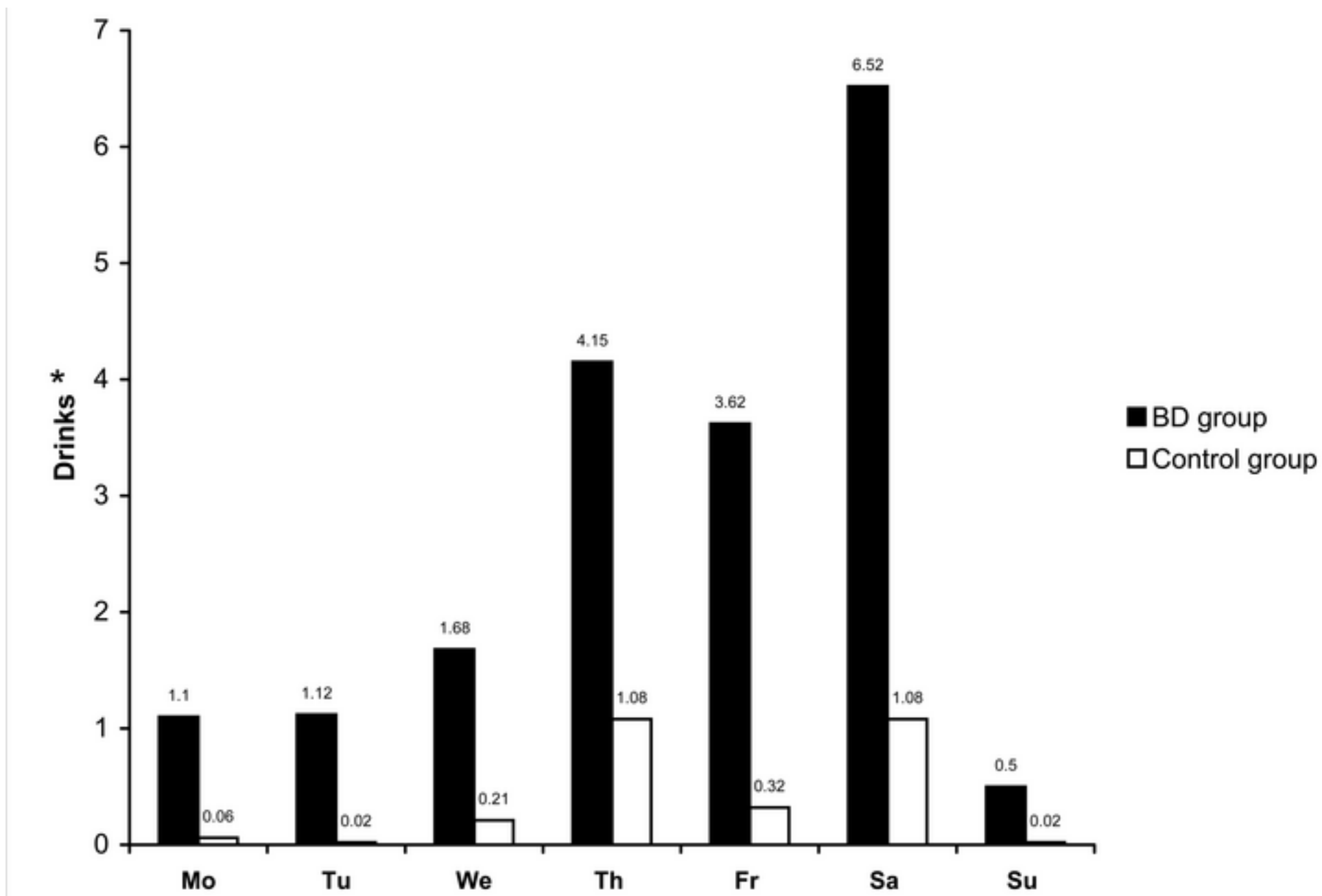
Behavioral Performance	Control	BD
Correct Response time (ms)	579.39 \pm 151.68	573.02 \pm 167.21
False alarms time (ms)	583.87 \pm 183.24	578.77 \pm 173.54
% Correct responses	84.42% \pm 7.82	84.77% \pm 11.2
% False alarms	3.21% \pm 1.61	3.43% \pm 1.9
% Omissions	1.13% \pm 0.45	0.95% \pm 0.56

Table 3. Brain areas with significantly lower activation associated to LPC in the binge drinking than in the control group for matching stimuli.

Anatomical region (BA)	MNI coordinates	Log-F-ratio
Anterior Prefrontal Cortex (aPFC)		
Superior Frontal Gyrus (10)	(20, 65, 10)	-2.88*
Medial Frontal Gyrus (10)	(15, 65, 15)	-2.86*
	(10, 65, 15)	-2.85*

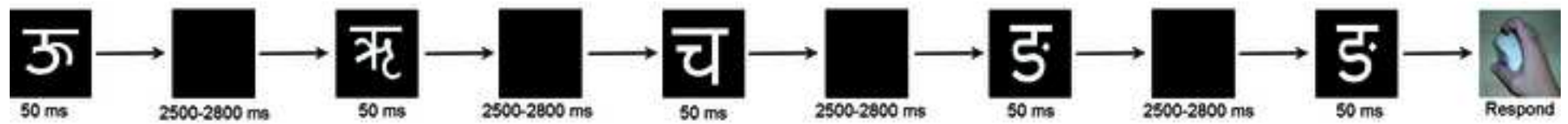
* corrected $P < 0.05$; BA: Brodmann area; MNI: Montreal Neurological Institute.

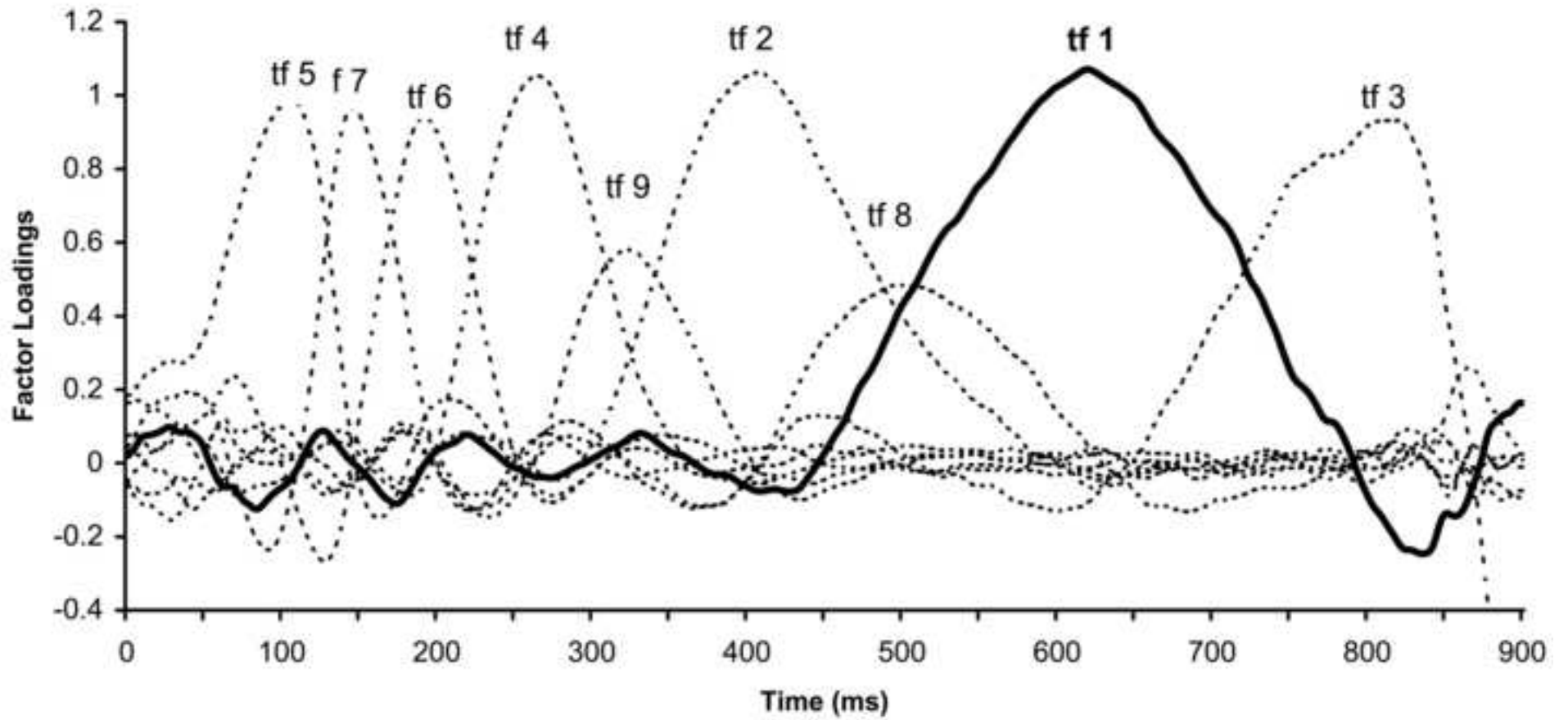
Figure 1_revised
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* 1 standard alcoholic drink equals 10 g of alcohol

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Postprint (final draft post-refereeing)

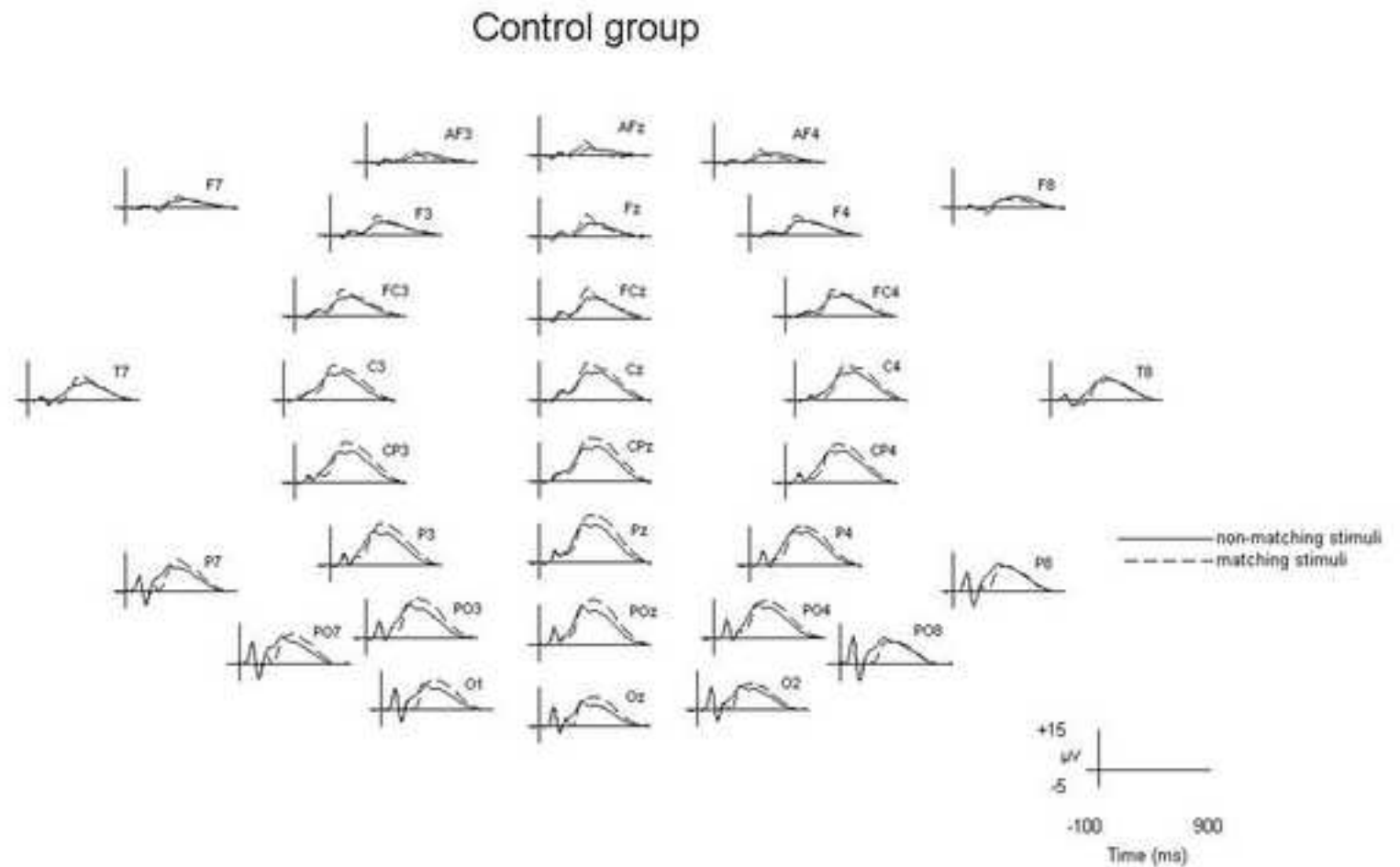
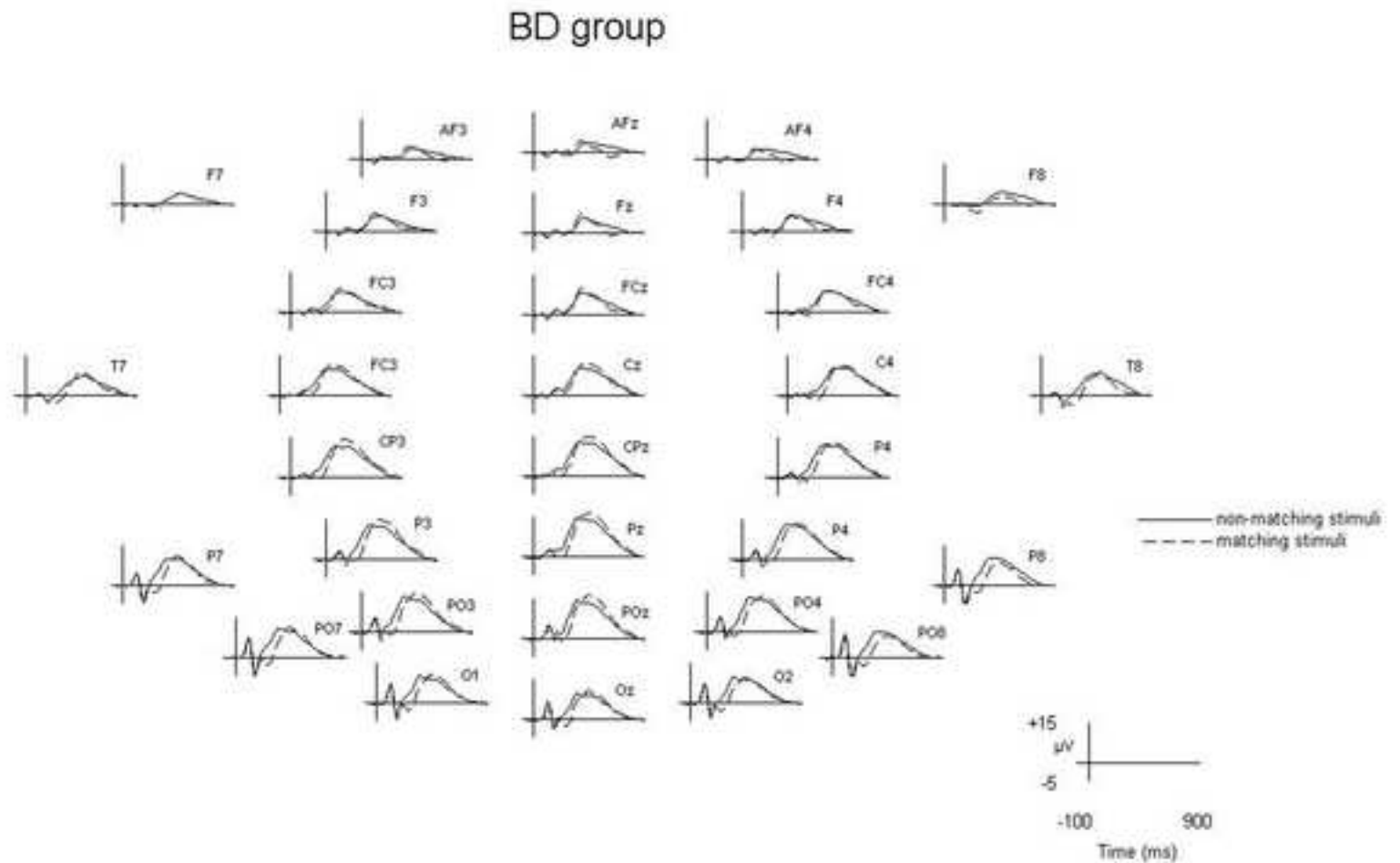
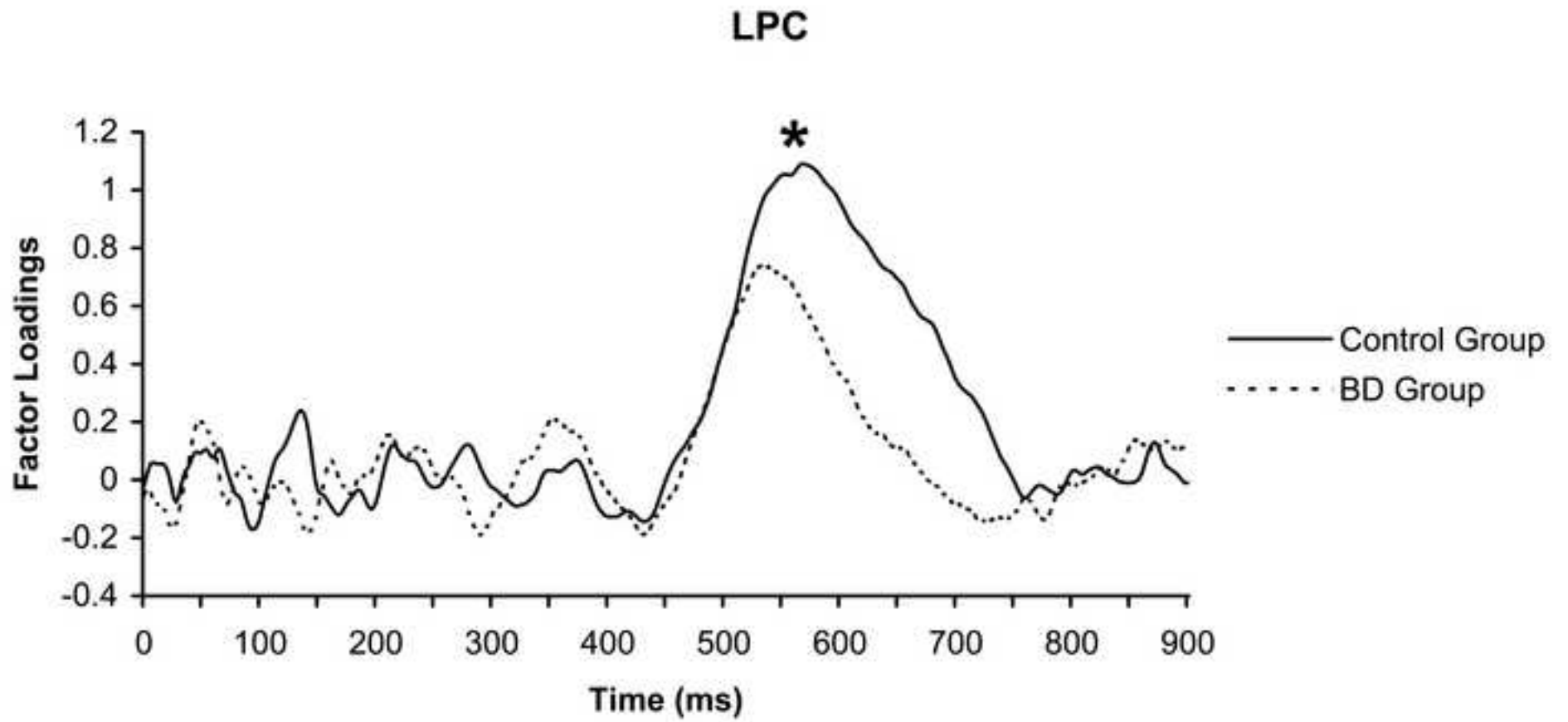
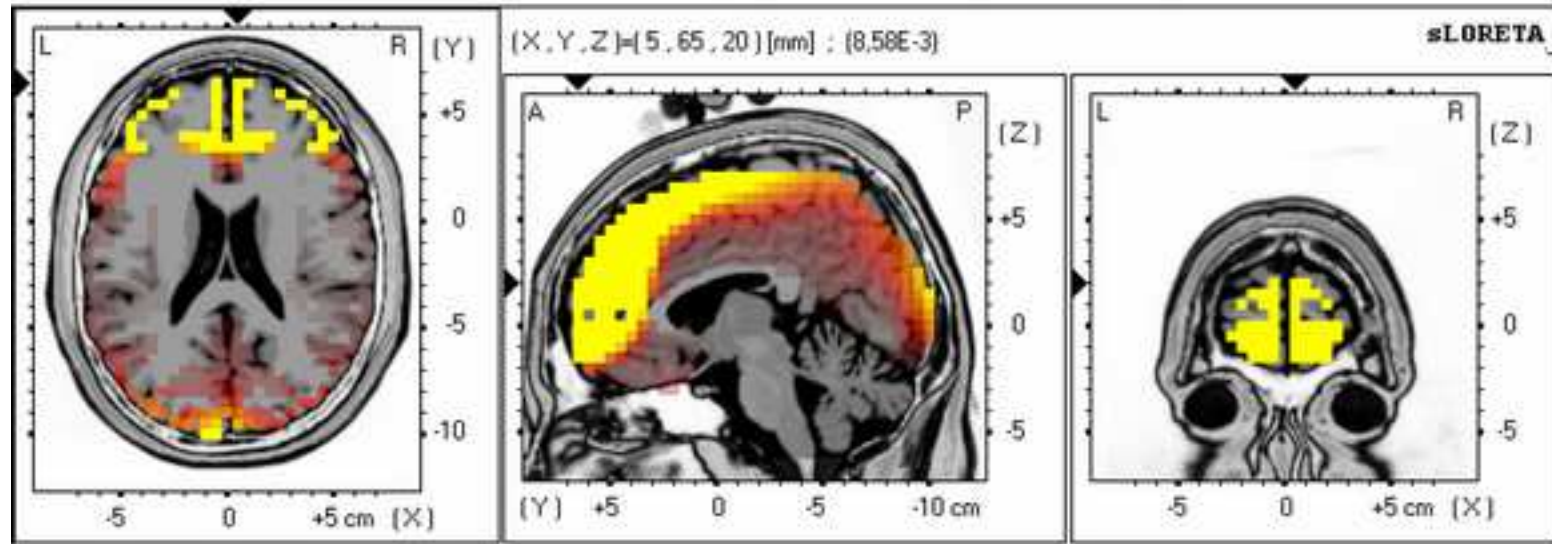
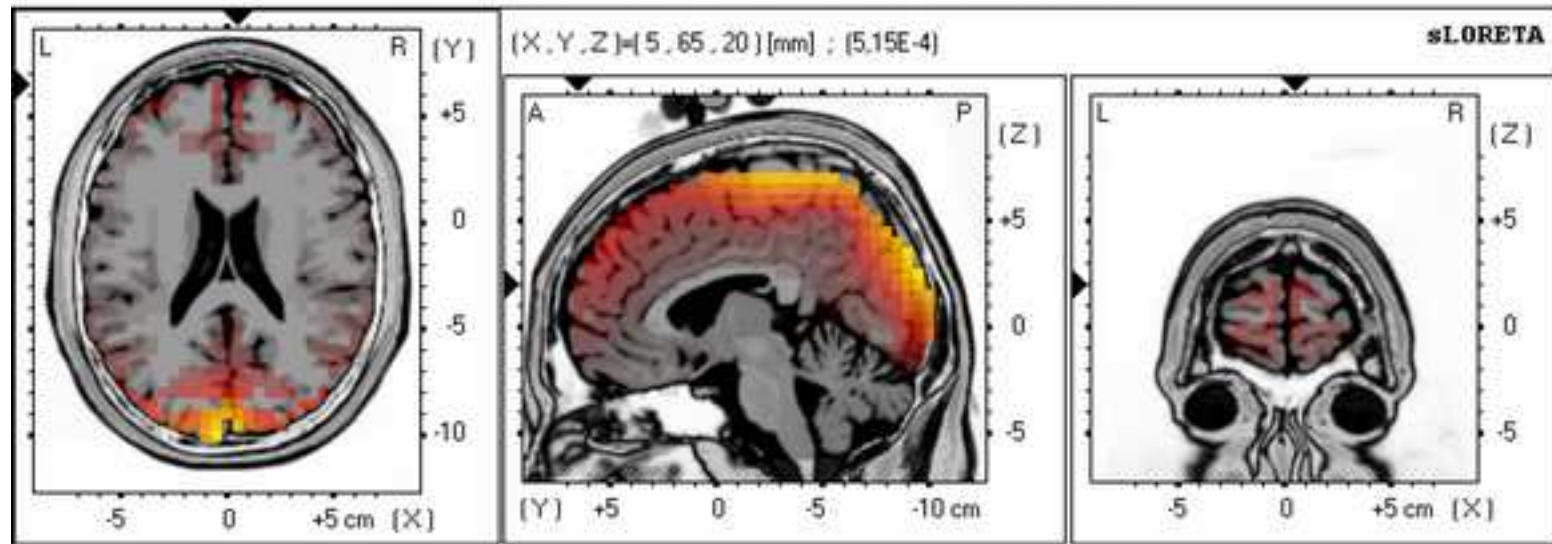


Figure 5_revised

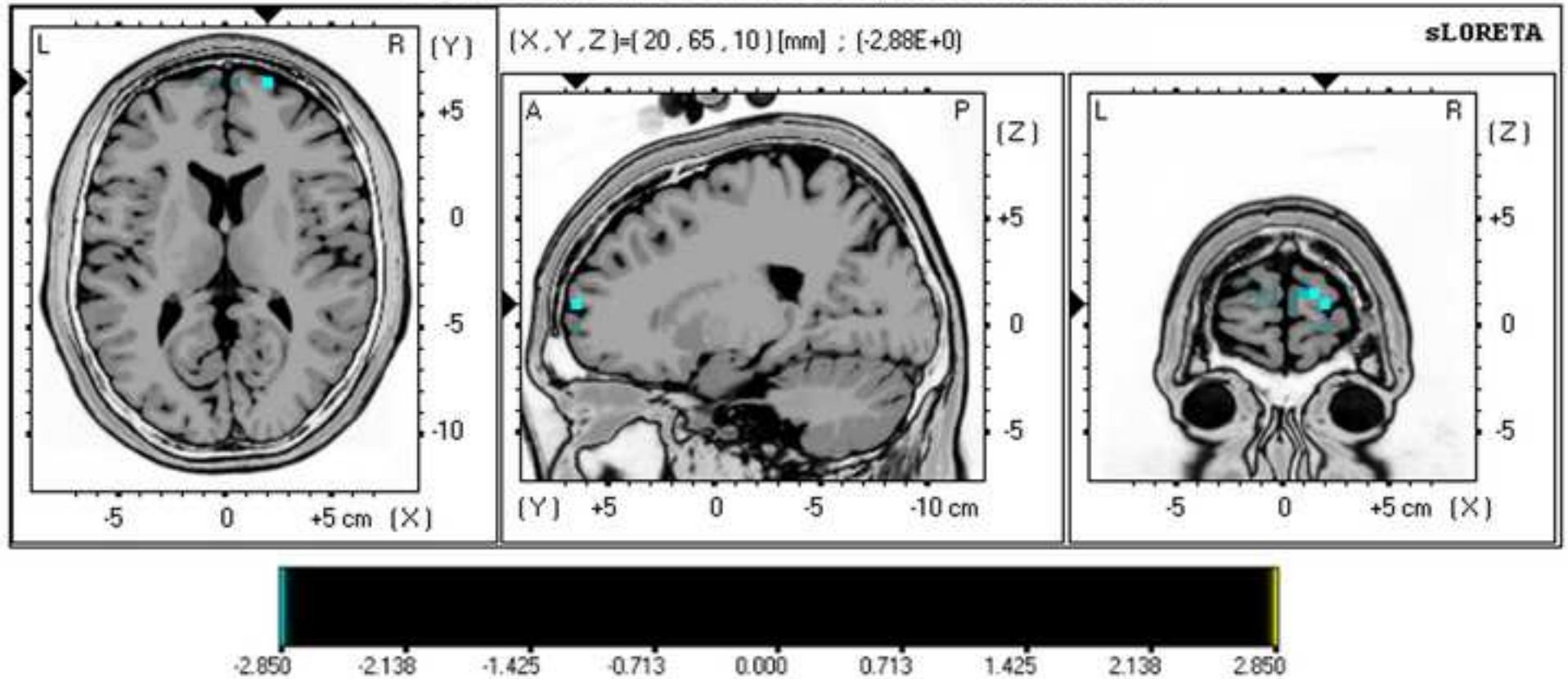
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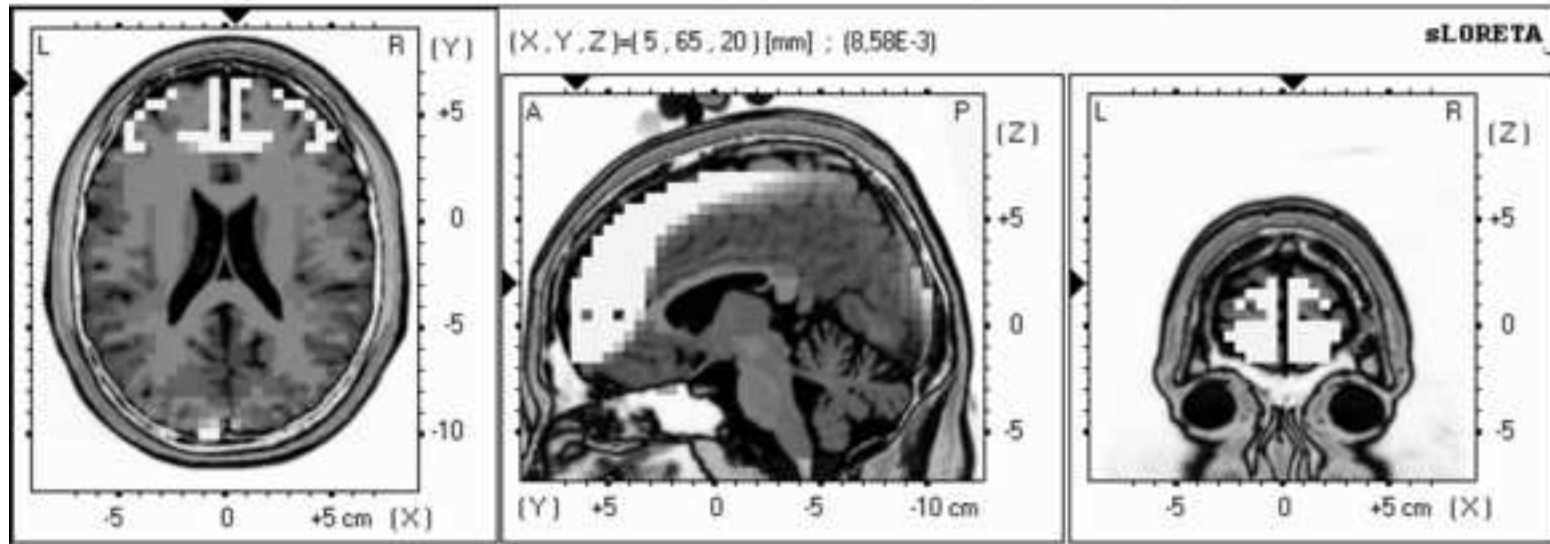


Control Group (matching stimuli)**BD Group (matching stimuli)**

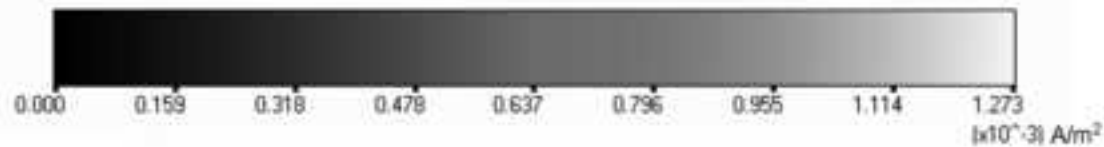
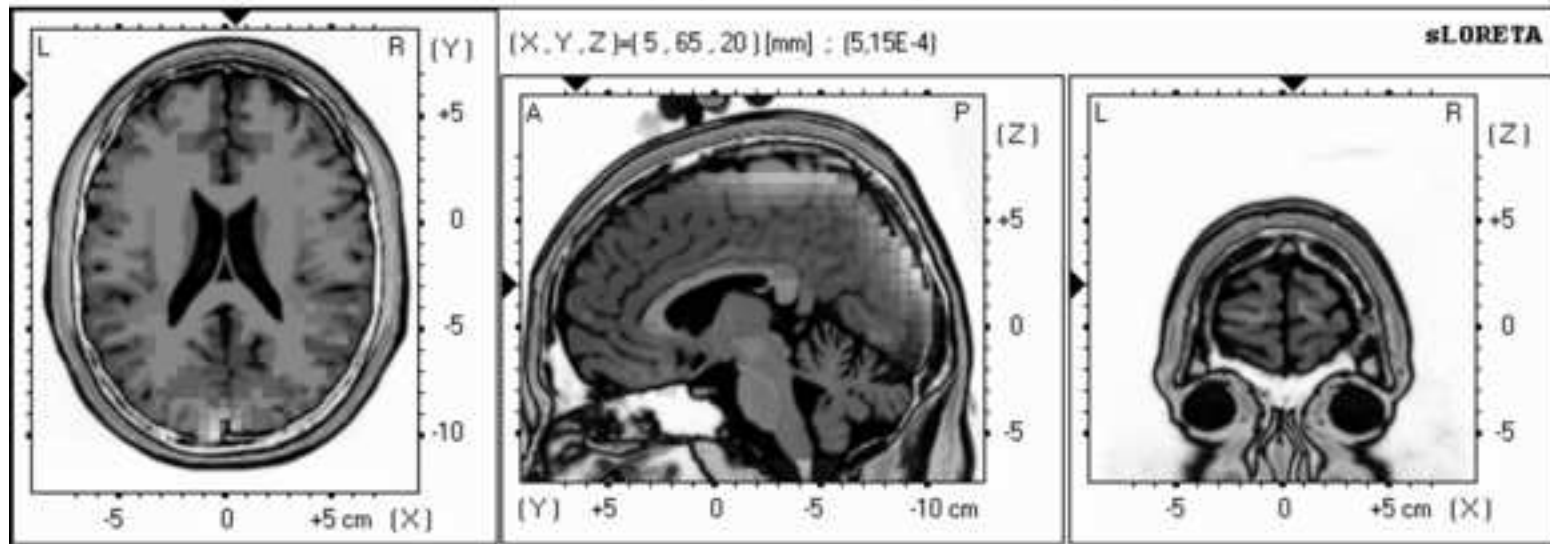
Between-group comparison (matching stimuli)



Control Group (matching stimuli)



BD Group (matching stimuli)



Between-group comparison (matching stimuli)

