

**EVOLUTION OF THE BINGE DRINKING PATTERN IN COLLEGE
STUDENTS: NEUROPHYSIOLOGICAL CORRELATES**

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Abstract: It is well-known that alcohol impairs response inhibition and that adolescence is a critical period of neuromaturation where cognitive processes such as inhibitory control are still developing. In the last years, growing evidence has showed the negative consequences of alcohol binge drinking on the adolescent and young human brain. However, the effects of cessation of binge drinking on brain functioning remain unexplored. The objective of the present study was to examine brain activity during response execution and inhibition in young binge drinkers in relation to the progression of their drinking habits over time. ERPs elicited by a Go/NoGo task were recorded twice within a two-year interval in 57 undergraduate students (25 controls, 22 binge drinkers and 10 ex-binge drinkers) with no personal or family history of alcoholism or psychopathological disorders. The results showed that the amplitude of NoGo-P3 over the frontal region correlated with an earlier age of onset of regular drinking as well as with greater quantity and speed of alcohol consumption. Regression analysis showed that NoGo-P3 amplitude was significantly predicted by the speed of alcohol intake and the age of onset of regular drinking. The group comparisons showed that, after maintaining a binge drinking pattern for at least two years, binge drinkers displayed significantly larger NoGo-P3 amplitudes than controls, whereas ex-binge drinkers were in an intermediate position between the two other groups (with no significant differences with respect to controls or binge drinkers). These findings suggest that binge drinking in young people may impairs the neural functioning related to inhibitory processes, and that the cessation of binge drinking may act as a brake on the neurophysiological impairments related to response inhibition.

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Abstract

It is well-known that alcohol impairs response inhibition and that adolescence is a critical period of neuromaturation where cognitive processes such as inhibitory control are still developing. In the last years, growing evidence has showed the negative consequences of alcohol binge drinking on the adolescent and young human brain. However, the effects of cessation of binge drinking on brain functioning remain unexplored. The objective of the present study was to examine brain activity during response execution and inhibition in young binge drinkers in relation to the progression of their drinking habits over time. ERPs elicited by a Go/NoGo task were recorded twice within a two-year interval in 57 undergraduate students (25 controls, 22 binge drinkers and 10 ex-binge drinkers) with no personal or family history of alcoholism or psychopathological disorders. The results showed that the amplitude of NoGo-P3 over the frontal region correlated with an earlier age of onset of regular drinking as well as with greater quantity and speed of alcohol consumption. Regression analysis showed that NoGo-P3 amplitude was significantly predicted by the speed of alcohol intake and the age of onset of regular drinking. The group comparisons showed that, after maintaining a binge drinking pattern for at least two years, binge drinkers displayed significantly larger NoGo-P3 amplitudes than controls, whereas ex-binge drinkers were in an intermediate position between the two other groups (with no significant differences with respect to controls or binge drinkers). These findings suggest that binge drinking in young people may impairs the neural functioning related to inhibitory processes, and that the cessation of binge drinking may act as a *brake* on the neurophysiological impairments related to response inhibition.

Keywords: Alcohol, Binge Drinking, Adolescence, Inhibitory Control, Response
Inhibition, Event-Related Potentials

Introduction

Inhibitory control is a core component of human behavior, generally defined as the ability to withhold or suppress actions or thoughts that are inappropriate. The broad range of psychiatric impairments that have been associated with inhibitory deficits, such as attention deficit hyperactivity disorder (Barkley, 1997; Nigg, 2001), obsessive compulsive disorder (Chamberlain et al., 2007; Penades et al., 2007) or substance use disorder (Verdejo-García et al., 2008), underlines the importance of this executive function. Alcohol abuse/dependence is one of the most common addictive behaviors (Rehm et al., 2005) and several studies point to a possible inhibitory deficit in alcoholics (Begleiter and Porjesz, 1999; Kamarajan et al., 2005).

Inhibitory control impairments related to alcohol use are especially worrying because failures in inhibition may weaken the ability to stop the alcohol intake and consequently promote the continuation of drinking (Field et al., 2008; Leeman et al., 2012; López-Caneda et al., in press). Adolescence is a period of life that is typically characterized by reduced inhibitory control (Casey et al., 2011; Luna et al., 2010), which might explain in part the increase in sensation/novelty seeking and risk taking behaviors observed during this stage (Dahl, 2004; Strang et al., 2013). Partly due to this elevated risk-taking behavior, adolescents and young people exhibit high rates of experimental drug use and substance use disorders (Rohde et al., 2001; Young et al., 2002). Alcohol is by far the most commonly used substance in occidental countries, with binge drinking (BD) being the dominant type of alcohol misuse during adolescence and youth (SAMHSA, 2009). This type of abusive drinking has generally been defined as the consumption of 5 or more drinks (4 or more for females) on one occasion within a 2-hour interval (which corresponds to blood alcohol concentrations around 0.08% or

above), at least once in the last two weeks or in the last month (Courtney and Polich, 2009; NIAAA, 2004).

In addition to the high prevalence of BD between adolescents and young people (around 10-40% of college students) (Archie et al., 2012; Caamaño et al., 2008; Johnston et al., 2012; Miller et al., 2007), and the major social and health consequences associated with it (traffic crashes, aggressions, unsafe sexual relations, low academic achievement, etc.) (Mota et al., 2010; Svensson and Landberg, 2013; Valencia-Martín et al., 2008; Viner and Taylor, 2007), the growing importance of the study of this phenomenon in the last decade comes from studies in animal models. These studies have shown that several BD episodes may cause more brain damage than an equivalent amount of alcohol without withdrawal episodes (Becker, 1994; Duka et al., 2004) and that this pattern of consumption may induce more harmful effects on the brain, as well as more cognitive impairments in adolescents than in adults (Crews et al., 2000; Risher et al., 2013; White and Swartzwelder, 2005).

Likewise, BD appears to be of particular concern in adolescents and young adults due to the major neuromaturational changes (such as synaptic pruning and myelination) that occur throughout this period (Squeglia et al., 2009; Guerri and Pascual, 2010). These developmental changes essentially involve the high-order association cortices, being the prefrontal cortex (PFC) the last region to reach maturity (Blakemore and Choudhury, 2006a; Gogtay et al., 2004). As a consequence of this brain maturation, cognitive functions supported in part by the PFC such as attention, working memory or inhibitory control are also developing and refining during this period of transition to adulthood (Casey et al., 2000; Luna and Sweeney, 2004; Yurgelun-Todd, 2007). Given that alcohol preferentially affects PFC (Moselhy et al., 2001; Oscar-Berman and Marinkovic, 2007) and directly reduces processes controlling inhibitory

control (Field et al., 2010; Perry and Carroll, 2008), the assessment of the neural dynamics of this still immature cognitive function in adolescents and young people with a BD pattern is of great interest.

A very common way to explore the neural correlates of response inhibition (the behavioral or motor dimension of inhibitory control [Diamond, 2013]) is the recording of event-related potentials (ERPs) during a Go/NoGo task. This task requires subjects to respond to some trials (Go stimuli) and to refrain from responding to others (NoGo stimuli). Two major ERP components related to response inhibition have been recorded: the NoGo-N2 component, a negative deflection peaking approximately 200-300 ms post-stimulus and reaching maximum amplitude at fronto-central electrodes; and the NoGo-P3 component, a positive wave peaking around 300-500 ms post-stimulus and with a more anterior distribution than the Go-P3 (Falkenstein et al., 1999; Kok et al., 2004). Although the debate about their functional meanings is still open, strong evidence relates the NoGo-N2 to conflict-monitoring processes and the NoGo-P3 to response inhibition (Bruin et al., 2001; Nieuwenhuis et al., 2003; Smith et al., 2008).

In a previous study (López-Caneda et al., 2012), our research group examined the consequences of maintaining a BD pattern for more than two years on the electrophysiological correlates of response inhibition. The main finding was the hyperactivation of the right inferior frontal cortex (rIFC) –a region typically involved in inhibitory control (Aron et al., 2004; Chambers et al., 2009)- during response inhibition, as well as a larger NoGo-P3 amplitude in youths engaged in BD for at least two years relative to aged-matched controls. This greater neural activation was interpreted as a compensatory neurofunctional mechanism that would allow binge drinkers (BDs) to achieve similar task performance as controls. Additional findings showing altered inhibitory functioning in young people with excessive alcohol intake come from other

recent study with heavy social drinkers, which reported delayed NoGo-P3 latencies in these subjects in an alcohol-related context (Petit et al., 2012b).

In adult chronic alcoholics, several studies have shown that neuropsychological performance as well as brain structure and function recover after a period of abstinence (Sullivan and Pfefferbaum, 2005; Bartsch et al., 2007). Similarly, behavioral and electrophysiological recovery of inhibitory control processes has been observed in drug abusers as a function of abstinence (Bell et al., in press; Morie et al., in press). Regarding BD, despite the growing evidence indicating that this drinking pattern can be associated with poor neuropsychological performance (Heffernan and O'Neill, 2012; Parada et al., 2011) as well as with anomalies in brain structure (Squeglia et al., 2012b; Lisdahl et al., 2013), connectivity (Jacobus et al., 2009; McQueeney et al., 2009) and functioning (Crego et al., 2010; Schweinsburg et al., 2011), the nature and the extent of the neuropsychological and neurofunctional impairments after giving up the BD pattern remain unknown. Recently, our research group reported that, while maintenance of BD was associated with lower verbal episodic memory and response monitoring than Non-BD, no significant differences were found between BD and Ex-BD (BD at initial but not at follow-up) nor between Non-BD and Ex-BD, i.e., the young Ex-BDs were in an intermediate position between controls and BDs (Mota et al., 2013).

In the present study, ERPs were recorded during a Go/NoGo task in a sample of young people who maintained or gave up this pattern of consumption over a two years interval and in a control group of abstemious and light drinkers. The aim was to assess the neurophysiological correlates of response inhibition associated to the evolution of drinking habits. We tested the hypotheses that measures related to the BD pattern of alcohol consumption correlate and predict the amplitude of the NoGo-P3 component of the ERPs, and that BD cessation may act as a *brake* on the neural processing alterations

related to response inhibition observed in BD subjects in our previous study (López-Caneda et al., 2012); this would be reflected in the ERPs as an *intermediate* NoGo-P3, i.e., lower amplitudes of the NoGo-P3 component in Ex-BDs than in BDs but larger than in controls.

Materials and Methods

Participants

Fifty-seven undergraduate students participated in the study. They were part of a longitudinal research following subjects from 18 to 23 years of age. They were evaluated at two different times, when they were 18-19 and 20-21 years old. On the basis of their responses to a questionnaire that 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) as well as other items regarding use of alcohol and other drugs, the subjects were included in three different groups: Control, BD and Ex-BD. The BD group consisted of those participants who (1) drank six or more standard alcoholic drinks (SADs; which equate to 10 gr of alcohol, according to the Spanish Health Authority's reference) on the same occasion one or more times per week, or (2) drank six or more SADs on the same occasion at least once a month and during these episodes drank at least three drinks per hour. This criterion fits well with other standardized criteria, because one Spanish SAD equals to 10 gr of alcohol, so the 6 drinks cutoff (60 gr) in two hours results in a blood alcohol concentration of 0.08 gr percent or above, which is the threshold established by the National Institute of Alcohol Abuse and Alcoholism for BD (NIAAA, 2004). Only participants who met these criteria at the time of both evaluations were selected (i.e. BDs had to maintain the drinking pattern for at least two years). Those subjects who

met the BD criteria in the first but not in the second evaluation were classified as Ex-BDs. Those who drank less than six SADs on the same occasion, less than once per month and at a maximum speed of consumption of two drinks per hour were included in the Control group. Thus, the sample comprised 25 controls (14 females), 22 BDs (11 females) and 10 Ex-BDs (7 females). Of this sample, ERP data from 46 participants were reported on previously (López-Caneda et al., 2012).

The exclusionary criteria were non-corrected sensory deficits, any episode of loss of consciousness for more than 20 min, history of traumatic brain injury or neurological disorder, personal history of psychopathological disorders (according to DSM-IV criteria), family history of major psychopathological disorders –including alcoholism and substance abuse- in first degree relatives, and use of illegal drugs except cannabis. Alcohol abuse was assessed in all subjects by the AUDIT. Participants with alcohol use disorder (AUDIT scores ≥ 20) were excluded.

The alcohol use measures were obtained in both evaluations mainly from the AUDIT and AUQ questionnaires, and subjects were referred to the past year to fill in it. These Measures of alcohol-related behavior were obtained in both evaluations as follows: Age of onset of regular drinking; total grams of alcohol in a standard week; number of times consuming 6 or more drinks per month; number of drinks in a standard drinking episode; and number of drinks consumed per hour (speed of alcohol consumption). These measures related to alcohol use encompass the three essential features generally used to define the BD pattern, i.e., quantity consumed in one occasion (number of drinks in a standard drinking episode), speed (number of drinks consumed per hour), and frequency of consumption (number of times consuming 6 or more drinks per month). The weekly quantity of alcohol intake (total grams of alcohol in a standard

week) was also considered here. The demographic and drinking characteristics of the three groups are shown in Table 1.

Procedure

The subjects were asked to abstain from consuming drugs and alcohol for 12 h before the experiment and not to partake in BD episodes in the 24 hours before the experiment, to prevent effects of acute alcohol intake and to rule out withdrawal effects. Additionally, they were instructed not to smoke or drink tea or coffee for at least 3 h before the assessments.

Participants had to perform a Go/NoGo task. They were instructed to fixate on a small cross located centrally on a CRT monitor. Squares or circles (green or blue) with a visual angle of $3^\circ \times 3^\circ$ were presented during 50 ms over the cross with a 1000-1400 ms interstimulus interval (onset-onset). Figures were equiprobably presented in a randomized order and their number ranged between 140 and 160. Participants had to press a button with their preferred hand to the Go trials (green circle and blue square) and not to respond to the NoGo trials (blue circle and green square).

All participants gave written informed consent and received monetary compensation for their participation. The experiment was undertaken in compliance with Spanish legislation and the Code of Ethical Principles for Medical Research Involving Humans Subjects outlined in the Declaration of Helsinki. The protocol was approved by the Bioethics Committee of the University of Santiago de Compostela.

Data analysis

Demographic and substance use variables were analyzed by one-way analyses of variance (ANOVA). With regard to behavioral data, only responses occurring between 100 and 1000 ms after the onset of a Go stimulus were considered as correct responses. The no-responses to NoGo stimuli were rated as correct inhibitions. Reaction time (RT) and percentage of correct responses and inhibitions were analyzed by one-way ANOVA.

EEG acquisition and analysis

The electroencephalogram (EEG) was recorded using a Braincap with 32 sintered Ag–AgCl electrodes located 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 and horizontal electrooculogram was recorded to control for eye movements and blinks. Electrode impedances were kept below 10 k Ω . EEG signals were continuously amplified and digitized at a rate of 500 Hz, and filtered with a 0.01–100 Hz band pass filter.

The EEG data were analyzed with BrainVision Analyzer software (Version 2.0.1). The blink correction method developed by Gratton and cols. (Gratton et al., 1983) was used to attenuate the contaminating effects of eye blinks. The data were 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, and epochs exceeding $\pm 80\mu\text{V}$ at any scalp electrode or those corresponding to incorrect responses (omissions or false alarms) were excluded. The number of rejected segments was similar across the two conditions (Go and NoGo) for the three groups.

ERP analysis

The EEG epochs corresponding to Go and NoGo trials were independently averaged. The ERPs were analyzed by a semiautomatic peak detection procedure and subsequently reviewed and manually corrected at each electrode. The P3 component was identified in the averaged waveforms elicited by Go and NoGo stimuli as the largest positive peak between 300 and 550 ms after the stimuli onset. Amplitude (μV) values of the P3 component were obtained for three regions by averaging the amplitudes measured at six electrode positions for each region: frontal (F3, Fz, F4, FC3, FCz, FC4), central (C3, Cz, C4, CP3, CPz, CP4) and parietal (P3, Pz, P4, PO3, POz, PO4). A repeated-measures ANOVA with one between-subject factor (Group: Control, Ex-BD and BD) and two within-subject factors (Evaluation: first and second evaluation; Region: frontal, central and parietal), was used to analyze each component (Go-P3 and NoGo-P3) separately (α level ≤ 0.05). Whenever appropriate, degrees of freedom were corrected by the conservative Greenhouse-Geisser estimate. All post hoc paired comparisons were performed with the Bonferroni adjustment for multiple comparisons, also with an α level ≤ 0.05 . Post hoc analyses were performed in some cases where significant main effects or interactions were not present because of the a priori interest in detecting subtle differences that could appear only in one of the two evaluation moments. Identical analyses were applied to the N2 component, which was identified as the largest negative peak between 200 and 320 ms after the stimuli onset.

Correlation analyses, corrected for multiple testing by bootstrap re-sampling (1000 replicates), were performed to determine whether some of the alcohol use measures obtained were associated with the mean amplitude of P3 in the frontal region for the NoGo condition and in the parietal region for the Go condition, the regions where the NoGo-P3 and the Go-P3 components, respectively, are optimally recorded (Falkenstein et al., 1999; Gajewsky and Falkenstein, 2013). Moreover, a

backward multivariate linear regression analysis was carried out to determine whether the alcohol-related measures that correlated with the P3 amplitude predicted this dependent variable.

Results

Substance Use Variables

At the first (eval1) and second (eval2) evaluation, groups did not differ in the regular use of tobacco or cannabis. However, groups differed in the following variables:

- Age of onset of regular drinking [$F(2,52) = 5.85; p = .005$]: BD subjects reported earlier age of onset of regular drinking than control subjects ($p < .001$).
- Total grams of alcohol in a standard week, both in the first [$F(2,51) = 21.14; p < .001$] and second [$F(2,51) = 43.77; p < .001$] evaluation: it was higher in BDs than in controls (eval1: $p < .001$; eval2: $p < .001$) and in Ex-BDs (eval1: $p = .004$; eval2: $p < .001$).
- Number of times per month consuming 6 or more drinks in a day, both in the first [$F(2,56) = 251.39; p < .001$] and second [$F(2,56) = 245.62; p < .001$] evaluation: at the first evaluation, it was higher in BDs and Ex-BDs than in controls, whereas at the second evaluation it was higher in BDs than in Ex-BDs and controls ($p < .001$ for all the pair comparisons).
- Number of drinks in a standard drinking episode, both in the first [$F(2,50) = 8.95; p < .001$] and second evaluation [$F(2,56) = 36.6; p < .001$]: at the first evaluation it was higher in BDs than in controls, whereas at the second evaluation it was higher in BDs than in Ex-BDs and controls ($p < .001$ for all the pair comparisons).
- Number of drinks consumed per hour (speed of alcohol consumption), both in the first [$F(2,56) = 65.38; p < .001$] and second [$F(2,56) = 13.41; p < .001$] evaluation:

at the first evaluation, it was higher in BDs ($p < .001$) and in Ex-BDs ($p < .001$) than in controls, whereas at the second evaluation it was higher in BDs than in Ex-BDs ($p = .029$) and controls ($p < .001$).

Behavioral Performance

Behavioral results are summarized in Table 2. There were not significant differences between groups (Controls, BDs and ExBDs) for any of the behavioral variables analyzed (RT, percentage of correct responses and percentage of correct inhibitions).

Electrophysiological results

The grand averages of the ERPs for each group in both conditions are shown in Figs 1 (Go condition) and 2 (NoGo condition).

Group comparisons

The analysis of the P3 component for the NoGo condition showed significant effects for the factor Region [$F(2,54) = 4.04, p = .02$], with larger amplitude on posterior than anterior regions (parietal > central > frontal; $p < .05$ for all the pair comparisons). The Evaluation factor had not a significant effect. The analysis neither showed significant Group effects nor a significant Group x Evaluation interaction. However, independent analysis for each evaluation moment revealed that in the second, but not in the first evaluation, the factor Group was significant [$F(2,54) = 4.4, p = .017$]. The post hoc analysis showed larger NoGo-P3 amplitudes in the BD than in the Control group [$F(2,54) = 3.79, p = .013$], but no differences were observed between the Control and Ex-BD groups, nor between the Ex-BD and the BD groups. The interactions Group x Region and Group x Evaluation x Region did not show significant effects, and the post

hoc analysis confirmed that the larger NoGo-P3 amplitude in the BD group relative to the control group in the second evaluation was significant in the three scalp regions (frontal [$F(2,54) = 4.02, p = .024$], central [$F(2,54) = 4.42, p = .017$] and parietal [$F(2,54) = 3.25, p = .046$]); differences did not emerge at any region between the Control and the Ex-BD groups, nor between the Ex-BD and the BD groups. This post hoc analysis also revealed significantly lower NoGo-P3 amplitudes in the second than in the first evaluation in the Control group on the frontal region [$F(1,53) = 4.04, p = .049$], while no differences were detected in the other two groups (see Fig 3).

The analysis of the P3 component for the Go condition only revealed significant effects for the factor Region [$F(2,54) = 28.36, p < .001$]. Unlike our first study (López-Caneda et al., 2012), the remaining factors did not reveal significant effects. This result may be due to loss of statistical power derived from the inclusion of the third group (the Ex-BDs), since subsequent analyses including only the Control and BD groups, showed that, as in the first study, the BDs had larger P3Go amplitudes than controls [$F(1,45) = 4.83, p = .033$].

The analysis of the N2 component did not show significant effects or interactions involving the Group factor in either of the two conditions, Go and NoGo.

Correlation and regression analysis

The results of the correlation analysis (Fig 4) revealed a negative correlation between the age of onset of regular drinking and the NoGo-P3 amplitude over the frontal region in the second evaluation [$r = -.332, p = .015$]. The frontal NoGo-P3 amplitude in the second evaluation was also positively correlated with the variables speed of alcohol consumption (number of drinks consumed per hour) [$r = .320, p = .015$] and weekly quantity of alcohol consumed (total grams of alcohol in a standard week) [$r = .345, p =$

.009]. The Go-P3 amplitude over the parietal region did not show significant correlations with any of the alcohol use measures. There were no significant correlations between the amplitude values of the Go-P3 and NoGo-P3 components and the alcohol use variables at the first evaluation.

Given that other psychological factors such as impulsivity or anxiety can influence the P3 amplitude (Rossignol et al., 2005; Russo et al., 2008), we performed a number of correlation analyses to assess whether impulsivity –as measured by the Barrat Impulsiveness Scale, BIS-11 (Patton et al., 1995)- and anxiety –as measured by the Symptom Check List-90-Revised, SCL-90-R (Derogatis, 2002)- were related to the amplitude values of Go-P3 and NoGo-P3. There were no significant correlations between the scores in these psychological tests and the Go-P3 and NoGo-P3 amplitudes in any region.

With regard to the backward multivariate linear regression analysis, the independent variables were those that showed a correlation with the amplitude values of NoGo-P3, i.e., age of onset of regular drinking, number of drinks consumed per hour and total grams in a standard week. The dependent variable was the NoGo-P3 amplitude over the frontal region. The results (shown in Table 3) revealed that earlier onset of regular drinking along with greater speed of alcohol intake predicted larger NoGo-P3 amplitudes over the frontal region during the second evaluation (percentage of explained variance = 15%).

Discussion

This is the first study to assess electrophysiological brain activity in young BD subjects including those that, after maintaining a BD pattern, abandon this form of heavy alcohol intake. The results showed that larger NoGo-P3 amplitudes over the frontal region

during the second evaluation correlated with an earlier age of onset of regular drinking as well as with greater quantity and speed of alcohol consumption. Likewise, greater speed of alcohol intake along with an earlier age of onset of regular drinking predicted larger NoGo-P3 amplitudes over the frontal region. Our findings also revealed that, while the BDs displayed larger NoGo-P3 amplitudes than controls during response inhibition at follow-up, the Ex-BDs had an intermediate NoGo-P3 amplitude, i.e., the ERP component related to inhibitory control did not differ from that observed in the BD group nor in the Control group.

Results from different neuropsychological, neuroimaging and psychophysiological studies have associated alcohol use-related measures with disruptions in cognitive performance as well as in brain structure and functioning of young BDs. For instance, an earlier onset of BD has been associated with poorer decision making (Goudriaan et al., 2007), and the peak number of drinks during a binge episode in the past 3 months has been shown to predict smaller cerebellar volumes (Lisdahl et al., 2013). Similarly, the number of alcohol doses consumed per occasion correlated with higher activity in the dorsomedial prefrontal cortex during a working memory task (Campanella et al., 2013), and an earlier onset of regular drinking and a greater quantity and intensity of consumption were linked to larger P3b amplitudes during an oddball task (López-Caneda et al., 2013).

In the present study, we found that larger NoGo-P3 amplitudes on the frontal region during the second evaluation were associated with an earlier age of onset of regular drinking as well as with greater speed of consumption and greater weekly quantity of alcohol intake. Likewise, greater speed of alcohol intake along with an earlier age of onset of regular drinking predicted larger NoGo-P3 amplitudes over the frontal region during the second evaluation. In other words, it seems that one of the

hallmarks of BD, the intensive and concentrated alcohol intake in a few hours, together with a younger age of starting regular drinking, increases the susceptibility to experience anomalies in neural activity associated with response inhibition. However, there were no significant correlations between the amplitude values of the Go-P3 and NoGo-P3 components and the alcohol use variables at the first evaluation. This may be due to that, at the time 1, subjects had not been binge drinkers for a long time and, consequently, the psychophysiological anomalies may not have emerged yet. However, significant correlations between the amplitude values and the alcohol use measures surfaced at the follow-up, which appears to indicate that the alcohol has an accumulative effect over time on the brain activity and therefore on the ERPs.

On the other hand, there are a growing number of studies revealing specific neurocognitive anomalies in adolescents and young people with a BD pattern. Cognitive processes such as attention or working memory have been found to be sensitive to the effects of heavy alcohol drinking (Hartley et al., 2004; Parada et al., 2012). Inhibitory control also appears to be particularly affected by BD. As such, neuropsychological studies have revealed poor performance in several tasks assessing inhibitory processes in young BDs (Nederkoorn et al., 2009; Scaife and Duka, 2009; Townshend and Duka, 2005).

Neurofunctional studies using ERPs and functional magnetic resonance imaging (fMRI) have also shown abnormal neural activity patterns in young BDs (Hermens et al., 2013; Maurage et al., 2013). In ERP studies, several components associated with different cognitive processes have been shown to be affected in young people with a BD pattern. Thus, components related to perception (P1/N1), attention (N2/P3), working memory (P3) or inhibitory control (NoGo-P3) have been found to display anomalous amplitude and latency values in the BDs with regard to their peer controls (Crego et al.,

2009, 2012; Ehlers et al., 2007; López-Caneda et al., 2012, 2013; Maurage et al., 2009, 2012; Petit et al., 2012a,b, 2013; Smith and Mattick, 2013; Watson et al., 2014).

Concerning the P3 component, three studies conducted by Campanella and cols. have shown longer P3 latencies in BDs, which have been considered as an index of decreased speed of neural processing related to decisional processes (Maurage et al., 2009, 2012) as well as a sign of prioritized processing of alcohol-related cues (Petit et al., 2012b). The effects of BD on the P3 amplitude are still controversial, since while some studies have shown increased P3 amplitude in BDs (Crego et al., 2012; López-Caneda et al., 2013; Petit et al., 2013; Watson et al., 2014) others have observed the opposite effect (Ehlers et al., 2007; Maurage et al., 2012). These apparently inconsistent results may be due to varying factors such as the experimental paradigms (oddball with and without alcohol cues, Go/NoGo, stop-signal and facial discrimination tasks), the reduced sample sizes (with no more than forty subjects with a BD pattern in any of the studies), or the heterogeneity of the BD populations (subjects with or without family history of alcoholism or psychiatric comorbidity, different quantity and frequency of alcohol consumption, etc.).

In the present study, as mentioned above, an increased NoGo-P3 associated with successful inhibition was observed in youths who had maintained a BD pattern of alcohol consumption for at least two years, compared to their peer controls. Given that P3 amplitude has been shown to increase with the amount of cognitive resources recruited to perform response inhibition tasks (i.e. the more intense the inhibitory process is, the larger the NoGo-P3 amplitude will be) (Pfefferbaum et al., 1985; Donkers and van Boxtel, 2004; Yuan et al., 2008), the enhanced NoGo-P3 amplitude in BDs observed in this study may reflect the use of additional neural resources to enable efficient response inhibition. The Ex-BDs were in an intermediate position between the

two extremes (controls and BDs), suggesting that once the BD pattern is abandoned, the need for an enhanced neural recruitment is diminished. Thus, cessation of binge alcohol intake could act as a *brake* on neural impairments underlying inhibitory control, thereby diminishing the “neural effort” or the allocation of additional cognitive resources to withhold the response.

The enhanced recruitment of neural regions during cognitive processing in young BDs is consistent with fMRI studies, which have reported increased neural activity related to verbal learning (Schweinsburg et al., 2010, 2011), decision making (Xiao et al., 2013), working memory (Squeglia et al., 2012a; Campanella et al., 2013) and inhibitory control (Wetherill et al., 2013) in young subjects with a BD pattern. Together, these results show that binge alcohol consumption may lead to compensatory brain activity, which would allow BDs to maintain an efficient behavioral performance.

An alternative interpretation for the neural activity patterns observed in BDs and Ex-BDs has to do with the neuromaturational changes occurring during adolescence and early adulthood. Adolescence is a period of relevant changes in brain volume and connectivity involving specially the PFC (Gogtay et al., 2004; Sowell et al., 2004). An important difference between the PFC and other cortical regions is the gradual decrease in the total amount of synapses (and the strengthening of remaining synaptic connections) that occurs during the transition from childhood to adulthood (Blakemore and Choudhury, 2006b; Giedd, 2004). This gradual reduction in synaptic density, along with the myelination processes, parallels the progressive improvement of cognitive abilities (Silveri et al., 2006, 2008; Yurgelum-Todd, 2007). Thus, from childhood to early adulthood, cognitive processes such as working memory or inhibitory control become more efficient (Luna et al., 2004; McAuley and White, 2011).

The refinement of cortical networks along with the cognitive development through adolescent years has been associated with increased “neural efficiency”, i.e., the transition from a greater and diffuse neural activity to a lower and focal cortical activation (Casey et al., 1997; Durston and Casey, 2006; Gaillard et al., 2000). As such, although the findings are still equivocal (Adleman et al., 2002; Luna, 2001; Rubia et al., 2007), several studies examining age-related differences in brain activation associated with inhibitory control have reported a progressive reduction in PFC activity during response inhibition from childhood to adulthood, which is linked to better inhibitory performance (Booth et al., 2003; Casey et al., 1997; Somerville et al., 2011).

Taking into account that the larger NoGo-P3 amplitude has been related to the use of more neural resources to perform an efficient inhibition (Donkers and van Boxtel, 2004; Yuan et al., 2008), the improvement in neural efficiency throughout adolescence would be expected to result in a reduction of the NoGo-P3 amplitude. In agreement with this hypothesis, in our study, a significant attenuation of NoGo-P3 amplitude between the first and second evaluation was observed over the frontal region only in the control subjects (Fig 3).

The different pattern of development of the NoGo-P3 component between groups might be related to the neuromaturational delay hypothesis associated with excessive alcohol intake. In this sense, the notion that BD may alter the synaptic pruning processes that take place in the PFC during adolescence and youth has been recently suggested from a study conducted by Squeglia and cols., which showed that female BDs had thicker cortices in frontal regions than female controls (Squeglia et al., 2012b). On the basis of these findings, the authors proposed a relationship between thicker frontal cortices and less neurodevelopment (reduced cortical pruning) as a result of excessive alcohol intake. In line with this proposal, we have recently observed larger

grey matter volume in the dorsolateral prefrontal cortex in BD subjects in comparison with controls, which correlated positively with the quantity and speed of alcohol intake (Doallo et al., 2013). Together, these findings are congruent with a potential neuromaturative delay of PFC in young BDs that would result in a less efficient neural functioning and could underlie the poor neuropsychological performance as well as the neurofunctional anomalies observed in these subjects (Jacobus and Tapert, 2013).

In sum, adolescents and young BDs might exhibit a neuromaturational delay linked to reduced neural efficiency which would lead to altered (increased) NoGo-P3 amplitude. The Ex-BDs would be in an intermediate position, displaying greater neural efficiency than persistent BDs but lower than controls. In either case, future structural and functional studies are needed to clarify the developmental pattern followed by subjects who cease (or persist in) the BD pattern.

All these findings highlight the major consequences of BD on the brain at different levels (cognitive, structural and functional) and draw attention to the need for interventions aimed to mitigate the harmful effects associated with alcohol use in young people. In chronic alcoholics, several studies have shown that after withdrawal, a partial reversibility of cognitive abilities as well as brain functioning and structure takes place (Colrain et al., 2012; Fein et al., 2006; Johnson-Greene et al., 1997; O'Neill et al., 2001; Rosenbloom et al., 2007; Sullivan and Pfefferbaum, 2005;). Animal studies with rats exposed to a BD pattern have also shown recovery from different brain anomalies induced by a single BD episode after abstinence (Zahr et al., 2010). Therefore, intervention strategies for reducing binge alcohol use could result in the recovery from the neurotoxic effects of BD. Importantly, given that excessive alcohol intake is associated with deterioration of inhibitory control abilities which, in turn, may promote the continued consumption of the substance (López-Caneda et al., in press; Noël et al.,

2010), therapeutic programs aimed at strengthening inhibitory control processes might be effective for reducing the binge alcohol use (e.g., Houben et al., 2011).

Finally, regarding the substance use variables, the three measures related to the characteristics defining the BD pattern, and consequently to the classification criteria (monthly consumption of 6 or more drinks, number of drinks per episode, and number of drinks per hour) confirmed the changes with time in Ex-BDs: they did not differ from BDs at the first evaluation or from controls at the second evaluation. However, some variables indicated that, at the first evaluation, those subjects who gave up BD two years later were lighter consumers than those who persisted: they were in an intermediate position between the BD group and controls (but without significant differences) in the age of onset of regular drinking and the number of drinks per episode, and, importantly, they were significantly different from the BD group (but not from controls) in the quantity of weekly consumption. This suggests that this measure might be relevant to discriminate between those subjects who will give up BD and those who will persist in this pattern of consumption.

This study displays some limitations that should be taken into account. Due to the reduced number of Ex-BDs participants, these data should be considered as preliminary. Moreover, although the Ex-BDs were in an intermediate position between the controls and the BDs, there were no significant differences with any of these groups, so the interpretation of the results is still tentative and new studies are necessary to test this trend. Likewise, the small sample size precluded us from exploring potential differences between males and females who gave up BD. Future studies with larger sample sizes will be necessary to confirm the present results and to explore the possible influence of gender.

In summary, this is the first study examining brain activity patterns in young people who, after maintaining BD habits for some time, give up this pattern of consumption. ERP analyses during a Go/NoGo task revealed that a larger NoGo-P3 amplitude over the frontal region during the second evaluation was associated with an earlier onset of regular drinking and with a greater speed and weekly quantity of alcohol intake; furthermore, an earlier age of starting regular drinking along with greater speed of alcohol intake predicted larger frontal NoGo-P3 amplitude. Moreover, while persistent BDs displayed larger NoGo-P3 amplitudes than controls during response inhibition, the Ex-BDs had an intermediate NoGo-P3 amplitude, i.e., the ERP component related to inhibitory control did not differ from that observed in the BD or in the Control group. These results suggest that (1) BD impairs the neural functioning involved in response inhibition, and (2) the cessation of BD could act as a *brake* on the neurophysiological impairments related to response inhibition. However, these interpretations require further investigation.

Finally, these findings have potential applied implications. The changes induced by BD in neural activity related to inhibitory control might contribute to the development of disinhibitory behaviors such as substance abuse. Our results appear to show that, once BD behavior ceases, electrophysiological anomalies involved in response inhibition also cease, so early intervention aimed to reduce/eliminate BD behavior could slow down the progress of these anomalies and the potential subsequent development of disinhibitory behaviors.

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Tables

Table 1. Demographic and drinking characteristics of the Control, Ex-Binge Drinking and Binge Drinking groups at the first and second evaluation (mean \pm SD).

	First Evaluation			Second Evaluation		
	Controls	Ex-Binge Drinkers ^b	Binge Drinkers	Controls	Ex-Binge Drinkers	Binge Drinkers
N (females)	25 (14)	10 (7)	22 (11)	–	–	–
Handedness (right/left)	23/2	10/0	21/1	–	–	–
Caucasian ethnicity (%)	100	100	100	–	–	–
Regular tobacco smokers	1	1	2	1	1	4
Regular use of cannabis (once a week)	0	1	3	0	0	0
Age of onset of regular drinking ^a	15.7 \pm 0.9*	15.1 \pm 0.7	14.5 \pm 1.4*	–	–	–
Number of years drinking alcohol regularly	2.8 \pm 1*	3.7 \pm 1	4.3 \pm 1.5*	4.6 \pm 1*	5.5 \pm 1	6.2 \pm 1.5*
Total grams of alcohol in a standard week	40.6 \pm 62.9*	128.7 \pm 56.5¥	373.5 \pm 268*¥	38.6 \pm 33.4*	72.7 \pm 60.4¥	213.7 \pm 90.8*¥
Number of times consuming 6 or more drinks in a day per month	0 \pm 0.1*‡	2.2 \pm 1.5‡	2.9 \pm 1.4*	0.12 \pm 0.2*	0.2 \pm 0.3¥	4*¥
Number of drinks in a standard drinking episode	2.5 \pm 3.6*	9.7 \pm 3.4	19.6 \pm 21.3*	2.9 \pm 2.1*	4.3 \pm 2.9¥	11.3 \pm 4.6*¥
Number of drinks consumed per hour (speed of alcohol consumption)	0.9 \pm 0.8*‡	3.3 \pm 0.8‡	3.1 \pm 0.6*	0.8 \pm 0.7*	1.2 \pm 0.7¥	2 \pm 0.9*¥

* $p < .05$; significant differences between controls and BDs.

‡ $p < .05$; significant differences between controls and Ex-BDs.

¥ $p < .05$; significant differences between Ex-BDs and BDs.

^a This refers to the age in which participants began to drink frequently, and not to the age of onset of the binge drinking pattern.

^b Note that the Ex-BDs were part of the Binge Drinking group during the first but not during the second evaluation.

Table 2. Behavioral data at the first and second evaluation (mean \pm SD).

<i>Behavioral Performance</i>	<i>Controls</i>	<i>Ex-Binge Drinkers</i>	<i>Binge Drinkers</i>
First Evaluation			
Response Time (ms)	526.74 \pm 143.46	538.07 \pm 135.45	531.66 \pm 139.03
% Correct Responses	93.92 \pm 4.78	92.48 \pm 5.03	94.34 \pm 4.64
%Correct Inhibitions	95.94 \pm 5.02	97 \pm 3.03	96.9 \pm 3.31
Second Evaluation			
Response Time (ms)	518.96 \pm 132.01	542.36 \pm 125.8	521.28 \pm 131.26
% Correct Responses	95.86 \pm 4.85	96.02 \pm 3.1	96.7 \pm 3
%Correct Inhibitions	96.69 \pm 4.24	97.19 \pm 3.35	97.63 \pm 2.46

Table 3. Results of backward multiple linear regression analysis performed on NoGo-P3 amplitudes over the frontal region during the second evaluation. Earlier age of starting regular drinking and greater speed of alcohol intake were both predictors of larger NoGo-P3 amplitudes.

	Variables entered*	Variables excluded*	R square	R square corrected	β coefficient standardized	F	<i>p</i>
Model 1	AORD, SAC, TGSW		.218	.170	TGSW $\beta = .212$ AORD $\beta = -.255$ SAC $\beta = .185$	4.56	.007
Model 2	AORD, SAC	TGSW	.185	.152	AORD $\beta = -.301$ SAC $\beta = .275$	5.66	.006

* F probability to enter the model $p \leq 0.05$; F probability to exit the model $p \geq 0.10$

AORD: Age of onset of regular drinking; SAC: Speed of alcohol consumption (number of drinks consumed per hour); TGSW: Total grams in a standard week.

Figure Legends

Figure 1. Grand average of ERPs to the Go trials at the two evaluations from the control (green line), Ex-BD (orange line) and BD (red line) groups. Averages are shown for FCz, CPz and POz.

Figure 2. Grand average of ERPs to the NoGo trials at the two evaluations from the control (green line), Ex-BD (orange line) and BD (red line) groups. Averages are shown for FCz, CPz and POz.

Figure 3. ERPs to the NoGo trials from the control (green line), Ex-BD (orange line) and BD (red line) groups at the frontal region (obtained by averaging F3, Fz, F4, FC3, FCz and FC4 electrodes), during the first (solid line) and second evaluation (dashed line).

* $p < .05$; significant differences between the first and second evaluation.

Figure 4. Correlations between NoGo-P3 amplitude and alcohol drinking variables. Larger NoGo-P3 amplitude over the frontal region during the second evaluation was associated with (a) earlier onset of regular drinking, (b) greater quantity of alcohol consumed during a standard week and (c) greater speed of alcohol intake during a drinking episode.

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Figure 1

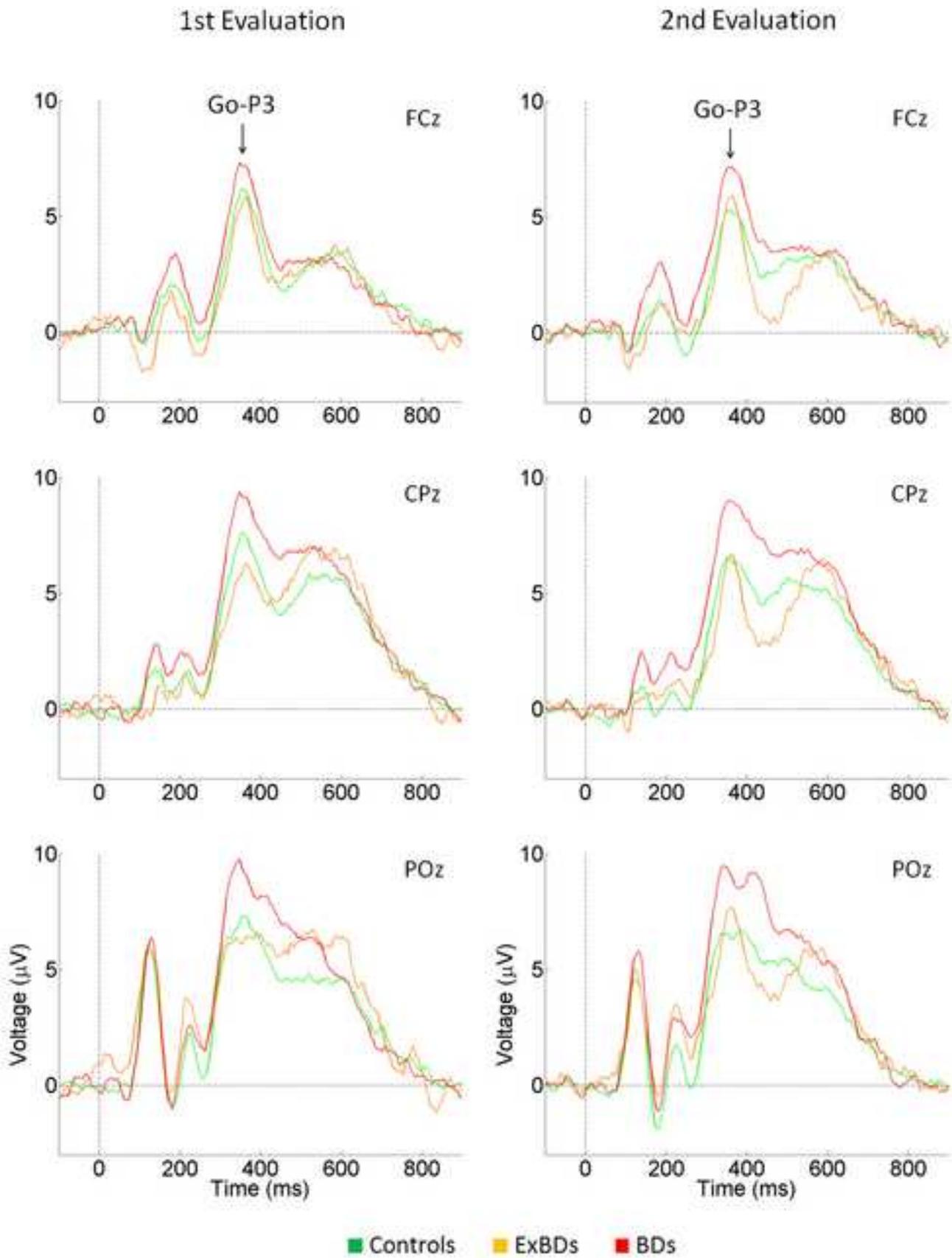


Figure 2

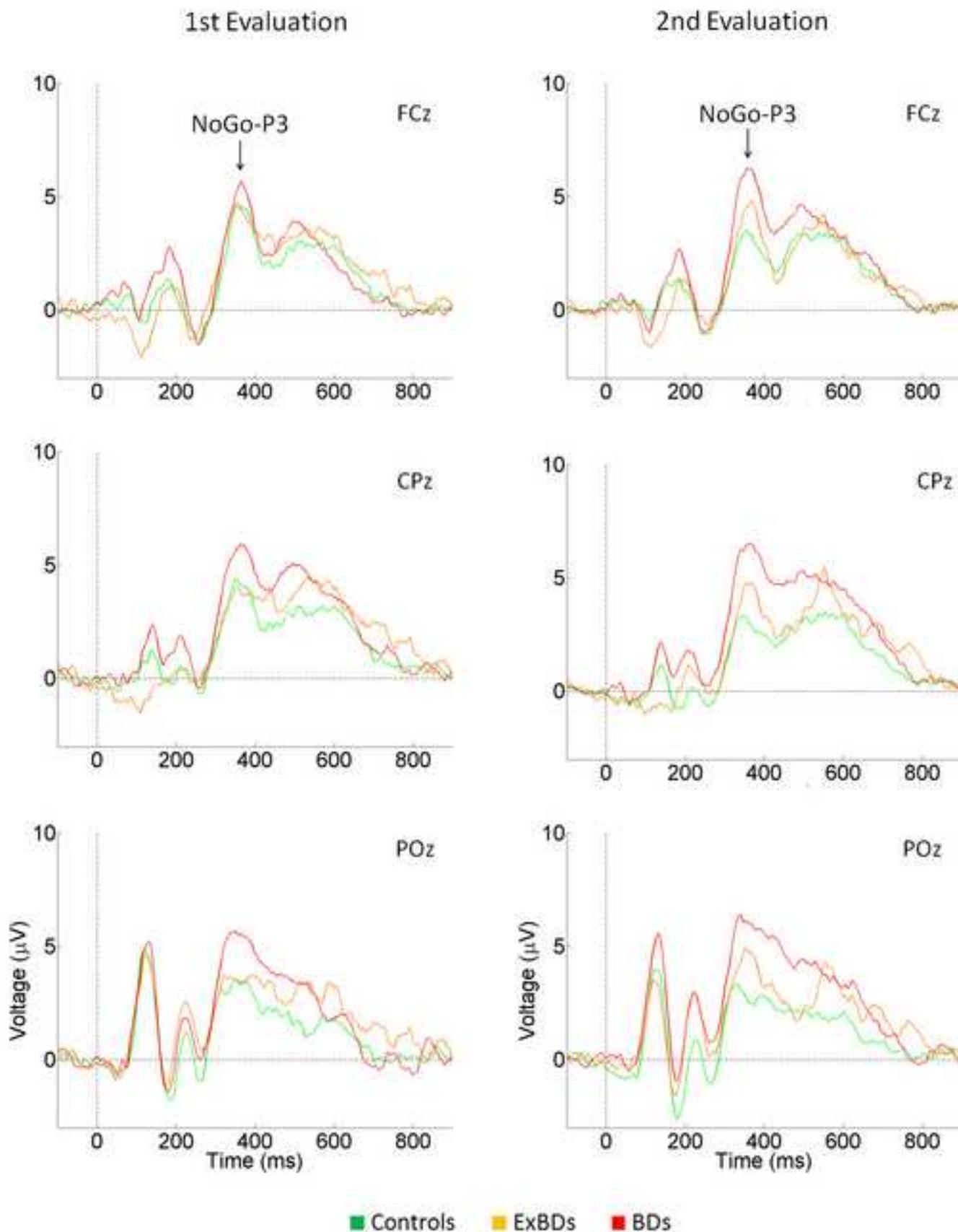


Figure 3

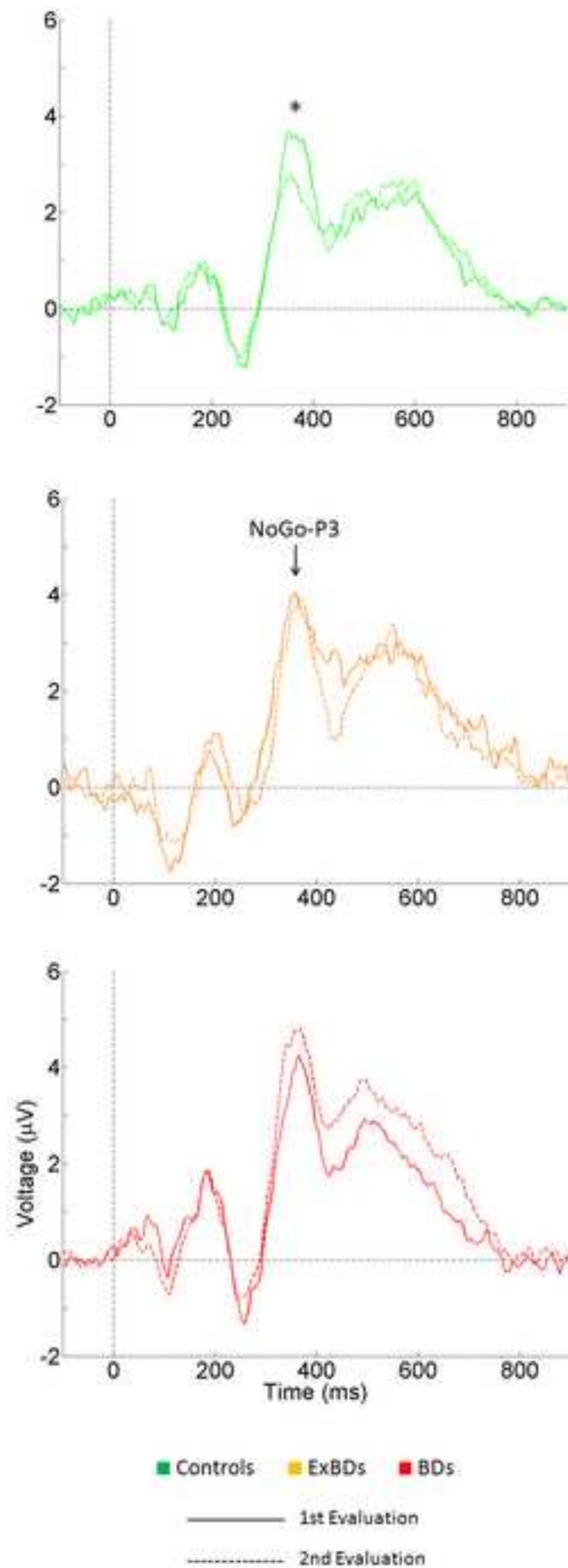


Figure 4

