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Decreased event-related theta power and phase-synchrony in young binge drinkers during target detection: An anatomically-constrained MEG approach

Angeles Correas[a], **Eduardo López-Caneda**[b], **Lauren Beaton**[a], **Socorro Rodríguez Holguín**[c], **Luis Miguel García-Moreno**[d], **Luis F. Antón-Toro**[e], **Fernando Cadaveira**[c], **Fernando Maestú**[e,f,g], and **Ksenija Marinkovic**[a,h]

[a] Department of Psychology, San Diego State University, San Diego, USA.

[b] Neuropsychophysiology Lab, Research Center on Psychology (CIPsi), School of Psychology, University of Minho, Braga, Portugal.

[c] Department of Clinical Psychology and Psychobiology, University of Santiago de Compostela, Spain.

[d] Department of Psychobiology and Methodology in Behavioral Sciences, Complutense University of Madrid, Madrid, Spain.

[e] Laboratory of Cognitive and Computational Neuroscience (UCM-UPM), Centre of Biomedical Technology (CTB), Madrid, Spain.

[f] Department of Experimental Psychology, Complutense University of Madrid, Spain.

[g] Network of Center for Biomedical Research (CIBER-bbn), Madrid, Spain.

[h] Department of Radiology, University of California at San Diego, San Diego, USA.

Abstract

Background: The prevalence of binge drinking (BD) has been on the rise in recent years. It is associated with a range of neurocognitive deficits among adolescents and young emerging adults who are especially vulnerable to alcohol use. Attention is an essential dimension of executive functioning and attentional disturbances may be associated with hazardous drinking. The aim of the study was to examine the oscillatory neural dynamics of attentional control during visual target detection in emerging young adults as a function of BD.

Method: Fifty-one first-year university students (18±0.6 years) were assigned to light drinking (LD, N=26), and BD (N=25) groups based on their alcohol consumption patterns. High-density magnetoencephalography (MEG) signal was combined with structural magnetic resonance imaging (MRI) in an anatomically-constrained MEG model to estimate event-related source power

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Please address correspondence to: Ksenija Marinkovic Ph.D., Department of Psychology, 5500 Campanile, Dr., San Diego State University, San Diego, CA 92182, USA. kmarinkovic@sdsu.edu, Telephone number: 619-594-1510.

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in theta (4–7 Hz) frequency band. Phase-locked co-oscillations were further estimated between the principally activated regions during task performance.

Results: Overall, the greatest event-related theta power was elicited by targets in the right inferior frontal cortex (rIFC) and it correlated with performance accuracy and selective attention scores. BDs exhibited lower theta power and dysregulated oscillatory synchrony to targets in the rIFC which correlated with higher levels of alcohol consumption.

Conclusions: These results confirm that a highly interactive network in the rIFC subserves attentional control, revealing the importance of theta oscillations and neural synchrony for attentional capture and contextual maintenance. Attenuation of theta power and synchronous interactions in BDs may indicate early stages of suboptimal integrative processing in young, highly functioning BDs.

Keywords

Binge drinking; alcohol; magnetoencephalography; theta oscillations; attention

1. INTRODUCTION

Binge drinking (BD) is highly prevalent among adolescents and young adults in most Western countries (Eurobarometer, 2010; Johnston, 2011;SAMHSA, 2013) and is associated with a wide range of negative social and health consequences (Hingson et al., 2017; Hingson and White, 2013). This pattern of consumption is characterized by intake of intoxicating quantities of alcohol in a short time interval interspersed with periods of abstinence (Courtney and Polich, 2009).BD is usually defined as imbibing five/four or more drinks for men/women within a two-hour interval, which is likely to bring blood alcohol concentration (BAC) to 0.08% or above (National Institute of Alcohol and Alcoholism, 2004). However, these levels are commonly exceeded by emerging young adults who engage in bouts of much higher levels of alcohol intake (Naimi et al., 2010; Patrick and Terry-McElrath, 2017; Terry-McElrath and Patrick, 2016).

Adolescence emerging into adulthood is a protracted but critical period of neurodevelopment characterized by profound changes (Sherman et al., 2014; Simmonds et al., 2014; Walhovd et al., 2012) which mainly involve prefrontal cortex (PFC) and other higher-order association areas (Gogtay et al., 2004; Lebel and Beaulieu, 2011) and contribute to refinement of cognitive efficiency (Casey et al., 2005). As it continues to mature well into mid 20’s, the adolescent brain is more sensitive to the impact of ethanol exposure, with the frontal lobes being particularly vulnerable (Cservenka and Brumback, 2017; Hermens et al., 2013; Jacobus and Tapert, 2013; Silveri et al., 2016; Squeglia et al., 2014). Extensive evidence obtained from rodent models indicates that BD during adolescence is a high risk factor for the development of alcohol-use disorders (AUD) and enduring neural changes (Crabbe et al., 2011; Crews et al., 2016).

Several studies have reported that BDs differ from light drinkers (LDs) on EEG measures in the absence of behavioral differences (Folgueira-Ares et al., 2017; López-Caneda et al., 2012, 2013). However, other studies report that BDs tend to have lower scores than light-drinkers (LDs) on tasks probing high-level cognitive abilities such as memory and executive functions (for reviews, see Stephens and Duka, 2008; Jacobus and Tapert, 2013; Petit et al., 2014). Attention is a key component of executive functions and is involved in minimizing distraction and in optimal allocation of cognitive resources to task-relevant stimuli (Diamond, 2013). Impairments of attention are related to increased impulsivity and may contribute to engaging in hazardous drinking (Crews and Boettiger, 2009; de Wit, 2009). Despite its importance for response inhibition and cognitive control, attention has been scarcely explored in BD population. Lannoy et al. (2017) used the Attention Network Task (Fan et al., 2005) and reported impairments of alerting and executive control dimensions of attention in BDs. Using the same task, Maurage et al. (2014) showed that alcohol-dependent individuals presented attentional deficits specifically in the executive control of attention compared with social drinkers. These results suggest that attentional disturbances might have a key role in the development of AUD in the context of broader cognitive impairments (Muller-Oehring and Schulte, 2014; Oscar-Berman and Marinković, 2007; Sullivan and Pfefferbaum, 2005). Convergence of neuroimaging and human lesions studies has indicated that the right-dominant fronto-parietal network is crucially involved in attentional processes (Klinke et al., 2017; Vossel et al., 2014). Functional MRI (fMRI) studies have confirmed engagement of a right-lateralized network during target detection with a nexus in the right inferior prefrontal cortex (Gitelman et al., 1999; Nobre et al., 1997; Shulman et al., 2010; Vossel et al., 2014).

A previous EEG study has reported alterations in event-related oscillations (ERO) in BDs during the same equiprobable Go/NoGo task as the one employed in the present study (López-Caneda et al., 2017). This study found lower delta and theta power during target detection in BDs. They proposed that this power decrease in low frequencies may reflect impairments in the neural circuit involved in both the activation and inhibition of a response. Moreover, ERO studies in individuals with AUD have reported attenuated power in slow frequencies (delta and/or theta) in alcoholics during Go/NoGo task (Colrain et al., 2011) and equiprobable Go/NoGo task (Kamarajan et al., 2004; Pandey et al., 2016; Porjesz et al., 2005) which has been interpreted as a deficiency in inhibitory and attentional processing.

Event-related theta (ERT) is sensitive to cognitive effort as it increases in response to higher demands of cognitive control (Brier et al., 2010; Cavanagh and Frank, 2014; Hanslmayr et al., 2008; Jensen and Tesche, 2002; Rosen et al., 2016). Furthermore, ERT is strongly modulated by alcohol. Acute alcohol intoxication attenuates ERT especially on trials evoking cognitive interference (Beaton et al., 2017; Kovacevic et al., 2012; Marinkovic et al., 2012; Rosen et al., 2016), indicating that alcohol primarily affects executive functions.

Theta oscillations have also been implicated in integrating task-relevant representations with top-down effects across long-range neural envelopes (Halgren et al., 2015; Hasselmo and Stern, 2014; Wang et al., 2005). Phase-locking values (PLV) are a measure of phase consistency between two signals (Lachaux et al., 1999) and are suitable for investigating co-oscillations between different brain areas at a level of an interactive dynamic network (Varela et al., 2001). It has been shown that PLVs between the lateral and medial prefrontal cortical areas are sensitive to cognitive conflict (Beaton et al., 2017) and that acute intoxication dysregulates those interactions in humans and rodents (Beaton et al., 2017;

Ehlers et al., 2012). There is a paucity of studies assessing task-induced functional connectivity in BDs with temporally sensitive methods. However, altered functional connectivity during resting-state has been reported in BDs compared to LDs (Correas et al., 2015; Correas et al., 2016).

The aim of the present study was to examine neural dynamics of the attentional circuitry during target detection in adolescents emerging into adulthood as a function of BD. To this purpose we employed an anatomically constrained MEG method (aMEG) which is a multimodal approach that combines whole-head MEG recordings and high-resolution MRI images within a distributed source model (Dale et al., 2000; Lin et al., 2004; Marinkovic et al., 2003). It allows for the estimation of *where* the oscillatory changes are occurring, and it provides a highly precise insight into the temporal sequence ("*when*") of the involved neural components. Maps of event-related power estimates and the associated time courses of source estimates were analyzed across time and cortical space in time-frequency domain (Kovacevic et al., 2012; Lin et al., 2004; Marinkovic et al., 2012; Rosen et al., 2016). Additionally, co-oscillations between the principally activated cortical regions provided insight into attentional function in real time and at the level of an interactive system in BD and LD groups (Beaton et al., 2017).

2. MATERIALS AND METHODS

2.1 Participants

Fifty-one first-year students of the Complutense University of Madrid (Madrid, Spain) participated in the study. They were assigned to a binge drinking (BD) (N=25, 13 females) or to a light drinking (LD) group (N=26, 14 females) based on a questionnaire and a semi-structured interview inquiring about their alcohol and other drug use. Participants provided a record of their daily alcohol consumption indicating the type(s) and the quantity of the beverage(s) they consumed in the past month as well as the length of time (in hours) it took them to imbibe these beverages (Table 1). Their estimated Blood Alcohol Concentration (*est*-BAC) was calculated for each drinking episode based on the information they provided for the past month, as well as their gender and weight, according to the following algorithm (Windmark, 1981):

$$estimatedBAC = \left(\frac{Galcohol}{Wxbw}\right) - mrxhours$$

where G corresponds to the highest level of alcohol (grams) consumed on one occasion in the previous month; W is the body weight (Kg); bw or body water is a constant related to the water content of the human body with a value of 0.68/0.55 for male/female; *mr* is the metabolism rate with a value of 0.15/0.18 for male/female. We considered the est-BAC as a rough index of alcohol intoxication for each subject. Participants reaching an est-BAC of 0.08% or above at least once during the previous month were classified as BDs. In contrast, the control group consisted of students who did not achieve that BAC in the past month. It is important to note that the legal drinking age in Spain is 18 years of age.

Participants completed personality tests related to impulsivity variables including Barrat Impulsivity Scale (BIS) (Patton et al., 1995) and Sensation Seeking Scale (SSS) (Zuckerman and Link, 1968). Their selective and sustained attention was measured with the D2 attentional test (Brickenkamp and Seisdedos, 2009), a neuropsychological test in which participants are asked to cross out any “d” letter. Also, their sensitivity to reward was assessed by means of the Iowa Gambling Task (IGT) (Bechara et al., 1994).

Prospective participants with family history of alcohol abuse were excluded from the study as well as individuals reporting personal history of psychiatric disorders based on DSM-IV-TR criteria (American Psychiatric Association, 2000) and/or psychopathological traits as assessed by the Symptom Checklist-90 Revised questionnaire (Derogatis and Melisaratos, 1983). Subjects reported no current medical condition and were medication free at the time of the study. They also completed the Alcohol Use Disorders Identification Test (AUDIT) (Guillamón et al., 1999) and subjects who scored 20 or above were excluded for having AUD. Tobacco smoking was a controlled variable. According to the Syndrome Nicotine Dependence Scale (Becoña et al., 2011), four participants fulfilled the criterion of nicotine dependence, three BDs and one LD.

Participants were asked to refrain from alcohol consumption for at least 24 hours prior to data acquisition. All of them provided written informed consent for the study and were monetarily reimbursed for their participation. The study was approved by the Ethics Committee of the Complutense University of Madrid. Principles of Declaration of Helsinki were followed.

2.2 Task

Participants performed a target detection task with equiprobable target (Go) and nontarget (NoGo) stimuli which consisted of blue/green squares/circles. Participants were instructed to fixate on a cross in the center of the screen and to press a button as fast as possible to targets (green circles and blue squares) and to withhold responding to non-target (blue circles and green squares). The stimuli were presented for 100 ms with a stimulus onset asynchrony (SOA) of 1,400 ± 200 ms within a visual angle of 3.4 degrees. They were presented in random order in two blocks of 200–225 stimuli (Figure 1). Half of subjects pressed the button with the left and half with the right hand in a counterbalanced manner.

2.3 Data acquisition and analysis

2.3.1 MRI—Structural MRI images were used to define the model for the volume conductor and the solution space for MEG source localization analysis. Images were acquired with a General Electric 1.5 Tesla using an eight-channel head coil. The imaging protocol consisted of: 3D T1-weighted high-resolution images using a Fast-Spoiled Gradient Echo sequence [TR/TE/TI=11.2/4.2/450 ms; flip-angle= 12°; FoV= 250 mm; acquisition matrix= 256 × 256; slice thickness=1 mm]. Structural images were used to reconstruct each person´s cortical surface with FreeSurfer software. Inner skull surface was used for a boundary element model of the volume conductor in the forward calculations. The solution space was approximated by ~5000 free-rotation dipoles along the gray-white matter surface in the cortex, with spacing between dipole locations ~7 mm (Kovacevic et al., 2012).

2.3.2 MEG—High-density MEG signals were recorded from 204 channels (102 pairs of planar gradiometers) with a whole-head Neuromag Vectorview system (Elekta) in a magnetically and electrically shielded room. The signals were recorded continuously with a 1000 Hz sampling rate and filtered online with a band pass filter 0.1–330 Hz. The position of magnetic coils attached to the skull, the main fiduciary points, as well as a large array of random points spread across the scalp were digitized with 3Space Isotrak II system for subsequent precise co-registration with structural MRI images. Trials with incorrect responses were excluded from the analysis. The number of included trials was equated across the target and nontarget task conditions for each subject. The data were analyzed with a time-frequency analysis stream that uses MATLAB routines (Beaton et al., 2017; Kovacevic et al., 2012; Marinkovic et al., 2012; Rosen et al., 2016) that incorporates publicly available packages including Fieldtrip (Oostenveld et al., 2011), EEGLab (Delorme and Makeig, 2004) and MNE (Gramfort et al., 2014). Continuous data were bandpass filtered from 0.1 to 100 Hz and epoched from −600 to 1000 ms relative to stimulus onset for the stimulus-locked analysis. For each epoch, the data were downsampled by a factor of 4 to 250 Hz. Epoched data were then passed through automatic threshold rejection to remove trials that were contaminated with artifacts. Independent component analysis was used to remove eye-blinks and heart beat artifacts (Delorme and Makeig, 2004). Complex power spectrum was calculated for each trial using convolution with complex Morlet wavelets (Lachaux et al., 1999) in 1 Hz increments from 4 to 7 Hz for theta band. The first and last 300 ms of each epoch were discarded to remove edge artifacts resulting from wavelet analysis. Wavelet results were visually inspected across all epochs for any additional artifacts. We used an anatomically constrained MEG (aMEG) source modeling which comprises cortically constrained minimum norm estimates of the event-related theta power (Dale et al., 2000; Lin et al., 2004). To estimate the noise covariance for calculation of the inverse and to prevent biasing the inverse solution, empty room data were detrended and band-pass filtered between 3 and 40 Hz. The signal-to-noise ratio equaling 5 (Lin et al., 2004; Marinkovic, 2003) was used for scaling of the noise covariance matrix in calculation of the inverse operator. The identity matrix was used for noise-sensitivity normalization of the source-space solution. The noise-sensitivity normalized estimates of total source power were obtained at each location on the cortical surface at each frequency. Source power estimates were calculated based on cortically constrained minimum norm estimates (Kovacevic et al., 2012; Lin et al., 2004; Marinkovic et al., 2012). For each subject, a map of total source power for theta was estimated by averaging across theta frequency (4–7 Hz) and across all trials for each condition. ERT power was baseline-corrected by subtracting the mean theta source power estimate in the 300 ms prestimulus period and expressed as percent signal change from baseline. Uncorrected theta power in the baseline did not differ between groups ($F(1,50) = 0.02$, $p = 0.86$) or conditions ($F(1,50) = 0.7$, $p = 0.37$) confirming that the stimulus-evoked changes were not affected by possible differences in the baseline. Intersubject averages were created by morphing each subject´s reconstructed surface onto an average representation after aligning their cortical sulcal-gyral patterns (Fischl et al., 1999) and averaging individual source power estimates.

Region-of-interest (ROI) analysis was conducted to further examine possible interactions of task condition, group, and gender on event-related changes in theta power. Unbiased ROIs were selected based on the overall group average across all subjects for each task condition and comprised dipole locations along cortical surface with most notable source power. The same set of group-based ROIs was used for all subjects in a manner blind to their individual activations by applying an automatic spherical morphing procedure (Fischl et al., 1999). Early visual activity was assessed in the occipital region (Occ) while the anterior (aIFC) and posterior inferior frontal cortices (pIFC) and sensorimotor cortices (sMOT) were examined bilaterally as shown in Figure 2. Additionally, co-oscillatory interactions between cortical ROIs were estimated by calculating phase-locking values (PLV) between pairs of frontal ROIs in each hemisphere (Figure 4) (Beaton et al., 2017; Lachaux et al., 1999).

A nonparametric cluster-based permutation test (CBPT) (Maris and Oostenveld, 2007), was used to test for significant group differences in event-related theta power, as well as in PLVs. At each time step, group differences were tested by means of a 1-way ANOVA test which provided F values used in the CBPT. Time clusters consisted of ≥25 contiguous time points yielding 100ms time windows which systematically showed group difference with a significance threshold $p <= 0.05$. Cluster-statistics were assessed through the sum of all F-values corresponding to the time steps comprised in cluster. This procedure was repeated 5000 times after shuffling the original group's labels which created a null distribution for each comparison. The cluster-statistics obtained from the original data set were compared with those in the randomized data, while keeping the maximum statistic at each repetition. The resulting CBPT p-value represented the proportion of the permutation distribution with cluster-statistic value of the original data. Only the time-cluster that survived the CBPT at $p < 0.05$ was used to define time windows for the subsequent analyses.

No significant effects of Gender were observed in any of the analyses. Nonparametric Spearman's rho coefficient was used to compute correlations.

3. RESULTS

3.1 Behavioral Performance

Behavioral performance was assessed by measuring accuracy in detecting targets and non-targets and reactions times to targets. Behavioral results are summarized in Table 2. BDs showed a marginal tendency to respond less accurately and with longer RTs in comparison to LDs.

3.2 MEG: Event-related theta

The aMEG method provided insight into spatio-temporal stages of the ERT power during target detection. As shown in Figure 2, there is an early theta increase estimated to the occipital cortex across both groups and conditions. However, subsequent theta increase was observed only to the target stimuli. In contrast, nontargets did not elicit appreciable ERT increase relative to the baseline. The greatest theta activity overall was observed in the right IFC peaking after ~450 ms. Both the right aIFC and pIFC were also sensitive to group differences with BDs showing attenuated theta to targets as compared to LDs (Table 3) during the 380–510 ms time window.

3.2.1.1 ERT correlates with alcohol intake, performance, and attention—

As shown in Figure 3, ERT power to targets in the right aIFC was positively correlated with response accuracy to targets ($r=0.29$, $p<0.05$) and with the total D2 attentional test score ($r=0.31$, $p<0.05$), indicating that right prefrontal theta power underlies successful target detection and higher attentional ability. In contrast, target-induced theta power estimated to the right aIFC was negatively correlated with the est-BAC ($r=-0.39$, $p<0.05$) and AUDIT scores ($r=-0.41$, $p>0.03$) in BDs. Correlations with the pIFC were very similar in pattern and significance indicating the association between lower theta power in the rIFC and higher levels of alcohol consumption which may underlie behavioral impairments.

3.2.2 Co-oscillations in theta band (4–7 Hz) estimated with PLVs—

To investigate functional interactions among the ROIs in real time, we estimated the degree of synchronous, in-phase co-oscillations by calculating the PLV in theta frequency band (Figure 4). The PLV between the right aIFC and pIFC areas to targets increased only in LDs $F(1,50)= 9.65$, $p<0.01$. Overall, synchronous co-oscillations were greater in LDs compared to BD as indicated by a main effect of group: $F(1,50)= 6.7$, $p<0.05$, and were greater for targets only, Group x Condition interaction: $F(1,50) = 6.84$, $p<0.05$. The synchrony was maximal in the time interval encompassing response execution (300–580 ms), indicating involvement of the ventrolateral prefrontal network. In addition, the PLV declined in BDs and was negatively correlated with the est-BAC ($r=-0.54$, $p<0.01$), suggesting that hazardous drinking levels are associated with dysregulation of network interactions.

4. DISCUSSION

The present study used a multimodal approach to examine theta band oscillatory activity and functional connectivity during target detection in adolescents emerging into adulthood as a function of binge drinking. The main findings can be summarized as follows: 1) the greatest event-related theta (ERT) was evoked by targets in the right inferior frontal cortex (rIFC); 2) It correlated with performance accuracy and selective attention scores, confirming the importance of rIFC in target detection, decision making, and response mapping. 3) Lower ERT to targets was observed in BDs compared to LDs in the rIFC. 4) Furthermore, ERT correlated negatively with the est-BAC and the AUDIT score in the BD group, lending support to the idea that lower attentional function in BDs is associated with heavy alcohol consumption. 5) Theta band co-oscillations between the right aIFC and pIFC were dysregulated in BDs indicating decreased connectivity of the prefrontal network during attentional engagement, response selection, and execution. The lower neural synchrony in BDs was associated with alcohol intake.

The IFC has been characterized as a critical substrate of cognitive control which refers to the ability to flexibly and strategically respond to contextual demands in agreement with past experiences and current goals (Aron et al., 2014; Brass et al., 2005; Chambers et al., 2009; Hampshire et al., 2010; Levy and Wagner, 2011; Munakata et al., 2011; Wiecki and Frank, 2013). Cognitive control is multiply determined by different underlying cognitive processes with specific contributions (Badre, 2008; Brass et al., 2005; Chikazoe, 2010; Criaud and Boulinguez, 2013; Koechlin et al., 2003; Levy and Wagner, 2011). It has been well established that the rIFC is engaged by tasks eliciting suppression of prepotent responses

(Aron et al., 2014; Chikazoe, 2010; Garavan et al., 1999; Swick et al., 2011; Wessel and Aron, 2017). However, inherent to those paradigms are non-inhibitory confounds such as attention to salient, infrequent stimuli. Indeed, there is extensive evidence of the rIFC recruitment during attentional tasks that impose no or minimal inhibitory requirements (Erika-Florence et al., 2014; Hampshire et al., 2010; Hampshire and Sharp, 2015). Therefore, rIFC does not seem to solely specialize for motor inhibition but is activated by salient cues capturing attention (Hampshire et al., 2009, 2010). Studies using attentional manipulations confirm that the rIFC is an essential hub of the ventral attentional network (Chica et al., 2013; Corbetta et al., 2008; Corbetta and Shulman, 2002). Moreover, the ventral prefrontal network is engaged during deliberate target detection (Hampshire et al., 2009; Indovina and Macaluso, 2007; Shulman et al., 2010; Vossel et al., 2014) which relies on attentional control, response mapping, and maintenance of task sets (Dosenbach et al., 2008). Results of the present study are aligned with such evidence as much greater ERT was elicited by target stimuli in the rIFC due to its salience. In comparison, equiprobable nontarget stimuli elicited virtually no theta in any of the frontal areas (Figure 2) subsequent to evoking equivalent early activity in the visual cortex. This finding is consistent with previous reports of greater theta to task-relevant stimuli with contributions of memory retrieval, attention, working memory, decision making, and continuous monitoring (Cavanagh and Frank, 2014; Cheyne et al., 2012; Halgren et al., 2015; Kovacevic et al., 2012; Nyhus and Curran, 2010; Sauseng et al., 2010; Womelsdorf et al., 2010). Furthermore, theta power scales with task difficulty and cognitive demands confirming its essential contributions to cognitive control (Beaton et al., 2017; Ishii et al., 2014; Kovacevic et al., 2012; Rosen et al., 2016). In the present study, ERT to targets in the rIFC correlated with better response accuracy and higher scores on attentional test (Figure 3) which supports the involvement of theta in attentional processing and responding to task-relevant stimuli.

Binge drinkers exhibited lower theta power to targets compared to LDs in the rIFC (Figure 2, Table 3). Higher levels of alcohol consumption were associated with lower theta in BDs (Figure 3), suggesting that it may potentially serve as an index of reduced cognitive capacity in young, highly functioning individuals as a function of their drinking levels. Group differences in task performance eluded statistical significance although BDs showed a marginal tendency to respond with longer reaction times and lower accuracy (Table 2). On a behavioral level, these results are in line with the attentional deficits observed in BDs (Lannoy et al., 2017) and in AUD individuals (Maurage et al., 2014; Muller-Oehring and Schulte, 2014; Oscar-Berman and Marinković, 2007; Tedstone and Coyle, 2004), suggesting that impaired attentional control might contribute to alcohol-related problems. Indeed, it has been well established that alcoholics manifest reduced ERT power during cognitive tasks (Campanella et al., 2009; Kamarajan and Porjesz, 2015; Pandey et al., 2012; Porjesz et al., 2005; Rangaswamy and Porjesz, 2014). Previous EEG studies have examined ERT with equiprobable Go/NoGo tasks in individuals with AUD and reported decreased theta power to both conditions (Kamarajan et al., 2004; Pandey et al., 2016). Similarly, a recent EEG study that used the same paradigm in a shared sample as the current study (López-Caneda et al., 2017) reported reduced power in delta and theta bands in BDs to both target and non-target stimuli. These findings were interpreted as reflecting dysfunctional response execution and response inhibition. They were partially replicated in our study inasmuch as we found lower

ERT in BDs. However, our results clearly indicate much greater neural engagement during target (Go) trials suggesting that the observed activity was primarily elicited by attention-inducing, target-relevant processes. In contrast, theta activity to task irrelevant NoGo trials was barely above baseline levels indicating negligible contributions of response inhibition. Furthermore, our method has permitted a more refined spatial specificity indicating selective sensitivity of the rIFC to higher levels of alcohol consumption with lower ERT to target trials in BDs. Additional studies are needed to explore these discrepancies, but they may be due to different data analysis methods and may reflect better spatial sensitivity of the MEG signal.

In a series of aMEG studies using different executive tasks and alcohol challenge in social drinkers, we have observed attenuated ERT in the prefrontal cortex during alcohol intoxication especially under higher cognitive load (Beaton et al., 2017; Kovacevic et al., 2012; Marinkovic et al., 2012; Rosen et al., 2016). Lower theta has also been reported in high-risk offspring of individuals with AUD (Kamarajan and Porjesz, 2015). Taken together, lower task-induced theta oscillations have been proposed as an endophenotype for susceptibility to AUD (Andrew and Fein, 2010; Hodgkinson et al., 2010; Porjesz et al., 2005; Rangaswamy and Porjesz, 2008; Salvatore et al., 2015).

Target processing relies on sustained selective attention. Imaging studies confirm that the rIFC may be involved in evaluating significance of salient events across sensory modalities (Downar et al., 2002). Its sensitivity to visual salience (Vossel et al., 2011) is supported by evidence from single-cell recordings in monkeys indicating that the IFC receives detailed visual information from the ventral visual pathway (Sakagami and Pan, 2007; Sakagami and Tsutsui, 1999; Scalaidhe et al., 1999). Functional specialization and material-specific sensitivity of micro-domains in the IFC has been shown with human intracranial recordings (Marinkovic et al., 2000). Attentional processing is essential not only for detecting relevant stimuli but also for managing distraction in a broader context of goal-dependent constraints. Altered behavioral and brain-based indices of distractibility have been observed in abstinent alcoholics (Ahveninen et al., 2000) while acute alcohol intoxication selectively impairs attention to novelty (Marinkovic et al., 2001). Increased impulsivity and vulnerability to distraction are strongly implicated in alcohol and drug addiction (Evenden, 1999). Inability to exert inhibitory control over drinking may result from an interaction of genetic predisposition and drug-induced deficits (Begleiter and Porjesz, 1999; Dick et al., 2010). IFC has been implicated in top-down attentional control and emotional reappraisal (Goldin et al., 2008; Green et al., 2011) and it may subserve the integration of attentional control, decision making, and top-down regulative influences, and their degradation in addiction (Goldstein and Volkow, 2002; Koob and Volkow, 2010).

Drawing on excellent temporal resolution of the MEG signal, the present study examined co-oscillations between the two principal activated areas in the rIFC in real time (Figure 4). We calculated PLVs in theta band to quantify consistency of the oscillatory phase between the aIFC and pIFC (Lachaux et al., 1999). Co-oscillations are known to transiently increase at the time of active interactions between two ROIs of interest (Beaton et al., 2017; Klopp et al., 2000; Tallon-Baudry and Bertrand, 1999). Theta oscillations are particularly suitable to investigate cross-cortical integration as they are primarily generated in superficial cortical layers (Halgren et al., 2015, 2018) and are sensitive to episodic encoding and retrieval (Anderson et al., 2010; Hanslmayr and Staudigl, 2014; Hasselmo and Stern, 2014; Klimesch et al., 2010; Womelsdorf et al., 2010). As shown in Figure 4, co-oscillations between the aIFC and pIFC were negligible on nontarget trials in both groups. In contrast, they were significantly greater to target stimuli in LDs during the time of attentional selection, response preparation, and execution. This suggests that the aIFC and pIFC were co-active during attentional control and motor response in LDs. Given their functional synchronization, the two areas appear to be linked in an interactive IFC network which is consistent with other evidence showing a high degree of interconnectivity in the IFC (Goulas et al., 2012). However, due to potential confounds due to field spread (Schoffelen and Gross, 2009), these findings should be considered with caution. The converging findings suggest that the IFC may not be organized into separable, specialized modules based on their specific functional profiles but that they are flexibly engaged and integrated by adaptive contextual maintenance (Reynolds et al., 2012). Studies investigating the functional organization of the IFC by manipulating hierarchical levels of rule representation have confirmed a lack of spatial differentiation across different representational levels (Pischedda et al., 2017). On that view, the contributions of the IFC to cognitive function are represented in spatially overlapping areas that are fluidly engaged to conform to task rules. Other studies have also suggested that the IFC and the neighboring anterior insular cortex represent a core hub for rule processing and maintenance of task sets, integrating different dimensions of cognitive control (Dosenbach et al., 2007; Menon and Uddin, 2010).

Our results indicate that the oscillatory synchrony within the IFC was dysregulated in BDs and their PLV decrease was associated with alcohol intake (Figure 4). Previous studies reported that alcohol intoxication abolished PLV during a task evoking cognitive control (Beaton et al., 2017; Ehlers et al., 2012). Altered connectivity in BDs has also been reported during wakeful resting-state as reflected in PLV measured with MEG (Correas et al., 2015). Similarly, resting-state functional connectivity MRI studies in individuals with AUD have found lower connectivity in the executive control (Kim et al., 2017; Müller-Oehring et al., 2015; Weiland et al., 2014) and reward networks (Camchong et al., 2013; Wang et al., 2016). Thus, the attenuated co-oscillations to targets observed in the current study may indicate suboptimal integrative processing that could underlie cognitive deficits in BDs.

5. CONCLUSIONS AND LIMITATIONS

Taken together, these results confirm essential contributions of the rIFC to attentional control in a target detection task which relies on sustained and selective attention, response selection and execution, and performance monitoring. Lower ERT to target stimuli was observed in the rIFC in adolescents emerging into adulthood as a function of BD. It was associated with higher alcohol intake and worse performance accuracy and scores on a test of attention further indicating an impairment in attentional control in BDs. Heavy consumption was further associated with deficient co-oscillations in the rIFC that may underlie impaired cognitive functions in BDs. These indices may assist in devising interventions aimed at reducing drinking levels in young emerging adults.

Given the cross-sectional nature of this type of observational cohort studies, it is not possible to make causal inferences about the main factors underlying the loss of cognitive control. Although the observed correlations between the neural indices and alcohol intake suggest that binge drinking is associated with decrease cognitive control, it cannot be excluded that these differences precede alcohol consumption.

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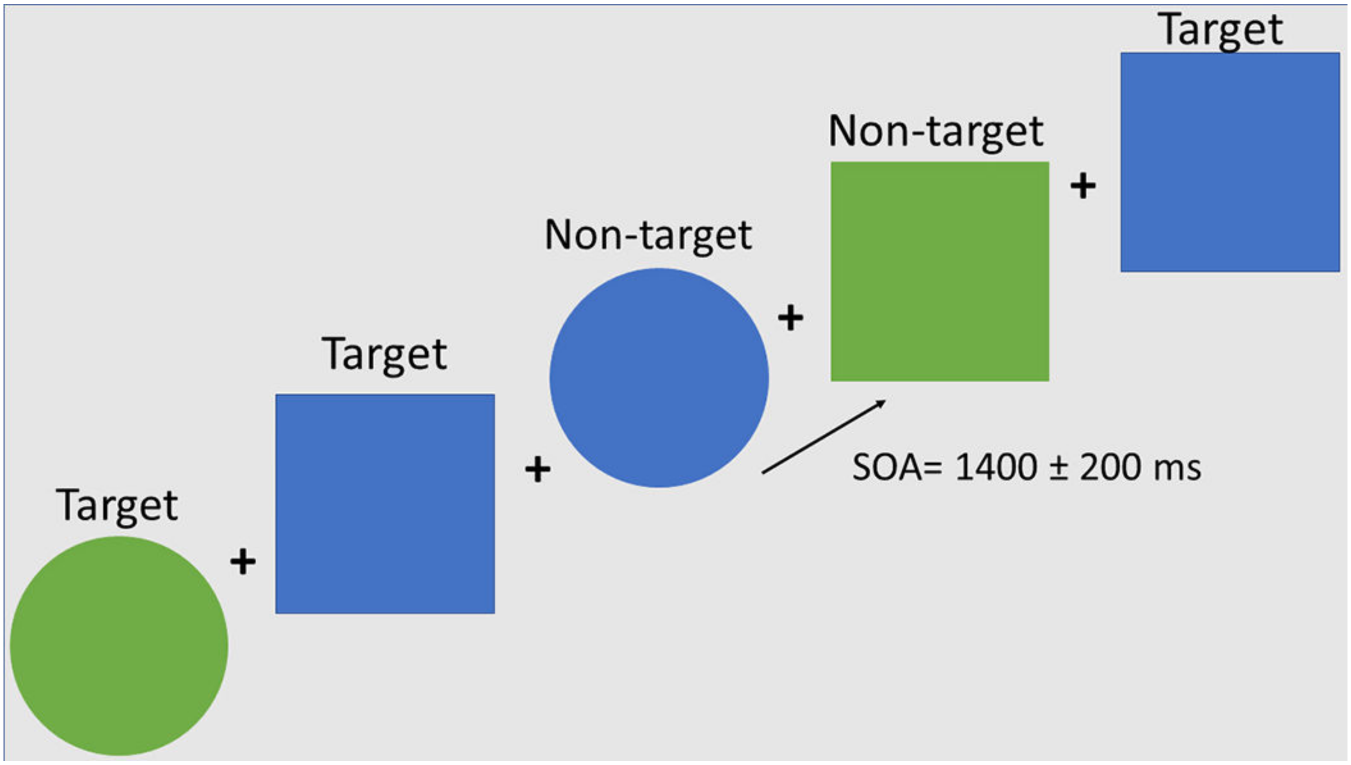

Figure 1.

Schematic diagram of the task. The stimuli were presented for 100 ms every 1400±200 ms.

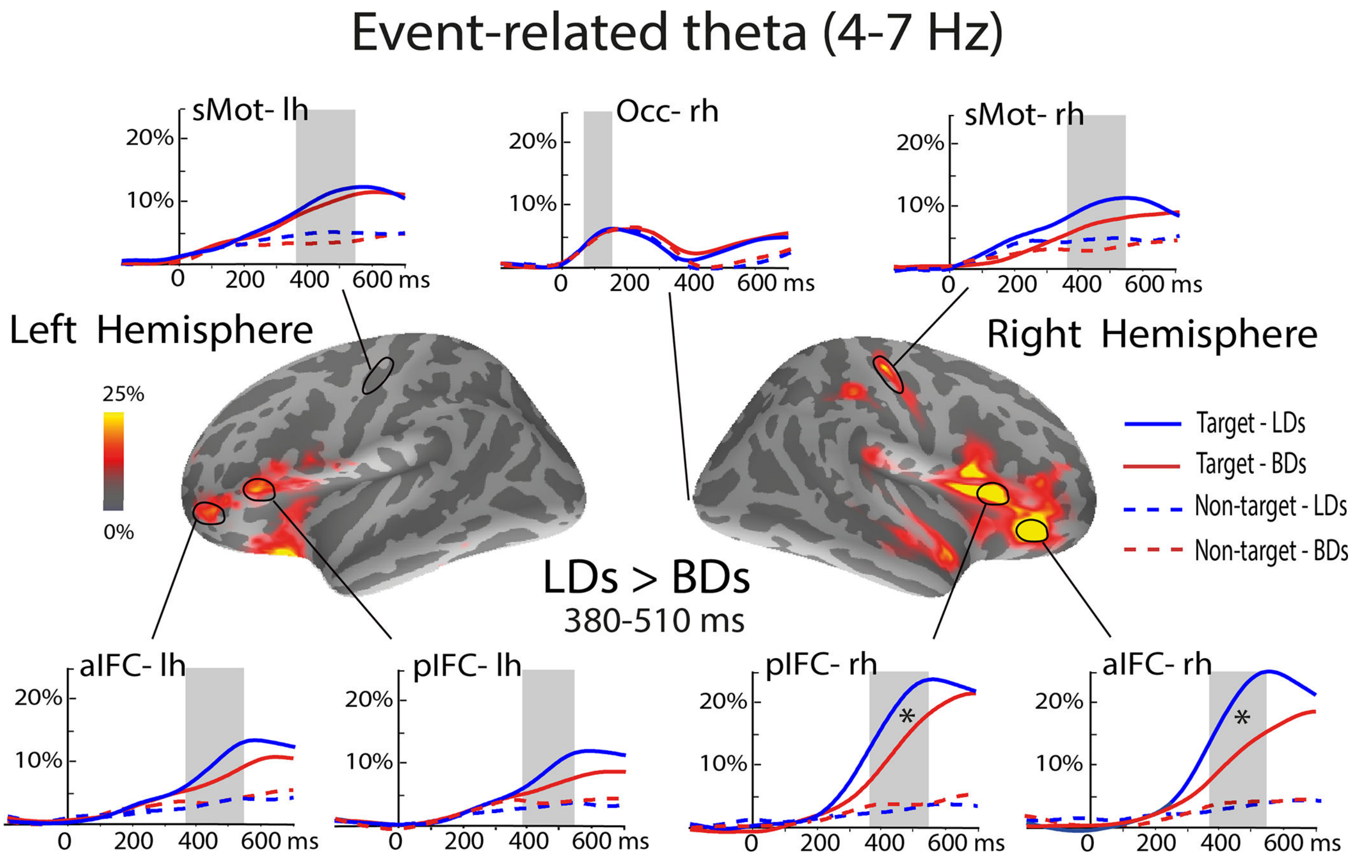

Figure 2.

Group-average difference maps (LD minus BD) of event-related theta source power. Time courses show theta power estimated to the anterior (aIFC) and posterior (pIFC) inferior frontal cortices, the sensorimotor (sMOT) areas and the occipital cortex (Occ) expressed as percent change from baseline. Targets evoked greater theta activity overall which was especially prominent in the rIFC. Theta power in the rIFC was reduced in BD compared to LD participants. Light-shaded vertical bars indicate the analyzed time windows: 50–150 ms (Occ) and the 380–510 ms for the anterior ROIs.

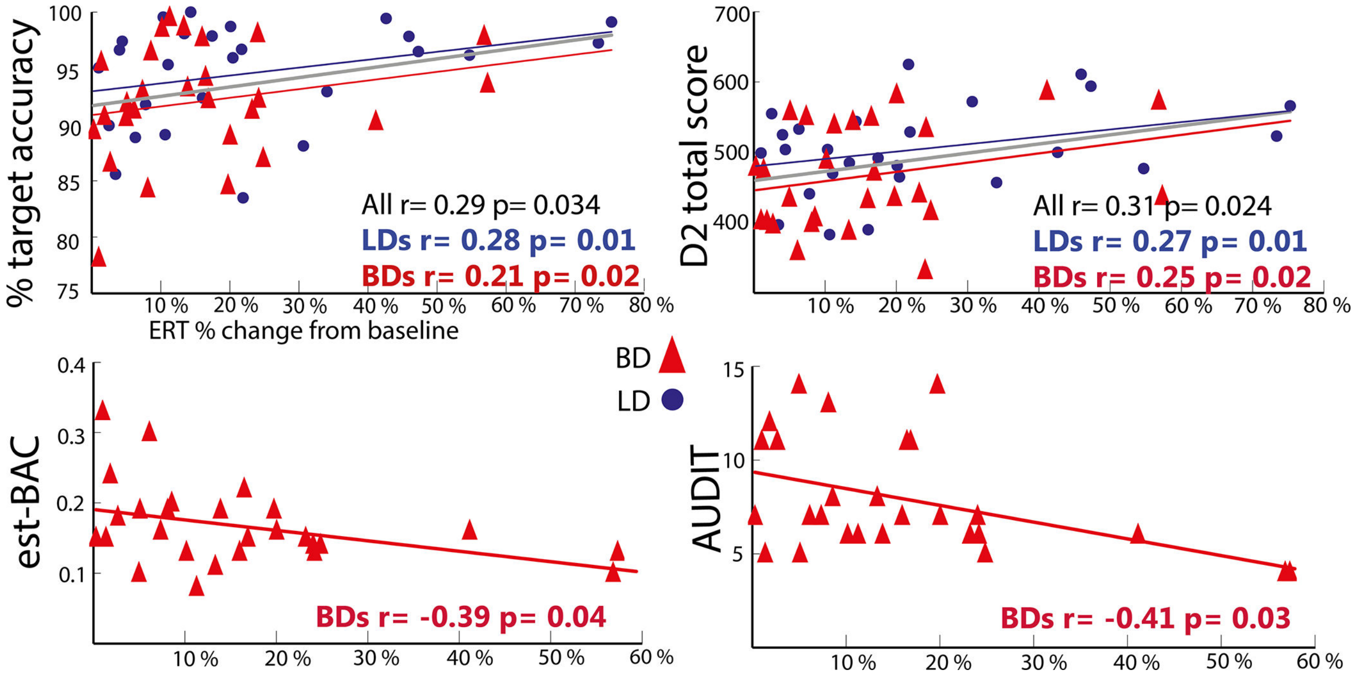

Figure 3.

Scatter plots of the correlations between target theta power in the right aIFC and the performance accuracy, D2 attentional test scores, the estimated BAC and the AUDIT scores.

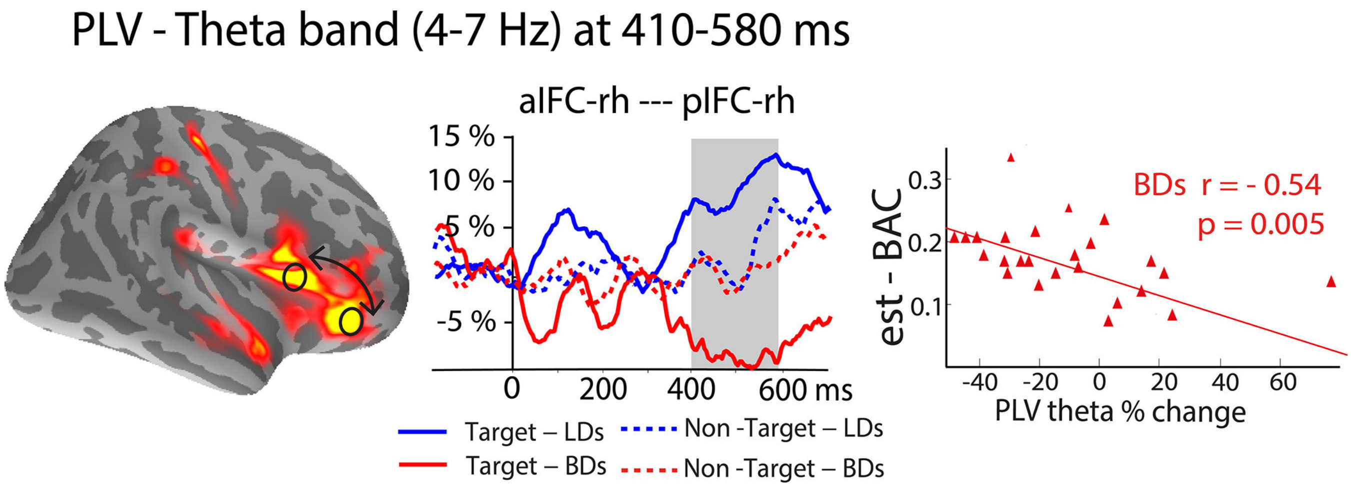

Figure 4.

Group-average maps of event-related theta source estimates and time courses of phase-locking values (PLV) calculated between the anterior and posterior inferior frontal cortices (aIFC and pIFC). The PLVs are expressed as percent change from baseline. The aIFC and pIFC of the right IFC showed increased oscillatory synchrony in light drinkers (LDs) form 410–580 ms where PLV decreased in binge drinkers (BDs) and correlated negatively with alcohol consumption (estimated blood alcohol concentration, est-BAC).

Table 1.

Demographic, drinking, personality and neuropsychological variables.

	LDs	BDs	U values
N (females)	26 (14)	25 (11)	164(chi^2)
Age	18±0.8	18±0.4	650
Est BAC	0.017±0.02	0.17±0.072	**702**[**]
Length of drinking (mos)	4.55±3.71	20.67±10.45	**205.5**[**]
Age of drinking onset	16.6±1.01	14.92±1.08	**83**[*]
Drinking days past mo.	1.5±1.8	7.82±2.2	**184.5**[**]
Drinks on a regular day	1.1±0.5	4±1.7	**267.5**[**]
Drinks on a heavy day	2.4±1.1	5.8±2.6	**248.5**[**]
Drunk days past mo.	0	4.84±2.56	**688.5**[**]
Total AUDIT score	1.7±1.3	7.7±1.9	**648**[**]
Sens. Seeking –Tot.	16.29±3.5	21.48±3.53	**257**[**]
Thrill & Adventure	5.76±2.66	7.58±2.35	278
Disinhibition	2.48±1.22	5.17±1.58	**322**[**]
Experience Seeking	5.56±1.58	5.43±1.77	175
Boredom Suscept	2.54±1.81	3.17±1.19	222
Barrat Impuls. - Tot.	38.87±10.6	44.38±11.5	241
Emotional	14.42±3.81	12.84±3.95	261.5
Motor	14.77±6.55	12.96±5.53	320
Non-planning	15±4.53	14.2±4.95	242
Attention D2 - Total	498.23±64.1	468.84±75.26	157
IGT – total earnings	12.89±21.85	11.15±20.5	216
IGT – total losses	19.03±17.25	21.6±29.3	204
Sleeping hours previous night	7.2±0.98	7.04±1.17	257.5

Mean±SD are listed for all variables. Group comparisons were calculated with a nonparametric Mann-Whitney U test except for age which was tested with chi^2. LDs: light drinkers; BDs: binge drinkers; estBAC: the highest estimated Blood Alcohol Concentration reached in the past month; AUDIT: Alcohol Use Disorders Identification Test; IGT: Iowa Gambling Task.

Significance level is indicated as follows:

[*] $p < 0.05$

[**] $p < 0.01$

[***] $p < 0.001$

Table 2.

Behavioral data for the LD and BD groups (mean±SD).

Behavioral Performance	LDs	BDs	t-test (49)	P-values
Reaction Time (ms)	509.08 ± 73.61	531.46 ± 74.32	1.03	p = 0.1
% correct Responses (target)	94.59 ± 4.5	92.01 ± 5.41	1.84	p = 0.09
% correct Non-Responses (non-target)	88.66 ± 7.8	86.76 ± 9.14	0.79	p = 0.45

Table 3.

MEG Theta Band Results.

ROIs	*Condition, F(1,50)*	*Group, F(1,50)*	*Condition × Group, F(1,50)*	*Target BD vs LD, F(1,50)*	*NonTarget BD vs LD, F(1,50)*
Right alFC	**41.65** ***	**4.1** *	**4.74** *	**4.74** *	0.006
Right plFC	**41.06** ***	**4.12** *	**4.18** *	**4.34** *	0.004
Right sMot	**21.25** ***	3.8	0.7	4.02	2.3
Left alFC	**30.1** ***	0.5	1.82	1.33	0.5
Left plFC	**28.68** ***	1.94	0.6	0.75	0.15
Left sMot	**20.54** ***	0.7	0.003	0.14	1.27
Occipital	0.97	0.31	0.001	0.02	0.03

ANOVA results for the Group and Condition main effects and interactions, as well as Group comparisons for the target and non-target conditions. Significance level is indicated as follows:

*p < 0.05

**p < 0.01

***p < 0.001.

Results are expressed as F-values (1,50).