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Topography, Power and Current Source Density of Theta Oscillations during Reward Processing as Markers for Alcohol Dependence

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Abstract

Recent studies have linked alcoholism with a dysfunctional neural reward system. Although several electrophysiological studies have explored reward processing in healthy individuals, such studies in alcohol dependent individuals are quite rare. The present study examines theta oscillations during reward processing in abstinent alcoholics. The electroencephalogram (EEG) was recorded in 38 abstinent alcoholics and 38 healthy controls as they performed a single outcome gambling task which involved outcomes of either loss or gain of an amount (10¢ or 50¢) that was bet. Event-related theta band (3.0–7.0 Hz) power following each outcome stimulus was computed using the S-transform method. Theta power at the time window of the outcome-related negativity (ORN) and positivity (ORP) (200–500 ms) was compared across groups and outcome conditions. Additionally, behavioral data of impulsivity and task performance were analyzed. The alcoholic group showed significantly decreased theta power during reward processing compared to controls. Current Source Density (CSD) maps of alcoholics revealed weaker and diffuse source activity for all conditions and weaker bilateral prefrontal sources during the Loss 50 condition as compared to controls who manifested stronger and focused midline sources. Further, alcoholics exhibited increased impulsivity and risk-taking on the behavioral measures. A strong association between reduced anterior theta power and impulsive task-performance was observed. It is suggested that decreased power and weaker and diffuse CSD in alcoholics may be due to dysfunctional neural reward circuitry. The relationship among alcoholism, theta oscillations, reward processing and impulsivity could offer clues to understand brain circuitries that mediate reward processing and inhibitory control.

Keywords

Alcoholism; Event-related oscillations (EROs); Theta power; Outcome-related negativity (ORN); Outcome-related positivity (ORP); N2, P3, Error-related negativity (ERN); Medial Frontal Negativity (MFN); Gambling task; Impulsivity; Risk-taking

INTRODUCTION

Alcohol dependence is characterized as a multifactorial disorder caused by biological, behavioral, and environmental factors. A variety of neurocognitive dysfunctions, as a result of impairments in several brain regions and/or neural circuitries, have been associated with

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alcoholism. In recent years, alcoholism has often been linked with decreased volume of the brain reward system [Makris et al., 2008] and with decreased neural activity in reward circuitry [Wrase et al., 2007; de Greck et al., 2009]. In normal healthy individuals, neuroimaging methods have outlined the structures involved in the neural reward processing system or circuitry [Breiter and Rosen 1999; Breiter et al., 2001; Delgado et al., 2000, 2003, 2005; Galvan et al., 2005; Nieuwenhuis et al., 2005a; Yacubian et al., 2007; Hampton et al., 2007; Xue et al., 2009]. Despite excellent spatial resolution, the neuroimaging methods suffer a major limitation of temporal resolution which has been only complemented by electrophysiological methods such as electroencephalogram (EEG), event-related potentials (ERPs) and event-related oscillations (EROs). In addition to millisecond-specific temporal resolution, these electrophysiological methods allow the possibility of exploring the functional brain dynamics during cognitive events. Therefore, several recent studies have employed ERPs and EROs to understand the more subtle, progressive, and time-domain specific neurocognitive changes during reward processing in gambling tasks that involved monetary loss and gain [Gehring and Willoughby 2002; Holroyd et al., 2004, 2006; Luu et al., 2004; Nieuwenhuis et al., 2004, 2005b; Hajcak et al., 2005, 2006, 2007; Toyomaki and Murohashi 2005; Yeung et al., 2005; Yu and Zhou 2006; Cohen et al., 2007; Marco-Pallares et al., 2007; Mennes et al., 2008; Kamarajan et al., 2008, 2009].

In general, ERP studies using gambling tasks to examine outcome processing have identified two major components: (1) a negative going component around 200–250 ms, and (2) a positive going component at about 300–500 ms [e.g., Gehring and Willoughby 2002; Nieuwenhuis et al., 2004; Holroyd et al., 2004; Hajcak et al., 2005; Kamarajan et al., 2009]. In our earlier work on reward processing in healthy normals, we presented a rationale and arguments to label these component as “outcome-related negativity (ORN)” and “outcome related positivity (ORP)”, respectively [Kamarajan et al., 2009]. We have also reported that theta oscillations during the time window of ORN and ORP components (200–500 ms) represent the neurocognitive underpinning related to reward processing (Kamarajan et al., 2008). Brain oscillations of different frequency bands have been shown to have specific functional significance [Basar 1999a]; the event-related theta-band in particular has been shown to be related to a variety of behavioral, cognitive, and motivational or emotional aspects of human information processing, including reward processing [e.g., Schacter 1977; Basar 1999b, 2000b, 2001a, 2006; Basar-Eroglu and Demiralp 2001; Kahana et al., 2001; Klimesch 1996, 1999, 1996, 1997a, 1997b, 2001a, 2001b, 2005b, 2006; Raghavachari et al., 2001, 2006; Luu et al., 2004; Trujillo and Allen 2007; Cohen et al., 2007; Knyazev 2007; Kamarajan et al., 2008]. Reward processing as unfolded during a gambling task involves a combination of behavioral, cognitive, motivational, and emotional states, which have been found to be mediated by brain oscillations in the theta band [Kamarajan et al., 2008]. Studies have demonstrated that the major ERP component of both error paradigms (i.e. ERN) and outcome paradigms (i.e. ORN) were predominantly composed of theta oscillations (e.g. Luu et al., 2003, 2004; Gehring and Willoughby 2004; Cohen et al., 2007). More convincingly, by using independent component analysis (ICA), Makeig et al. [2002] identified that the largest independent contributors to the ERN were in the theta frequency range. However, it should be mentioned that only a few studies have analyzed theta oscillations during a gambling paradigm. For instance, Gehring and Willoughby [2004] found that frontally focused theta (4–7 Hz) activity was observed during the loss condition. Cohen et al. [2007] found that losses, compared to wins, were associated with enhanced power and phase coherence in the theta frequency band. Further, Marco-Pallares et al. [2008] reported that the ORN for loss was associated with increased theta power.

Several ERP studies during reward processing in healthy human subjects have been reported since early 1980s (e.g., Homberg et al., 1980, 1981; Begleiter et al., 1983; Otten et al., 1995; Ramsey and Finn 1997; Gehring and Willoughby 2002; Yeung and Sanfey 2004; Hajcak et

al., 2006; Kamarajan et al., 2008, 2009). These studies have yielded a set of electrophysiological correlates/parameters of reward processing, and these parameters derived from normal individuals can be applied in and compared with clinical conditions, especially those relating to reward deficiency syndrome (RDS) [Blum et al., 2000]. Alcohol dependence has been viewed as a reward deficiency syndrome [Bowirrat and Oscar-Berman 2005], and a few attempts have been already made to employ these electrophysiological methods to study reward processing in alcoholic individuals. Porjesz et al. [1987] reported that abstinent alcoholics showed a significant decrease in P3 amplitude in response to incentive stimuli in abstinent alcoholics. Fein and Chang [2008] reported smaller amplitude in feedback negativity in treatment-naïve alcoholics with a greater family history density of alcohol problems compared to controls. In a recent ERP study of reward processing in our laboratory, we have demonstrated amplitude reduction in ORN and ORP components of the ERPs in male alcoholics in comparison to healthy controls [Kamarajan et al., 2010]. However, oscillatory mechanisms of reward processing in alcoholics has not yet been explored, and the present study is the first to examine the event-related theta activity during the time-window of the ORN and ORP components. While studies have already reported changes in theta oscillations during the performance of cognitive tasks in alcoholics [Kamarajan et al., 2004, Jones et al., 2006], offspring of alcoholics [Kamarajan et al., 2006; Rangaswamy et al., 2007], heavy drinkers [de Bruin et al., 2004], and alcohol-administered to healthy individuals [Krause et al., 2002], no study has as yet examined theta activity during reward processing in alcoholics.

The overarching aim of the current study is to examine the oscillatory changes in theta activity during reward/outcome processing in abstinent male alcoholics as compared to healthy controls. Specifically, the study attempts to examine total theta activity (comprising both phase-locked and non-phase-locked activities) during reward processing in alcohol dependent individuals while they performed a gambling task. As both ORN and ORP components are predominantly composed of theta oscillations [e.g., Luu et al., 2003, Luu et al., 2004; Gehring and Willoughby 2004; Cohen et al., 2007; Kamarajan et al., 2008], the time window for the analysis of theta activity will be analogous to the ORN and ORP activations as reflected in the time-frequency representation [for details, see Kamarajan et al., 2008]. Further, since our earlier ERP studies showed that current density of ORN and ORP components provided additional information such as sources and sinks of current flow and topography during reward processing [Kamarajan et al., 2008, 2009, 2010], we have examined the current source density (CSD) of theta oscillations in the present study. In addition, as alcoholics are reported to have increased impulsivity [e.g., Dom et al., 2007; Chen et al., 2007; Kamarajan et al., 2010], the current study attempts to analyze the behavioral measures of impulsivity and risk-taking. Since our previous studies showed a significant correlation between ERP/ERO measures and behavioral measures of impulsivity and risk-taking in normal subjects as well as in alcoholics [Kamarajan et al., 2008, 2009, 2010], we have further attempted to test the association between theta power and impulsivity measures in the present study. We hypothesized that alcoholics will show decreased theta power and significant changes in CSD activations, along with increased impulsivity and/or decision-making. The findings of the present study may offer important clues regarding frontal lobe involvement in terms of event-related theta activity, reward processing, and impulsivity in alcoholism, and thus may help appraise some of the related models of alcoholism, such as reward deficiency syndrome (RDS) and neural disinhibition.

MATERIALS AND METHODS

Participants

The sample consisted of two groups of adult males: 38 abstinent alcoholics (age range = 24–46 years; mean = 38.41; SD = 6.38) and an equal number of healthy controls (age range =

1835 years; mean = 21.26; SD = 3.27). The mean age of the alcoholics was significantly higher than that of the controls ($t = 14.85$; $p < 0.001$). Groups were matched for education (Alcoholic: 12.11 ± 2.96 years; Control: 12.49 ± 1.85 years; $t = -0.66$; $p = 0.5118$) and the score on Mini Mental State Examination (MMSE) [Folstein et al., 1975] (Alcoholic: 27.65 ± 1.97 ; Control: 27.82 ± 2.08 ; $t = -0.357$; $p = 0.7222$). Control subjects were recruited through newspaper advertisements and notices, while the abstinent alcoholics (DSM IV alcohol dependence) were recruited from in-patient or out-patient local hospitals/clinics in Brooklyn, NY. The alcoholic subjects were required to be abstinent from alcohol intake for at least 30 days, and those who were receiving treatment medication, such as antabuse and/or psychoactive drugs were excluded from the study to control for the effect of drugs on EEG. All participants did not have any personal and/or family history of other major medical or psychiatric disorders, although alcoholics with drug abuse and other externalizing disorders have been included in the sample; alcoholics but not controls who had family history of alcoholism were also included in the study.

Subjects who had positive findings (for their recent drug use within 48 hours) in the urine screen and Breathalyzer test were excluded from the study. Further, subjects with hearing or visual impairment, liver disease, or head injury were excluded from the study. The institutional review board of SUNY Downstate Medical Center at Brooklyn, NY approved the experimental procedures and ethical guidelines of this study.

The Gambling Task

The gambling task used in the study, known as the single outcome gambling (SOG) task is illustrated in Fig. 1. At the start of the experiment, a *choice stimulus* (CS) with two numbers 10 (left box) and 50 (right box), with a monetary value in US cents, was displayed for 800 ms. The subject was instructed to select one number by pressing the left button for '10' or the right for '50'. The selected number, appeared 700 ms after the CS disappeared and lasted for 800 ms inside a green box (to indicate a gain) or a red box (to indicate a loss), and was thus designated the *outcome stimulus* (OS). Thus, there were four possible outcomes: namely, gain 50 (+50), loss 50 (-50); gain 10 (+10), and loss 10 (-10). The subject had to respond by selecting either 10¢ or 50¢ (US cents) within 1500 ms of CS onset. If the subject did not respond/select within the specified time, the OS would not appear, and the next CS would appear as next trial. The inter-trial interval was 3000 ms throughout the experiment. There were 172 trials in this experiment. While the event of loss (in red) and gain (in green) in the OS was maintained at equal probability, the order of appearance was pseudo-randomized. The subjects were not aware of the probability or sequence of the task. The task was presented in two blocks and each block lasted for 4 minutes; the procedure was identical in both blocks. At the end of each block, the net/overall loss or gain for the entire block (e.g., Gain \$4.50) was displayed. The subject was instructed to press any button to start the next block.

Measures of Impulsivity

There were two impulsivity measures used in the study: 1) Barratt impulsiveness scale, version 11 (BIS-11) [Barratt 1985; Patton et al., 1995], a self-rated measure that assesses trait-related impulsivity, and 2) task-related behavioral (TRB) scores were derived from the performance of the gambling task. The behavioral scores that were derived from performance of the gambling task and from the impulsivity measures have been elaborated in our earlier studies on healthy controls [Kamarajan et al., 2008, 2009]. The BIS-11 consists of thirty items, yielding a total score, and additional scores for three subcategories: motor impulsivity (acting without thinking), cognitive impulsivity (making decisions quickly), and non-planning (lack of prior planning or of future orientation). The TRB scores were of 2 categories: 1) reaction time for the task conditions and responses, and 2) selection

frequency that represents the number of times a particular amount (10 or 50) was chosen following either the outcome of loss in the previous trial(s) or a losing or gaining trend in the previous 2, 3, and 4 trials. The gaining and losing trends were computed based on the resultant outcome of the cumulative account of the preceding outcomes. For example, if the previous three outcomes were -10, -10, and +50, then the trend was considered to be a *gain* (of 30¢), whereas if the previous three outcomes were +10, +10, and -50 then the trend would be considered as a *loss* (of 30¢). The entire list of the TRB scores can be found in our previous papers [Kamarajan et al., 2008, 2009].

EEG Data Acquisition and Signal Analysis

The subjects were comfortably seated in front of the computer monitor placed 1m away. EEG activity was recorded on a Neuroscan system (Versions 4.1 & 4.3) using a 61-channel electrode cap which included 19 electrodes of the 10–20 International System and 42 additional electrodes (see Fig. 2). The electrodes were referenced to the tip of the nose and the ground electrode was at the forehead (frontal midline). Eye movements were recorded using a supraorbital vertical lead and a horizontal lead on the external canthus of the left eye. Electrode impedance was maintained below 5 kΩ. The EEG signals were recorded continuously with a bandpass at 0.02–100 Hz and amplified 10,000 times using a set of amplifiers (Sensorium, Charlotte, VT). The data consisted of different sampling rates (256, 512, and 500 Hz) and were resampled at 256 Hz during the signal analysis for the sake of uniformity of signals.

The EEG signals were decomposed using the S-transform signal processing method. The methods used in this study have been explained in detail in our earlier paper [Kamarajan et al., 2008]. The S-transform was introduced by Stockwell et al. [1996], and has been shown to produce reliable estimates of localized power of nonstationary evoked potential time series [Chu 1996; Theophanis and Queen 2000]. This method has been applied in several recent studies to analyze time-frequency signals of event-related oscillations [Jones et al., 2004, 2006; Kamarajan et al., 2006, 2008; Padmanabhapillai et al., 2006a, 2006b; Rangaswamy et al., 2007]. The S-transform is considered to be a generalization of the Gabor transform [Gabor 1946] and an extension to the continuous wavelet transform. The S-transform generates a time-frequency representation (TFR) of a signal by integrating the signal at each time point with a series of windowed harmonics of various frequencies as follows:

$$ST(f, \tau) = \frac{|f|}{\sqrt{2\pi}} \int_{-\infty}^{+\infty} h(t) \cdot e^{-\frac{(\tau-t)^2 f^2}{2}} e^{-i2\pi f t} dt$$

where $h(t)$ is the signal, f is frequency, τ is a translation parameter, the first exponential is the window function, and the second exponential is the harmonic function. The S-transform TFR is computed by shifting the window function down the signal in time by τ across a range of frequencies. The window function is Gaussian with $1/f^2$ variance and scales in width according to the examined frequency. This inverse dependence of the width of the Gaussian window with frequency provides the frequency-dependent resolution. The amplitude envelope of the complex-valued S-transform TFR is calculated by taking the absolute value $|ST(f, \tau)|$. In the current study, event-related total power (ERO_{TOT}) (which is a combination of both phase-locked and non-phase-locked activity) was computed and analyzed across groups and conditions. Theta band (3–7 Hz) was further divided into θ_1 or low theta (3–5 Hz) and θ_2 or high theta (5–7 Hz) for further analysis. For each task condition, total power for each of the theta bands (3–7 Hz, 3–5 Hz, and 5–7 Hz) was acquired by the average of TFR data in individual trials of 1000 ms (pre-stimulus 200 ms

and post-stimulus 800 ms). The filter setting to extract theta bands included a 5th order Chebyshev type I filter (two-step cascade type) with ripple factor (ϵ) of 0.108 and ripple attenuation (R_p) of 0.05. For the purpose of statistical analysis, mean theta power was extracted from the amplitude envelope within TFROI corresponding to 200–500 ms of post-stimulus time window within which both N2 and P3 components of outcome trials had their peaks [see, Kamarajan et al., 2008 for detail]. The trials exceeding 100 μV were removed for artifacts. The minimum number of artifact-free trials in all conditions for each subject was kept at 15 for the analysis.

CSD Mapping

The CSD maps were constructed from the Laplacian transformed data as described by Wang and Begleiter [1999]. This method has been applied in our earlier studies [Kamarajan et al., 2005, 2009]. Since the recorded potential at each electrode represents the resultant contributions from several adjacent and distal sources, local sources can not be clearly estimated [Nunez 1981]. The CSD transform acts as a spatial filter and provides an estimate of the local radial current density [Hjorth 1975; Nunez 1981; Nunez and Pilgreen 1991] and represents components of the primary neural activity in the scalp region [Hjorth 1991]. In the present study, the CSD maps representing theta power sources ($\mu V^2/r^2$, where r =head radius in cm) were created and compared visually for both absolute values and Z-scores for each of four outcomes (–50, –10, +50, and +10) and for control and alcoholic groups separately.

Statistical Analysis

Thirty-six electrodes that represented 6 scalp regions were selected for the statistical analyses (see Fig. 2). The theta power was analyzed by performing a linear mixed model of the Analysis of Variance (ANOVA) using the Statistical Analysis System (SAS, version 9.2) (SAS Institute Inc., NC 27513, USA). The values with ± 4 standard deviations were considered as outliers and removed from the data before the analysis. The covariance structure used in the model was ‘Compound Symmetry’ which has a constant variance and covariance. The model included five factors as fixed effects: Valence (loss, gain), Amount (50¢, 10¢), Region (frontal, central, parietal, occipital, left-temporal, and right-temporal) and Electrode (6 electrodes) as within-subjects factors, and Group (alcoholic, control) as a between-subjects factor. One-way ANOVA was used for the follow-up analyses of pair-wise comparisons between the 1) alcoholic vs. control group, 2) loss vs. gain condition, and 3) 50¢ vs. 10¢. A Bonferroni correction procedure for multiple comparisons was employed.

The sample characteristics and behavioral scores between groups were compared using independent sample t-tests. The correlations between theta power variables and behavioral variables were computed as described in our earlier work [Kamarajan et al., 2009]. Initially, factor analysis, using principal component analysis with varimax rotation, was performed to reduce the theta variables ($N = 108$) as well as the TRB variables ($N = 24$) into a few specific factors. Then, Pearson bivariate correlations were performed to analyze the relationship between behavioral factors and theta power. Theta variables for the factor analysis comprised nine electrode sites (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4), four conditions (+50, +10, –50, –10), and three theta frequencies (θ , θ_1 , θ_2). Only the factors that accounted for at least 10% of total variance were retained for further correlational analysis. However, factor analysis was not done on BIS scores as they were already factorized in the original work [Barratt 1985; Patton et al., 1995].

RESULTS

Temporal and Spatial Characteristics of Theta Activity in Alcoholics and Controls

The waveforms of ERPs and all theta bands (θ , $\theta 1$, and $\theta 2$) during Loss 50 and Gain 50 conditions are shown in Fig. 3 (Panels A and B). A partial phase-alignment of the theta activity corresponding to the ORN (200–300 ms) and ORP (300–400 ms) components was observed. Alcoholics showed decreased amplitude in both broadband (θ) and subbands ($\theta 1$ and $\theta 2$) of theta activity, and this difference was more pronounced during the loss condition. The time-frequency representations for each condition and group are shown in Fig. 3 (Panels C and D). Theta (3–7 Hz) power during 200–500 ms after the onset of an outcome stimulus was selected for the analysis. Although the alcoholics, as compared to controls, have reduced theta power during prestimulus baseline as well as poststimulus activation, the peak theta activation (in each group) as well as the group differences are more apparent and robust in the time window of 200–500 ms, which is the region of interest for the analysis of event-related theta power. As shown in Fig. 3, the alcoholic group showed markedly significant reductions in theta power (at 200–500 ms) during each outcome condition.

Topographic maps of theta power in alcoholic and control groups during loss and gain conditions are shown in Fig. 4 (Panels A and B). Visual analysis of the topographic maps showed that the alcoholic group appeared to have decreased theta activity during each outcome condition. Statistical analyses of this observation are reported in the next section (see Figure 5). High theta ($\theta 2$) power in alcoholics had an additional activity at occipital electrodes. In both groups, loss conditions had an anterior focus of theta activity while the gain conditions involved both anterior (primarily for $\theta 2$) and posterior (primarily for $\theta 1$) regions.

The CSD maps of theta power between 200–500 ms during each outcome in the control and alcoholic group are shown in Fig. 4 (Panels C and D). Controls showed a strong anterior focus of theta activity, particularly during loss conditions, while alcoholics showed weaker source activity compared to controls, especially at the frontal electrodes. During the –50 condition, while controls had a single and stronger midline prefrontal source, alcoholics showed bilateral and weaker prefrontal sources. In addition, the alcoholic group showed more diffuse source activity compared to controls, especially during gain conditions. In both groups, loss conditions had predominant anterior sources while gain conditions had both anterior and posterior sources.

Theta Activity across Conditions and Groups in the Mixed Model

The statistical results of the mixed model ANOVA are shown in Table I and the follow-up analyses (in bar-graphs) are shown in Figure 5. While the main effect for Group was not significant, 2-way and 3-way interactions of Group with other factors (Valence, Amount, Region) were highly significant. While the 3-way interaction of Group \times Valence \times Region was highly significant for all theta bands (θ , $\theta 1$, $\theta 2$), the other important 3-way interaction Group \times Amount \times Region was not significant for any of the theta bands, suggesting that the effect of Valence (loss vs. gain) on theta power (variance) was greater than that for the Amount. Since alcoholics were significantly older than controls, age was not found to be a significant factor in the ANOVA model. Specifically, age had neither a main effect (as Age and Age² were not significant) nor an interactive effect with Group (as Age \times Group and Age² \times Group were not significant) on theta power, indicating that age did not have significant bearing on theta power.

Bar-graphs of the follow-up analysis involving the pair-wise comparisons of mean theta power across groups (control vs. alcoholic group) during each outcome condition at three electrode sites (Fz, Cz, and Pz) are shown in Fig. 5 (Panel A). Alcoholics showed

significantly reduced theta power compared to controls (after Bonferroni correction) during all outcomes at one or more electrode sites. Comparisons across valence (loss vs. gain) (as shown in Fig. 5, Panel B) were significant only in the control group for theta broadband (3–7 Hz) and low theta band (3–5 Hz). However, in both groups, Loss was larger than Gain at the Fz electrode and Gain was larger than Loss at Cz and Pz electrodes. None of these comparisons were significant after Bonferroni corrections. Further, none of the comparisons between larger amount (50¢) and smaller amount (10¢) were significant either before or after the Bonferroni corrections, except for a single significance in low theta at Fz in the control group prior to Bonferroni adjustment.

Behavioral Data on Impulsivity and Risk-Taking

Comparisons of the BIS and the selection frequency (representing the number of times a particular amount, either 50¢ or 10¢, is selected while performing the gambling task) between the control and alcoholic groups are shown in Fig. 6. Alcoholics showed significantly higher impulsivity scores in motor, non-planning, and total scores of the BIS (Fig. 6, Panel-A). Further, alcoholics selected the larger amount (50¢) more frequently and the smaller amount (10¢) less frequently in the face of losing trends (Fig. 6, Panel-B). In other words, alcoholics showed more risk-taking behavior compared to controls who ‘played safe’ by selecting 10¢ more frequently during the losing trends. On the other hand, none of the scores of reaction time was significant between the groups.

The PCA method was used to extract specific factors from the variables of TRB scores and theta power separately. Factors converged at 25 and 50 iterations for TRB and theta variables, respectively. Factors that accounted for more than 10% of the total variance were retained (Table II). Total variance accounted for by TRB and theta factors were 81.16 % and 59.64 % respectively. The four TRB factors were: 1) All the RT variables, 2) Selection frequency for 50¢ following losing trends (positive loadings) and for 10¢ following gaining trends (negative loadings), 3) Number of times selecting 50 following gaining trends, and 4) Number of times selecting 10 following gaining trends. The four Theta factors were: 1) θ , θ_1 , and θ_2 power during +50 and +10 conditions at frontal and central leads, 2) θ , θ_1 , and θ_2 power during –50 condition at parietal and central leads, 3) θ and θ_2 power during –10 condition at frontal and central leads, and 4) θ , θ_1 , and θ_2 power during +50 condition at parietal and central leads.

Table III shows the correlation between Theta factors and behavioral (TRB and BIS) factors. BIS factors did not show any correlations with factors of theta power. On the other hand, Factor-2 of the TRB variables (i.e. selection frequency following losses) had a significant negative correlation with factor-1 of theta power (i.e. anterior theta power during gain conditions).

Summary of Major Findings

1. While a partial phase-alignment corresponding to the peaks/troughs of ORN (200–300 ms) and ORP (300–400 ms) components was observed in the theta waveforms in both control and alcoholic groups, alcoholics showed decreased amplitude in both broadband and subbands of theta activity especially during Loss condition (Fig. 3, Panels A and B).
2. Time-frequency (TF) plots showed that the alcoholic group, compared with the control group, showed markedly decreased theta power (200–500 ms) during each outcome condition (Fig. 3, Panels C and D).
3. It was obvious in the topographic maps that the alcoholic group had markedly reduced theta activity during each outcome condition. High theta (θ_2) power in

alcoholics had additional (and possibly intruding) occipital activity. In both groups, loss conditions had anteriorly focused theta activity while gain conditions involved both anterior maxima (primarily for Θ_2) as well as posterior maxima (primarily for Θ_1) (Fig. 4, Panels A and B).

4. CSD activity showed drastically weaker source activity in alcoholics compared to controls, especially at the frontal electrodes. During the loss condition (-50), controls had a single and stronger midline prefrontal source, and alcoholics showed bilateral and weaker prefrontal sources. Further, the alcoholic group showed more diffuse source activity compared to controls, especially during gain conditions. In both groups, loss conditions had predominant anterior sources and gain conditions had both anterior and posterior sources (Fig. 4, Panels C and D).
5. Mixed model ANOVA revealed that Group (as a factor) had significant 2-way and 3-way interactions with valence and/or amount, although the main effect for group was not significant (Table I).
6. Follow-up analyses using one-way ANOVA showed:
 - i. significantly reduced theta power in alcoholics compared to controls during all outcomes (Fig. 5, Panel A)
 - ii. although the topographic pattern of 'anterior focused loss' and 'posterior focused gain' was observed in both control and alcoholic groups, the differences between loss and gain were significant only in the control group for broadband theta and low theta (Θ_1) power (prior to Bonferroni correction) (Fig. 5, Panel B)
 - iii. none of the comparisons between amounts (50¢ vs. 10¢) with the same valence was significant (before adjusting for Bonferroni corrections) excepting a single comparison in the control group during the gain condition for low theta at Fz (not illustrated)
7. Comparison of behavioral data across groups suggested that (i) alcoholics had significantly higher impulsivity in motor, non-planning, and total scores of BIS (Fig. 6, Panel-A), and (ii) alcoholics selected 50¢ (for betting) more frequently in the face of two consecutive losses and following the losing trends during the previous trials. Further, alcoholics selected 10¢ less frequently during the losing trends (Fig. 6, Panel-B).
8. Factor analysis identified meaningful components of TRB variables and Theta power variables (Table II). Theta factor-1 (anterior theta power during gain conditions) had a significant negative correlation with TRB Factor-2 (selection frequency following losses). In other words, individuals with reduced anterior (predominantly frontal) theta power during gain conditions more frequently bet with 50¢ in the face of loss.

DISCUSSION

The present study examined reward/outcome processing in abstinent alcoholics and healthy controls in terms of event-related theta activity during the time window of ORN and ORP. Since ORN and ORP components are primarily composed of theta oscillations [Luu et al., 2003, 2004; Gehring and Willoughby 2004; Cohen et al., 2007; Kamarajan et al., 2008], the present study hypothesized that alcoholics, compared to controls, will show features of deficient theta activity. The findings of the present study have demonstrated that alcoholic individuals showed deficient theta activity compared to normal controls. Further, theta activity was associated with impulsivity, and alcoholics showed more impulsivity and risk-

taking behavior. The major findings that are relevant to the goals of the present study are discussed in detail in the light of research studies in the scientific literature as below.

Theta Activity during Reward Processing in Alcoholics and Controls

The robust finding of the present study is that alcoholics, compared to controls, showed a significant reduction in theta activity, and this finding has been graphically illustrated (Figs. 3 and 4) as well as statistically demonstrated (Fig. 5). The present study is the first ERO study to report reward processing dysfunction in alcoholics, although there have been a few ERP studies. Earlier, in a study from our lab, Porjesz et al. [1987] reported that alcoholics manifested lower P3 voltages to all visual stimuli regardless of incentive values (i.e. baseline and two monetary reward conditions). Fein and Chang [2008], using the Balloon Analogue Risk Task (BART) which measures risk-taking propensity, reported smaller ORN amplitudes in treatment-naïve alcoholics with a greater family history density of alcohol problems. In a recent study from our group employing the gambling task used in the current study, we reported that alcoholics showed decreased amplitudes in ORN and ORP components [Kamarajan et al., 2010]. These findings strengthen the view that alcoholics may have a dysfunctional neural mechanism related to reward processing. This view is further supported by the recent imaging studies that reported both structural [Makris et al., 2008] and functional deficits [de Greck et al., 2009] in the neural reward system of alcohol dependent individuals.

Using other cognitive paradigms, studies have demonstrated event-related theta changes related to alcohol use, viz., alcohol dependence, direct effect of alcohol intake, and regular alcohol use and social drinking. For example, event-related theta power was found to be reduced in alcohol dependent individuals during response inhibition in a Go/NoGo task [Kamarajan et al., 2004] as well as during target detection in a visual oddball task [Jones et al., 2006]. Using an auditory memory task, Krause et al. [2002] reported that the administration of alcohol (i.e. the direct effect of alcohol intake) decreased the early-appearing event-related synchronization (ERS) responses during auditory encoding and increased the later-appearing event-related desynchronization (ERD) responses during retrieval in the theta band. Further, during a mental-rehearsal task, heavily drinking students (with regular use of alcohol) had more synchronization in the theta band than lightly drinking students (with social drinking) [de Bruin et al., 2004]. These studies may essentially support the view that theta activity may serve as an effective measure characterizing neurocognitive deficits in alcoholism.

It is important to note that there is strong evidence in the research literature for the view that a decrease (or desynchronization) of event-related theta power during cognitive/affective processing suggests weaker/suppressed task processing, while increased theta activity (or synchronization), on the other hand, indicates more efficient processing. Several ERO studies performed during cognitive processing include the following: memory [e.g., Klimesch 1996, 1999; Doppelmayr et al., 1998, 2000], working memory [e.g., Krause et al., 2000a; Raghavachari et al., 2001, 2006; Schmiedt et al., 2005], creative thinking [e.g., Razumnikova 2007], intelligence [Doppelmayr et al., 2005], cognitive workload [e.g., Sammer et al., 2007], face perception [Basar et al., 2007], motor planning [Caplan et al., 2003], executive function [Gonzalez-Hernandez et al., 2002], response inhibition/execution [e.g., Kamarajan et al., 2004, 2006], visual target discrimination [Karakas et al., 2000b; Jones et al., 2006; Rangaswamy et al., 2007], Stroop effect [Hanslmayr et al., 2008], emotion processing [Krause et al., 2000b; Doppelmayr et al., 2002; Aftanas et al., 2003], error processing [e.g., Luu et al., 2004; Trujillo and Allen 2007], and outcome processing [Gehring and Willoughby 2004; Cohen et al., 2007]. Since the phenomenon of decreased theta power has been observed in a wide variety of cognitive processes, this may indicate a generic deficiency in neurocognitive processing in alcoholics. On the other hand,

significantly reduced theta power in alcoholics *during reward processing* may suggest a specific dysfunction in the neural reward processing mechanism of alcohol dependent individuals.

Although there have been several studies on event-related theta, little is known about the specificity of theta activity to represent a cognitive phenomenon. Therefore, it could be debated whether the deficient theta activation (during a gambling task) represents a specific dysfunction in reward processing or a general deficiency in neurocognitive processing for performing any given cognitive task. In this regard, Yordanova et al. [2002, 2003] maintained that event-related theta activity may reflect a general processing demand during stimulus evaluation by stating that since event-related theta is “consistently observed across different modalities, a transient theta-dominated state may reflect a processing stage that is obligatory for stimulus evaluation, during which interfering activations from other frequency networks are minimized.” However, on the other hand, several studies have attributed task-specific cognitive functions to theta activation [e.g., Raghavachari et al., 2001; Aftanas et al., 2002; Bastiaansen et al., 2002a, 2002b; Luu et al., 2004; Yordanova et al., 2004; Jacobs et al., 2006; Krause et al., 2007; Trujillo and Allen 2007; Hanslmayr et al., 2008; Marco-Pallares et al., 2008]. Although it seems unresolved that deficient theta power in alcoholics represents a general or task-specific cognitive processing, it is reasonable to state that alcoholics may have both generic deficits in stimulus processing as shown in basic oddball tasks [e.g., Porjesz and Begleiter 1985, 1993, 2003 e.g., Porjesz and Begleiter 2005; Cohen et al., 1994; Jones et al., 2006] and domain-specific deficits, such as inhibitory processing assessed by Go-NoGo tasks [Cohen et al., 1997; Fallgatter et al., 1997; Kamarajan et al., 2004, 2005]. Addressing a similar issue, an fMRI study by Pochon et al. [2002] found that monetary reward induced an increased activation in the areas already activated by working memory processing (i.e. a network including the dorsolateral prefrontal cortex and the lateral frontopolar areas) and additionally in the medial frontal pole. This study showed that although common neural structures subserve both cognitive load and reward processing, reward circuitry additionally involved specific brain areas. In sum, it may be suggested that decreased ERO theta power during reward processing could suggest a generic cognitive deficit as well as a specific deficiency for reward processing.

Topography of Theta Power and Current Source Density

Topography of surface theta power and CSD sources indicated markedly weaker theta activation during reward processing in alcoholics, especially at frontal areas (Fig. 4). On the other hand, differences in the location and strength of CSD sources between controls and alcoholics suggested a possible dysfunction in the integrity of brain reward circuitry in alcoholic individuals. The diffuse source activations in all outcome conditions in alcoholics may be suggestive of additional or intruding non-specific activations—either pre-existing or reward-induced activations—in the neural reward circuitry of alcoholics, in contrast to more focused or specific activations in controls. Prior ERP studies have reported similar differences in CSD activations in alcoholics during stimulus discrimination and during response inhibition [Ji et al., 1999; Rodriguez Holguin et al., 1999; Hada et al., 2000; Cohen et al., 2002; Kamarajan et al., 2005]. Further, in a gambling paradigm, our earlier ERP study reported that alcoholics showed decreased current density activations at several brain regions [Kamarajan et al., 2010]. The current study is the first of its kind to report dysfunctional CSD activation of event-related theta band in alcohol dependent individuals. On the other hand, perhaps worth mentioning is the unusual finding in the topography of theta power (see Fig. 4, Panels A and B) in alcoholics, that showed occipital activations in all outcome conditions during high theta activity, which was completely absent in controls. Since this activity was a contribution from high theta (5–7 Hz) band, it is possible that it is the result of “spill-over” of low alpha activity (with occipital focus) in alcoholics, though the

explanation requires further investigation. Another possibility is that the occipital activity (possibly closer to 7 Hz) could be interrupting slow alpha input from the (continuing) visual sensations during the visual feedback of an outcome stimulus, which lasts for 800 ms, while the theta activity measured is between 200–500 ms.

Overall, these topographic differences in alcoholics during reward processing may indicate a possible dysfunction in the neural reward circuitry. Prior findings, from both neuroimaging and electrophysiological studies, have reported dysfunctional neural reward systems in alcoholics. Many fMRI studies have identified the areas involved in reward processing in healthy individuals [e.g., Breiter and Rosen 1999; Knutson et al., 2000, 2001, 2003; Delgado et al., 2003, 2005; McClure et al., 2004; Nieuwenhuis et al., 2005b; Marco-Pallares et al., 2007; Camara et al., 2008], and a few imaging studies have documented the impairments in the key brain areas of reward circuitry in alcoholics [Wrase et al., 2007; Makris et al., 2008; de Greck et al., 2009]. Therefore, in the light of earlier reports on reward processing in normals as well as in alcoholics, decreased theta power and weaker and diffuse current density observed in alcoholics may suggest a dysfunctional reward circuitry which might serve as a hallmark feature of alcoholism.

It should be noted that the findings and scope of the present study could potentially address the question of the role of frontal lobes in reward processing and in alcoholism. In this regard, the key findings of the present study that may serve as evidence for possible frontal lobe dysfunction in alcoholics during reward processing are: 1) decreased theta power at frontal areas in alcoholics, 2) weaker and diffuse CSD source in frontal areas in alcoholics, and 3) anterior theta power (composed mainly of frontal electrodes) during gain conditions was correlated with risk-taking behavior or behavioral impulsivity (assessed by the alcoholic group's higher selection frequency of 50¢ following losses). The role of frontal lobes in reward processing has been well documented. For example, neuroimaging studies have found that frontal lobes, especially the prefrontal areas including the medial frontal areas, play a critical role in the modulation of the reward circuitry [e.g., Knutson et al., 2000, 2001, 2003; Pochon et al., 2002; Gilbert and Fiez 2004; Nieuwenhuis et al., 2005b; Yarkoni et al., 2005; Krawczyk et al., 2007; Bruguier et al., 2008; Fujiwara et al., 2009; Weber et al., 2009]. Further, electrophysiologically, since the origin of event-related theta activity itself is reported to be in the frontal lobes, decreased/dysfunctional theta system can be attributed to an impairment in frontal lobe functioning. According to Basar et al. [2001b], 'frontal theta' is considered to be a major oscillation of the human frontal cortex and has a response-controlling function. Several studies have reported the frontal origin of event-related theta oscillations during several cognitive paradigms, as mentioned earlier. Our previous studies with this gambling paradigm found frontal activations (in cingulate cortex) during reward processing [Kamarajan et al., 2008, 2009] in healthy individuals, and identified reduced frontal activations in alcoholic individuals [Kamarajan et al., 2010]. Additionally, reduced frontal activity (in terms of decreased current density activation) has been found in subjects with high impulsivity and alcoholism [Chen et al., 2007; Dom et al., 2007]. Reviewing the frontal lobe impairments in alcoholics, Moselhy et al. [2001] summarized that alcoholics had manifested frontal lobe dysfunctions at the neurophysiological, morphological and neuropsychological levels. Therefore, it may be stated that the deficient theta activity during reward processing observed in alcoholics could be primarily due to the impaired frontal lobes which in turn could have contributed to a variety of cognitive and executive deficits including the reward processing. It is also possible that other component parts of the brain reward circuitry could have contributed to these deficits, as this circuitry involves complex connections with several brain regions viz., medial prefrontal cortex, medial ventral striatum, medial ventral pallidum, septal complex, bed nucleus of stria terminalis, medial and lateral preoptic area, lateral and posterior hypothalamic areas, lateral habenula, posterior ventral tegmental area, midbrain raphe and rostromedial tegmental nuclei, medial and dorsal

raphe nuclei, laterodorsal tegmental area, periaqueductal gray, and parabrachial nucleus [Ikemoto 2010]. It may be summarized that although frontal lobes (especially prefrontal cortices) play a crucial role in addiction in general [Crews and Boettiger 2009], vulnerability for developing and maintaining addiction involves multiple and complex neurocircuitries subserved by both cortical and subcortical regions at different stages of addiction [Koob and Volkow 2010].

Impulsivity, Reward, Theta Oscillations, and Alcoholism

In the current study, there were three important findings that may interlink the domains of impulsivity, reward, theta oscillations and alcoholism: 1) alcoholics had significantly higher impulsivity in motor, non-planning, and total scores of BIS (Fig. 6, Panel-A); 2) alcoholics selected 50¢ more frequently in the face of loss while controls selected 10¢ more frequently following losing trends (Fig. 6, Panel-B); and 3) anterior theta power during gain conditions (Theta factor-1) had a statistically significant negative correlation with selection frequency following losses (TRB Factor-2) suggesting that individuals with reduced anterior (predominantly of frontal) theta power during gain conditions selected 50¢ more frequently or 10¢ less frequently in the face of losses (Table III). The first finding links impulsivity and alcoholism as alcoholics had more trait impulsivity as assessed by BIS than that of controls. The second finding links alcoholism with risk-taking behavior (or impulsive responding) since alcoholics betted with 50¢ more frequently in the face of losses as against controls who 'played safe' by selecting 10¢ more frequently following losses or during a losing trend. The third finding, on the other hand, connects the frontal theta activity with risky/impulsive reward processing, i.e. the lower the frontal theta power the more frequent the risky choice (i.e. betting with 50¢ in the face of loss). It should be noted that similar interlinks between variables such as impulsivity, reward-related responses, alcoholism and electrophysiological (ERP/ERO) measures have been previously reported from our lab [e.g., Chen et al., 2007; Porjesz and Rangaswamy 2007; Kamarajan et al., 2008, 2009, 2010] and elsewhere [e.g., Nagoshi et al., 1991; Finn et al., 1999; Justus et al., 2001; Petry 2001; Bjork et al., 2004; Mitchell et al., 2005; Dom et al., 2006a, 2006b, 2007].

In our previous studies in healthy normals, it was found that impulsivity was associated with theta power [Kamarajan et al., 2008] as well as with ERP measures of reward processing [Kamarajan et al., 2009]. Similar to the findings of the present study, we demonstrated links among impulsivity, reward-related behavior, alcoholism and ERP measures in a sample of abstinent alcoholics and healthy controls [Kamarajan et al., 2010]. In terms of the significance of impulsivity, many studies have attempted to explain impulsivity in terms of its role in alcoholism and related disorders. Specifically, neurocognitive models of addiction disorders often implicate impulsivity as a major component. For example, according to Dom et al. [2007], impulsivity is a complex multidimensional construct and linked with the pathogenesis of addictive disorders. It has been proposed that the primary motivation circuitry involving cortical–striatal–thalamocortical loops were putatively involved in impulsivity, decision-making and the disorders of alcohol/drug addiction and pathological gambling [Chambers et al., 2003; Chambers and Potenza 2003]. Goldstein and Volkow [2002] conceptualized alcohol/drug addiction as a syndrome of impaired response inhibition and salience attribution, and summarized the involvement of the frontal-subcortical circuits in addiction disorders. Chen et al. [2007] reported that high impulsivity was associated with reduced frontal activation and alcoholism. Further, many researchers have considered impulsivity as the key vulnerability marker for substance-use disorders, especially alcoholism [Verdejo-Garcia et al., 2008, a review]. Further, it has been suggested that the concepts of impulsivity, disinhibition and risk propensity forms the vulnerability not only for substance use disorders but the entire rubric of disinhibitory or externalizing psychopathology [Krueger et al., 2002; Iacono et al., 2008]. Similar to our finding in

alcoholics, Cantrell et al. [2008] suggested that decision-making on the Iowa Gambling Task in those with alcohol dependence and related disinhibitory disorders may reflect an insensitivity to future consequences that is common to the covariance among these disorders but not unique to any one disorder. Fein et al. [2004] observed that long-term abstinent alcoholics, compared with controls, had more externalizing symptoms, showed personality profiles associated with a proneness to social deviance, and made more disadvantageous decisions on a simulated gambling task. Further, connecting the dimensions of electrophysiology, impulsivity and markers of psychopathology, Hall et al. [2007] suggested that oscillatory correlates of cognitive control and/or impulsivity may assume a critical importance in identifying/establishing markers for the externalizing disorders associated with elevated impulsivity and disinhibition. Taken together, our current study has convincingly demonstrated the relationship between anterior theta response and impulsivity, and therefore we suggest that frontal theta oscillations can potentially serve as a useful marker for differentiating the alcoholics from the normal control and the high impulsive individuals from the low impulsive individuals.

Reward Deficiency in Alcoholism

The primary findings of the current study, viz., decreased theta power and weaker, diffuse CSD activations, have been interpreted to underlie dysfunctional brain reward circuitry. Since alcoholism has been considered to be a part of the reward deficiency syndrome (RDS) by many researchers [Blum et al., 2000; Comings and Blum 2000; Bowirrat and Oscar-Berman 2005; Wrase et al., 2007; Makris et al., 2008; Diekhof et al., 2008; de Greck et al., 2009], it is worth exploring the validity of this possibility based on existing theories and findings as well as the findings of the present study. In our previous study on reward processing in alcoholics [Kamarajan et al., 2010], we explained the finding of reduced amplitude in ORN and ORP components as a possible dysfunction in the reward circuitry in alcoholics. However, we cautioned that the RDS model may not be sufficient to explain all the dimensions that may encompass the etiology of alcoholism and related disorders. Since alcoholics manifest neurocognitive disinhibition [Begleiter and Porjesz 1999; Kamarajan et al., 2004, 2005; Porjesz et al., 2005; Porjesz and Rangaswamy 2007; Chen et al., 2007; Rangaswamy et al., 2007; Iacono et al., 2008] as well as deficient reward processing [Porjesz et al., 1987; Blum et al., 2000; Bowirrat and Oscar-Berman 2005; Wrase et al., 2007; Makris et al., 2008; Diekhof et al., 2008; de Greck et al., 2009], our view is that alcoholism and other related disorders are the outcome of dysfunctions in both of these primary mechanisms (i.e. disinhibition and reward deficiency). Therefore, addictive disorders, inclusive of alcoholism, can be considered as a pathology of both reward processing and behavioral/cognitive control.

This proposition of a two-dimensional approach to addiction has been supported by several researchers. For example, Diekhof et al. [2008], in their review, have outlined the neural mechanisms underlying reward processing and decision-making processes in the healthy brain as well as pathophysiological alterations in the neural reward system observed in addictive and mood disorders. Integrating both dimensions as possible mechanism for addiction and drug-seeking behavior, Schoenbaum et al. [2006] reasoned that addicted individuals commonly exhibit a decreased ability to control the desire to obtain drugs (i.e. inhibitory control), despite knowledge about the aversive consequences following drug intake or the low expectation of actual pleasure expected from the drug (i.e. decision-making and reward consequences). While explaining theories on addiction, Robinson and Berridge [2003] state that the compulsive character of drug seeking, the obvious lack of inhibitory control and the lack of ability to avert/reduce risk can be due to pathologically amplified incentive salience of the drug. Incentive salience occurs when stimuli associated with drug-taking behavior begin reinforcing themselves. When the drug becomes maximally salient at

the expense of other available (naturally) rewarding stimuli, it can affect all stages of reward processing [cf. Diekhof et al., 2008]. Further, Longe et al. [2009], in their fMRI data, observed functional connectivity between the lateral prefrontal cortex and the ventromedial prefrontal cortex during a high cognitive (memory) load context and during a highly motivational context, but not in the context of reward alone. Therefore, it is likely that although the reward processing deficiency observed in the current study may only partially explain the mechanism of alcohol addiction, reward processing as such may be an important dimension in alcohol/drug addiction. On the other hand, a multidimensional approach might help explain the multi-factorial nature of alcoholism and related disorders. Nevertheless, it still remains a challenge as to how the deficiency in monetary reward processing is intricately related to drug-seeking behavior. Addressing this specific issue, Wrase et al. [2007] reported in their interesting fMRI finding that detoxified alcoholics showed reduced activation of the ventral striatum during anticipation of monetary gain but showed increased ventral striatal activation in response to alcohol-associated cues, suggesting that alcoholics craved for the pharmacological effects of alcohol to a greater extent than other conventional rewards such as monetary rewards. It is expected that similar studies in the future will shed more light on these complex issues.

CONCLUSIONS AND FUTURE DIRECTIONS

The current study has illustrated a possible deficiency in neural reward processing in detoxified, abstinent alcoholics in terms of decreased theta power, and weaker, diffuse CSD activations and differences in topographic patterns, thus suggesting that power and topography of theta EROs during reward processing may serve as a marker for alcohol dependence. The model of reward deficiency only partially explains reward- and/or drug-seeking behavior, and therefore a multi-dimensional approach involving several factors such as reward processing, disinhibition, motivational context, drug salience, and reinforcement learning may help integrate the neurocognitive factors that cause, maintain and perpetuate alcoholism and related disorders. It is further suggested that future studies should analyze these factors in offspring at high risk for developing alcoholism in order to further parse the state-related from the trait-related variables that may be involved in a predisposition. A major limitation of this study is that the mean age of the alcoholics was higher than that of the controls, although age did not significantly affect theta power across groups; the statistical analysis showed neither main effects of age nor interaction effects of age with group. However, it is suggested that future studies replicate the findings of the present study using an age-matched control group.

Future studies are essential in order to determine additional information by using all the ERO measures (evoked/phase-locked, induced/non-phase-locked and total power) along with ERP measures. Although the oscillations and ERP approaches each has merits of its own, both approaches are alternative or complementary methods to examine the same phenomena. While the ERP method has been used to identify and explain the (sequence of) sensory and cognitive events (or components) in the time-domain data of the averaged EEG activity, the ERO method presents both time and frequency information in evoked, induced and total EEG activities during neurocognitive processing. A detailed comparison of both approaches have been discussed elsewhere by several authors [Basar, 1980; Karakas et al., 2000a, 2000b; Makeig et al., 2002; Jansen et al., 2003; Klimesch et al., 2004; Jones et al., 2006; Andrew & Fein, 2010]. It would also be of interest to compare theta power across resting EEG, prestimulus baseline, and (post-stimulus) event-related oscillations in alcoholics and controls. Finally, future studies should focus on the application of gambling paradigms to a large spectrum of externalizing disorders, in order to understand the specific as well as common features among these disorders, which may help understand the neural and functional underpinnings of alcoholism and related disorders.

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ABBREVIATIONS

ERO	Event-related oscillations
ORN	Outcome-related negativity
ORP	Outcome-related positivity
ERN	Error-related negativity
MFN	Medial frontal negativity
SOG task	Single outcome gambling task
CSD	Current Source Density
BIS	Barratt impulsivity scale
TRB scores	Task-related behavioral scores

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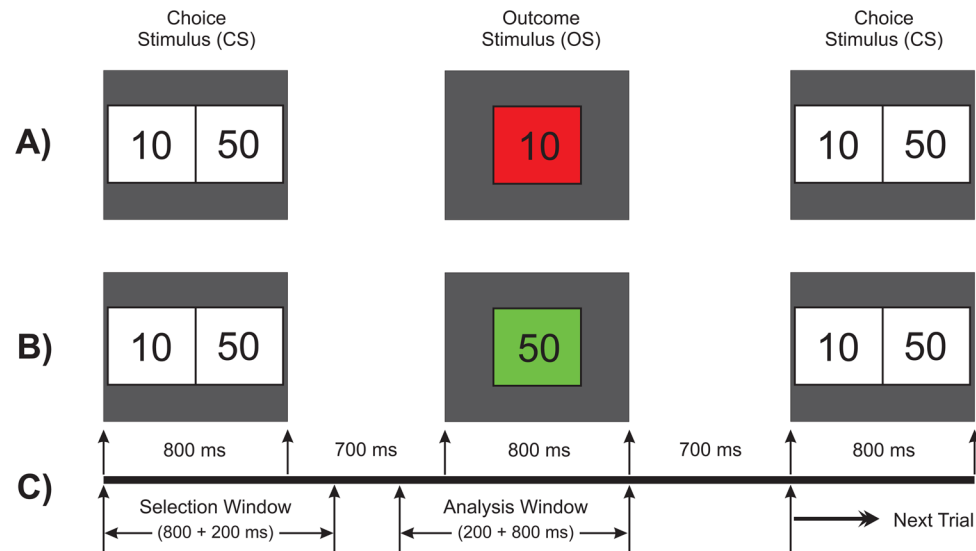


Figure 1. Schematic illustration of the gambling task used in this experiment. (A) a typical trial showing a loss of 10 in red box; (B) another trial having a gain of 50 in green box; and (C) the time duration for the task events: the selection window (1000 ms) wherein the subject selects either of the numbers and the analysis window (200 ms pre-stimulus + 800 ms post-stimulus) represents the time segment that was used for the time-frequency (S-transform) analysis.

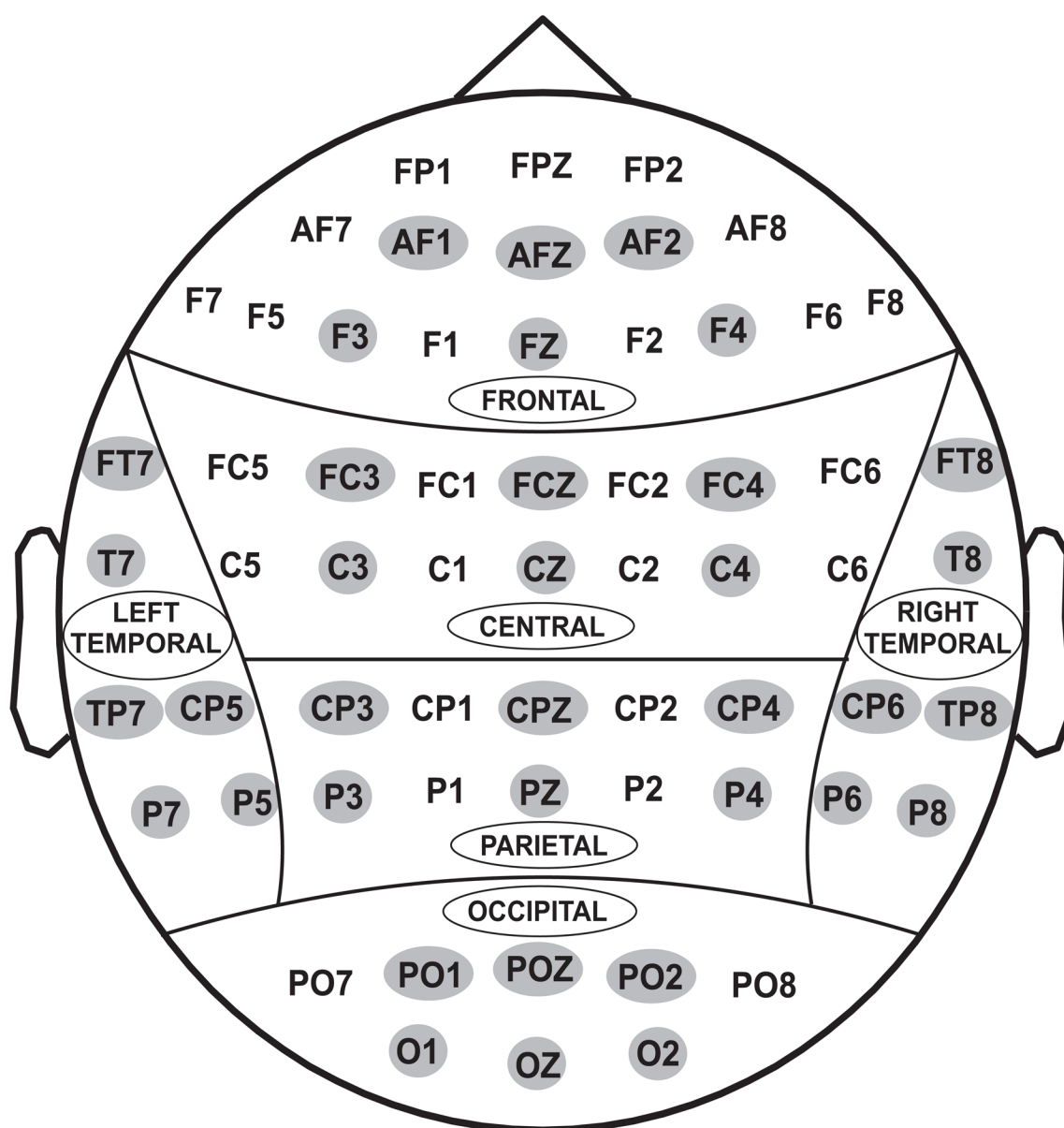


Figure 2.

Sixty one electrodes as recorded from the surface of the scalp. For statistical analyses, only 36 electrodes (as highlighted) were selected to represent 6 electrodes in 6 regions of the brain viz., frontal, central, parietal, occipital, left-temporal and right-temporal.

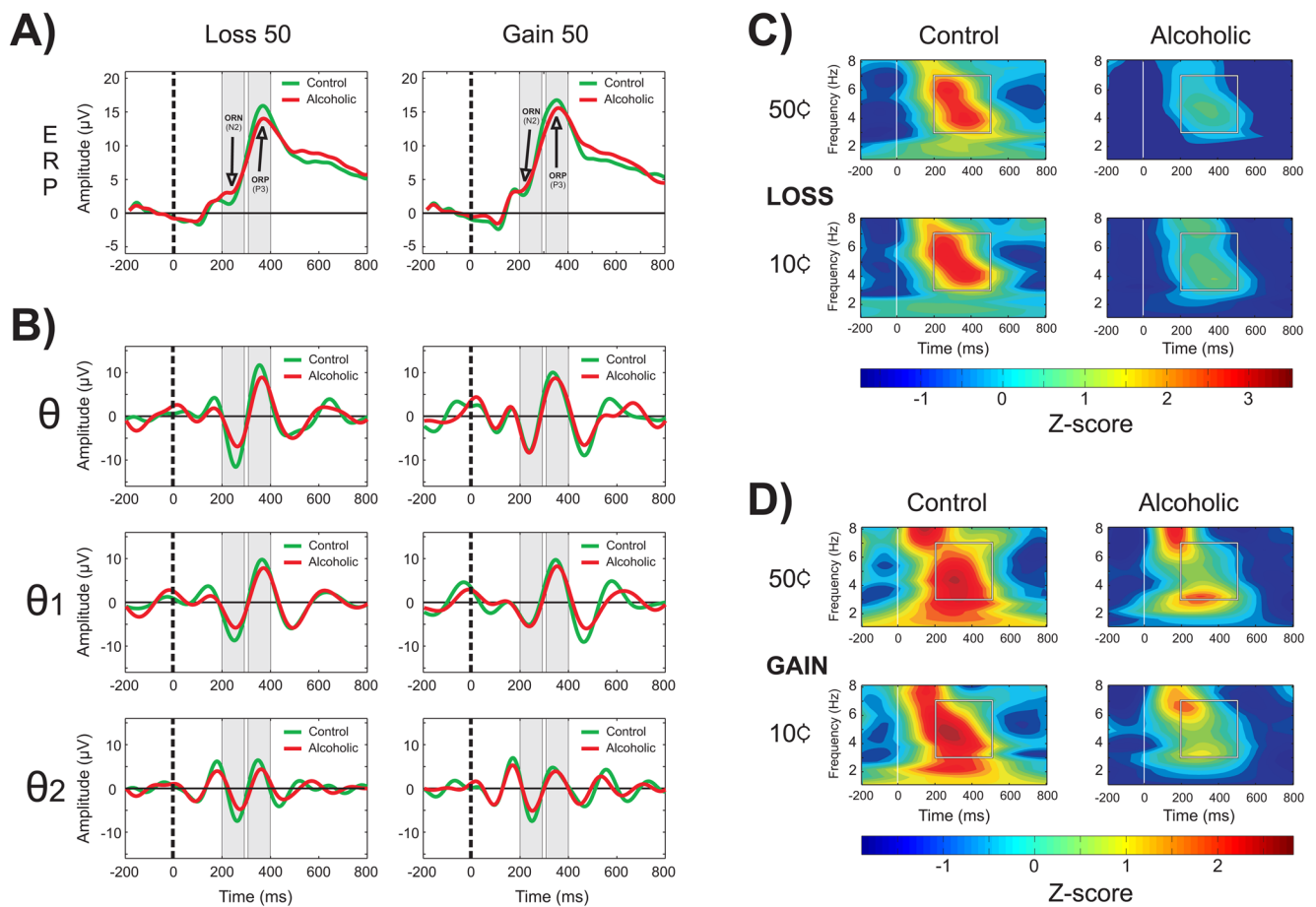


Figure 3.

The grand-averaged ERP waveforms are shown in Panel-A. In Panel-B, theta bands (rows 2–4) during Loss 50 and Gain 50 conditions at Fz electrode are shown. The region of ORN and ORP peaks and the corresponding theta activity during the time window are shaded in gray color. There is a partial phase-alignment of the theta activity corresponding to ORN (200–300 ms) and ORP (300–400 ms) components. Alcoholics showed decreased amplitude in both broadband (3–7 Hz) and sub-bands (3–5 Hz and 5–7 Hz) of theta activity and this difference was more pronounced during the loss condition. Time (in ms) is shown on the X-axis and the amplitude (in μV) is represented on the Y-axis. The dashed vertical line (at 0 ms) represents the onset of an outcome stimulus. Panels C and D represent the time-frequency (TF) plots during the loss condition at Fz electrode and the gain condition at Pz electrode in the alcoholic and control groups. The white line at 0 ms represents the onset of the outcome stimulus. The square box inside each plot marks the time-frequency region of interest, namely the time interval of 200–500 ms across the theta frequency range 3–7 Hz for the analysis. The alcoholic group showed a significant reduction in theta power during each outcome condition. The color scale represents the theta power in terms of Z-scores which were computed from the overall data (representing all groups and conditions) and hence are comparable among the TF plots.

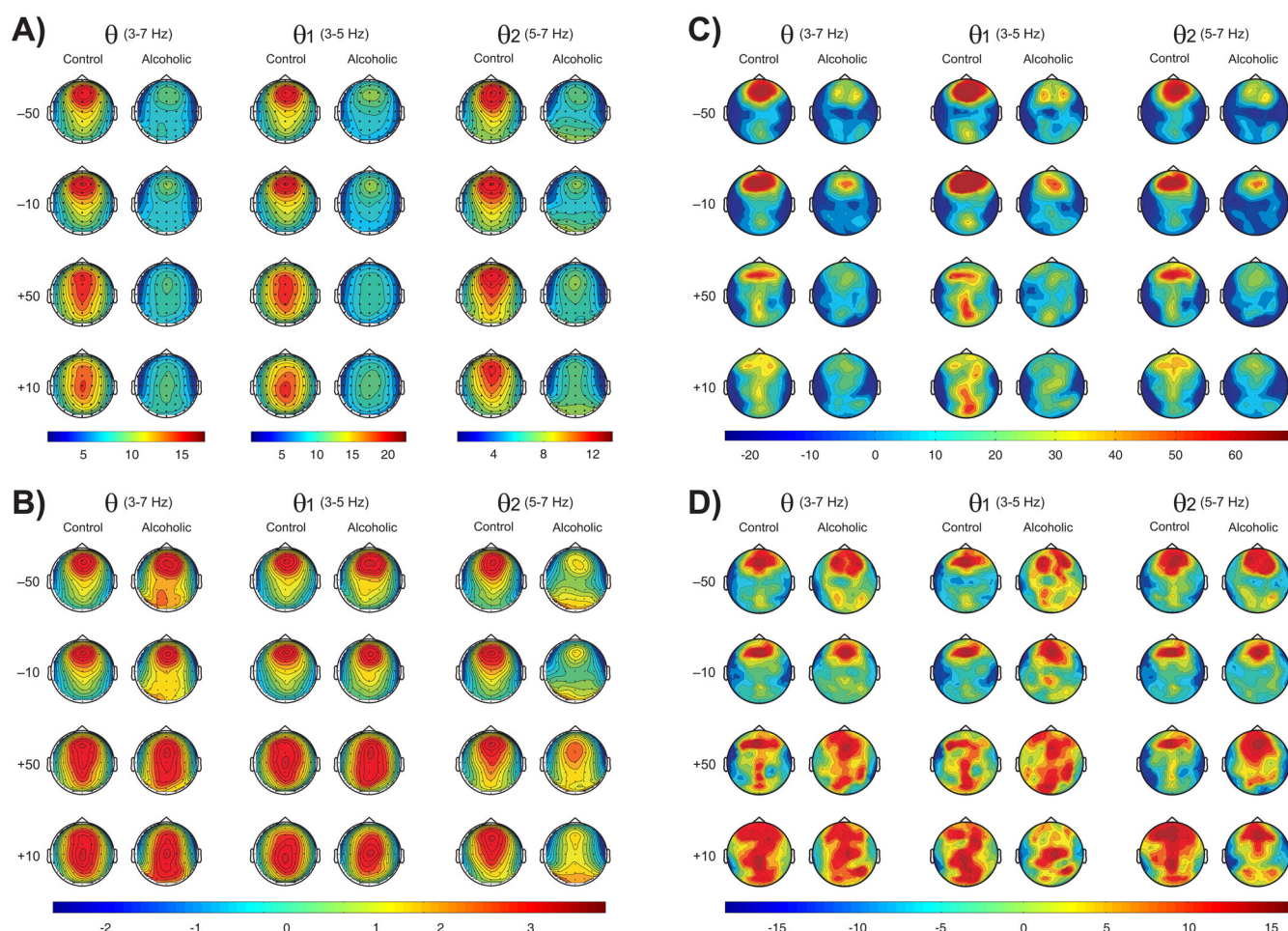
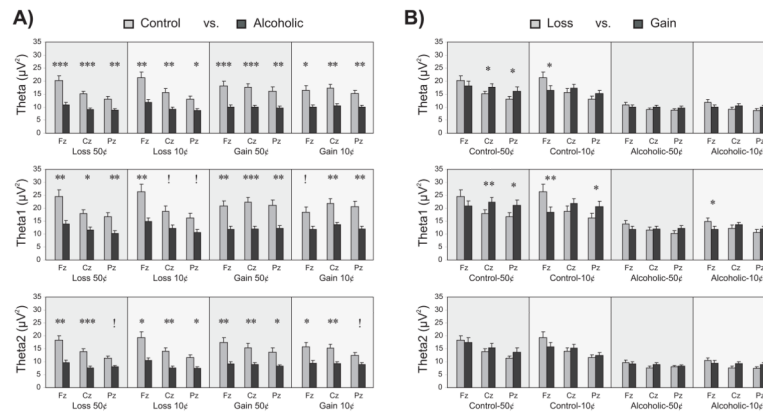


Figure 4.

Topographic maps of theta power (in μV^2) in alcoholic and control groups during loss and gain conditions are shown in Panels A and B. The top set of head maps (Panel A) represent the absolute power and the bottom set (Panel B) represents the Z-scored power. In both groups, loss conditions manifested anterior theta activity while the gain conditions involved both the anterior region (primarily for θ_2) and the posterior region (primarily for θ_1). The alcoholic group showed significantly decreased theta activity during each outcome condition. High theta (θ_2) power in alcoholics had additional activity at the occipital area. The Z-score maps can be compared for the shape of the activation and not for the intensity as the Z-scoring was computed for each headmap separately. The CSD maps (power/ r^2 , where r =head radius in cm) between 200–500 ms during the outcomes (–50, –10, +50, and +10) in the control and alcoholic groups are shown in Panels C and D. The top set of topographic maps (Panel C) represents the Laplacian transformed (CSD) values of theta power and the bottom set (Panel D) represents the Z-scored values of CSD power. Controls showed a strong frontal focus particularly during loss conditions, while alcoholics showed weaker source activity compared to controls, especially at the frontal electrodes. During the –50 condition, while controls had a single and stronger midline prefrontal source, alcoholics showed bilateral and weaker prefrontal sources. The alcoholic group also showed more diffuse source activity compared to controls, especially during gain conditions. In both groups, loss conditions had predominant anterior sources while gain conditions had both anterior and posterior sources. The Z-scored maps can be compared only for the shape of the

CSD activation and not for the intensity since the Z-scoring was computed for each headmap separately.

**Figure 5.**

In Panel-A, the bar graphs show the pair-wise comparisons of mean theta power (in μV^2) across groups (control vs. alcoholic group) during each outcome condition at three electrode sites (Fz, Cz, and Pz). Alcoholics show significantly decreased theta power during all outcomes. The asterisks (*) indicate the level of significance (* $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$) after the Bonferroni correction for multiple comparisons and the exclamation mark (!) indicates the loss of significance after the Bonferroni correction. In Panel-B, the bar graphs show the pair-wise comparisons of mean theta power (in μV^2) across valence (loss vs. gain) during 50¢ and 10¢ conditions in control and alcoholic groups at three electrode sites (Fz, Cz, and Pz). In both control and alcoholic group, Loss was larger than Gain at Fz electrode and Gain was larger than Loss at Cz and Pz electrodes. The comparisons (between loss and gain) were significant only in the control group for theta broadband and for low theta prior to Bonferroni adjustment. In the alcoholic group, although a similar pattern (anterior loss and posterior gain) is observed, the differences are not significant. None of the comparisons was significant after Bonferroni correction.

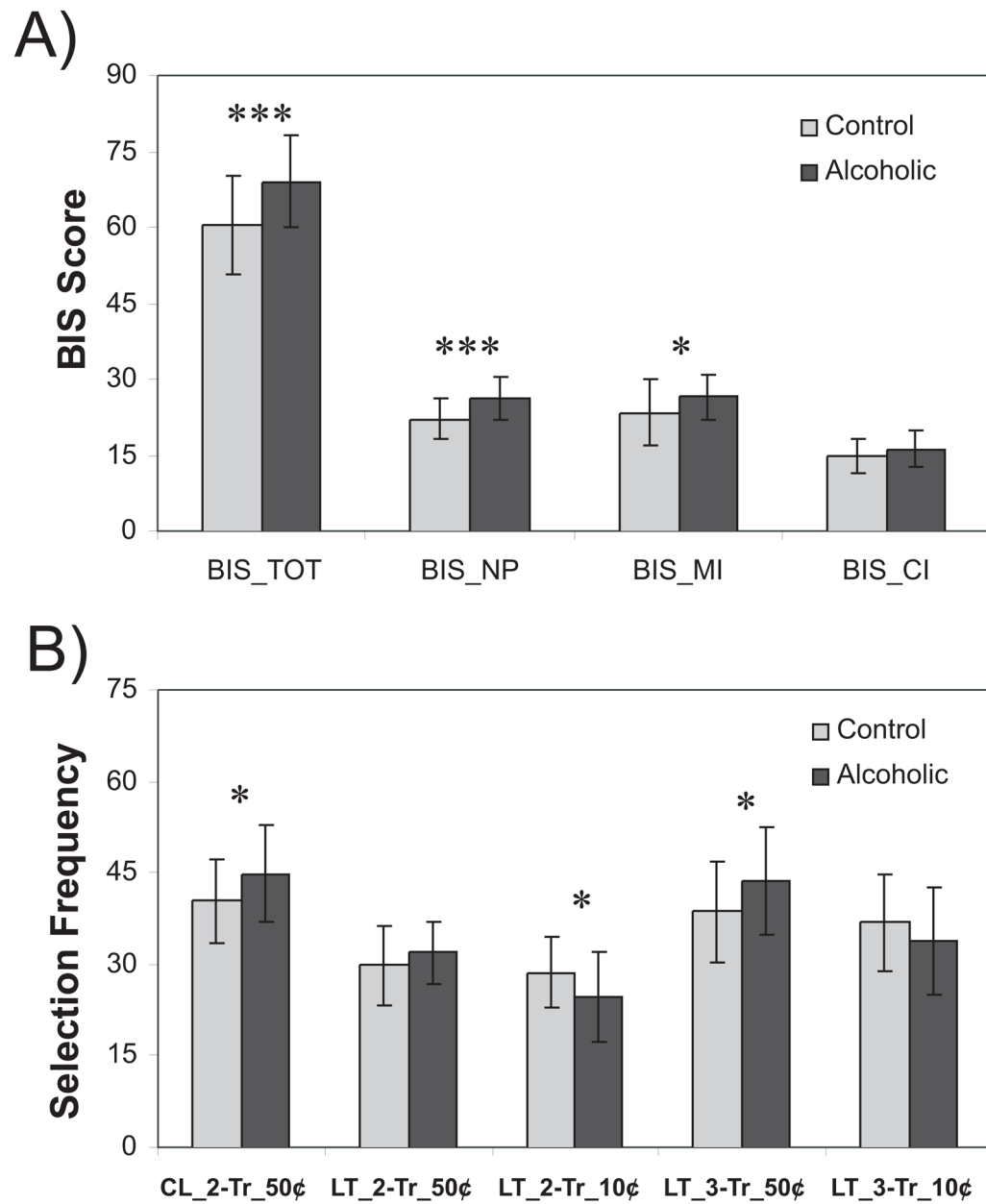


Figure 6.

The behavioral data of BIS scores (Panel-A) and selection frequency between control and alcoholic groups (Panel-B). For the BIS, alcoholics showed significantly higher impulsivity in motor (MI), non-planning (NP), and total scores (TOT). As for the selection frequency, alcoholics selected 50¢ (for betting) more frequently in the face of consecutive losses (CL) during previous two trials (2-Tr) and following the losing trends (LT) during previous three trials (3-Tr). Further, alcoholics selected 10¢ less frequently during the losing trends. The error-bar represents 1 SD.

TABLE I

ANOVA results with the F-value, p-value, and significance level for the main and interaction effects. The statistical significance is marked with asterisks.

	Theta full band (Θ)		Low theta band ($\Theta 1$)		High theta band ($\Theta 2$)	
	F	p	F	p	F	p
Group	0.61	0.4356	0.02	0.8972	1.47	0.2290
Valence	16.93	<0.0001***	25.99	<0.0001***	3.99	0.0494*
Amount	1.92	0.1696	11.29	0.0012**	0.40	0.5290
Region	533.48	<0.0001***	415.72	<0.0001***	434.54	<0.0001***
Group \times Valence	28.23	<0.0001***	33.15	<0.0001***	15.68	0.0002***
Group \times Amount	7.15	0.0092**	2.39	0.1267	5.63	0.0203*
Group \times Region	126.65	<0.0001***	49.37	<0.0001***	141.82	<0.0001***
Valence \times Amount	0.07	0.7851	0.00	0.9531	0.00	0.9833
Valence \times Region	28.87	<0.0001***	46.13	<0.0001***	8.94	<0.0001***
Amount \times Region	0.72	0.6083	1.27	0.2754	0.11	0.9895
Group \times Valence \times Amount	7.16	0.0092**	1.33	0.2524	13.60	0.0004***
Group \times Valence \times Region	8.36	<0.0001***	7.54	<0.0001***	5.91	<0.0001***
Group \times Amount \times Region	2.23	0.0510 ^{ms}	0.53	0.7515	1.98	0.0809 ^{ms}
Valence \times Amount \times Region	0.86	0.5061	2.07	0.0684 ^{ms}	0.57	0.7226
Electrode (Region)	31.57	<0.0001***	22.90	<0.0001***	24.67	<0.0001***
Age	0.59	0.4452	0.02	0.8820	1.40	0.2415
Age \times Group	0.81	0.3708	0.05	0.8246	1.80	0.1837
Age ²	0.66	0.4198	0.04	0.8362	1.51	0.2237
Age ² \times Group	0.73	0.3969	0.03	0.8584	1.71	0.1949

* p < 0.05

** p < 0.01

*** p < 0.001

^{ms} p < 0.10 (Marginal Significance)

TABLE II

Description of factors obtained from TRB variables and Theta variables that accounted for more than 10% of total variance. For each factor, eigenvalue, percentage of variance accounted for, loading index (r), and the number of variables above the loading threshold [N] are listed. Only the factors that had significantly high positive ($r \geq +0.5$) and negative ($r \leq -0.5$) loadings have been selected.

Factors	Eigen Value	Accounted variance (in %)	Variables with positive loadings, (r), and [N]	Variables with negative loadings, (r), and [N]
TRB Factor-1	10.25	37.96	All the RT variables (0.93 to 0.98) [10]	None
TRB Factor-2	5.60	20.73	SF for 50 following losing trends/trials (0.93 to 0.85) [5]	SF for 10 following losing trends (-0.54 to -0.73) [3]
TRB Factor-3	3.33	12.33	Number of times selecting 50 following gaining trends (0.85 to 0.91) [3]	None
TRB Factor-4	2.74	10.14	Number of times selecting 10 following gaining trends (0.77 to 0.89) [3]	None
Theta Factor-1	23.91	22.13	θ , θ_1 , and θ_2 during +50 and +10 conditions at anterior areas: frontal (0.59 to 0.86) [18] and central leads (0.53 to 0.67) [15]	None
Theta Factor-2	13.78	12.76	θ , θ_1 , and θ_2 during -50 condition at posterior areas: parietal (0.56 to 0.85) [9] and central leads (0.55 to 0.84) [9]	None
Theta Factor-3	13.63	12.62	θ and θ_2 during -10 condition at anterior areas: frontal (0.68 to 0.81) [6] and central leads (0.66 to 0.79) [11]	None
Theta Factor-4	13.10	12.13	θ , θ_1 , and θ_2 during +50 condition at posterior areas: parietal (0.64 to 0.79) [9] and central leads (0.55 to 0.68) [8]	None

SF, Selection frequency or the number of times an amount (50¢ or 10¢) is chosen for betting.

TABLE III

Correlation between Theta factors and Impulsivity factors (BIS and TRB). Correlation coefficient (r) and the level of significance (p) before correcting for multiple testing are shown. The minus sign (–) indicates a negative correlation. Theta factor-1 (anterior theta power during gain conditions) has a statistically significant negative correlation with TRB Factor-2 (selection frequency following losses).

Factors	Theta Factor-1		Theta Factor-2		Theta Factor-3		Theta Factor-4	
	r	p	r	p	r	p	r	p
BIS_Total	0.00	0.9872	-0.10	0.4131	-0.16	0.1817	-0.18	0.1334
BIS_NP	-0.05	0.6868	0.01	0.9086	-0.12	0.3196	-0.19	0.1111
BIS_MI	0.02	0.8553	-0.21	0.0822	-0.16	0.1914	-0.21	0.0827
BIS_CI	0.02	0.8766	0.03	0.7997	-0.05	0.6676	0.05	0.6774
TRB Factor-1	-0.12	0.3025	-0.09	0.4598	0.05	0.6536	0.04	0.7263
TRB Factor-2	-0.27	0.0173 *	0.01	0.9433	-0.01	0.9534	-0.09	0.4231
TRB Factor-3	-0.07	0.5755	0.22	0.0591	0.01	0.9580	0.05	0.6776
TRB Factor-4	-0.15	0.1931	-0.01	0.9294	-0.05	0.6675	-0.11	0.3629

* p < 0.05