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Reduced Parietal Delta and Theta Event Related Oscillations in Alcoholics During Early Visual Processing

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ABSTRACT

Background: Chronic alcoholism is associated with widespread structural and functional brain changes that underlie cognitive and behavioral deficits. Electroencephalography (EEG) provides insight into the real-time dynamics of altered sensory and cognitive processing in alcoholism. While prior research shows event-related potential (ERP) and event-related oscillations (EROs) differences, less is known about the early timeframes after visual tasks. **Objective:** This study aimed to characterize ERO differences between alcoholics and healthy controls using EEG recorded during a visual oddball task, with a focus on the first 100ms post-stimulus.
Methods: Publicly available EEG data from 10 alcoholic and 10 control subjects were analyzed. After preprocessing, time-frequency analysis was conducted to examine spectral power changes in delta (2-4Hz), theta (4-8Hz), alpha (8-12Hz) and beta (12-30Hz) bands. Power differences between 50-100ms were statistically compared between groups. **Results:** Alcoholics showed significantly reduced parietal delta ($p=0.03996$) and theta ($p=0.04995$) power compared to controls between 50-100ms. Large effect sizes were found for parietal delta (Cohen's $d=0.94$) and theta ($d=0.78$). No significant differences were seen in alpha or beta bands. **Conclusion:** The pronounced parietal delta and theta reductions likely signify disrupted early sensory encoding and attention orienting in alcoholism. The findings reveal that alcoholism impacts even the initial stimulus registration stages, as evidenced by oscillatory disturbances within the first 100ms. Early EROs could serve as useful endophenotype markers in alcoholism research.

Introduction

Alcohol use disorder (AUD) is a major public health concern, with severe alcoholism affecting over 14 million adults in the United States alone and claiming 65000 deaths annually (Rehm et al, 2014). Chronic excessive alcohol consumption yields both structural and functional brain alterations. These transformations manifest as cognitive and behavioral impairments in alcoholics, including deficits in executive functions such as working memory, attention, response inhibition, and cognitive flexibility (Erdozain et al, 2014).

Patients with chronic alcoholism, and those at high-risk for the disorder, including their offspring, exhibit brain abnormalities. These anomalies have been identified through diverse methodologies, encompassing electrophysiological, neuroimaging, and neuropsychological techniques like magnetic resonance imaging (MRI), positron emission tomography (PET), and electroencephalogram (EEG). While MRI and PET provide insights into brain structure and metabolism, EEG offers millisecond-level temporal resolution, crucial for decoding real-time cognitive processes. Moreover, EEG is non-invasive, cost-effective, and versatile.

AUD, a complicated disorder influenced by genetic and environmental factors, can benefit from the identification of "endophenotypes" or biological markers that bridge the gap between disease and genotype (Kendler et al, 2003; Porjesz et al, 2005). In addition to providing insight into genetic markers of AUD, these

biomarkers hold the potential to detect vulnerable individuals, facilitating early intervention. Electrophysiological measures within EEGs, called Event-related potentials (ERP) and Event-related oscillations (ERO), present strong candidates for these endophenotypes (Porjesz et al, 2005).

ERPs are time-locked neural responses elicited by sensory, motor, or cognitive events, exemplified by "oddball" paradigms where frequent ("standard" or "non-target") stimuli are interspersed with rare ("oddball" or "target") stimuli. A specific ERP component, the P300, characterized by a positive deflection in voltage approximately 300-700 milliseconds post-stimulus, is especially prominent following target stimuli. Alcoholics typically exhibit a diminished P300 amplitude, a phenomenon attributed to impaired attentional resource allocation, and issues with contextual and memory updating (Polich et al, 1994; Zhang et al, 1997).

In close relation to ERPs are event-related oscillations (EROs), also termed Event-Related Spectral Perturbations (ERSPs). EROs decompose the EEG into its constituent time-frequency components emanating from varied brain locales. Serving as communication conduits among extensive neuron populations, EROs correlate with cognitive and integrative functions. Oscillatory systems, namely delta (2-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), and beta (12-30 Hz), play pivotal roles in these neural networks (Basar et al, 1999). Contrary to the traditional "additive model of ERP generation," it's posited that ERP components arise from the superimposition of ongoing EEG oscillations that reset their phases in stimulus response (Gruber et al, 2005; Makeig et al, 2002). EROs bifurcate into two classes: 'evoked' or 'phase-locked' oscillations, which maintain phase alignment across cognitive event trials, and 'induced' or 'non-phase-locked' oscillations. Together, they constitute the 'total' power ERO (Jones et al, 2006b).

In the expansive Collaborative Study on the Genetics of Alcoholism (COGA), event-related EROs have been meticulously examined as potential endophenotypes of AUD (Rangaswamy and Porjesz, 2008; Johnson et al, 2023). Rather than focusing solely on psychiatric diagnoses—which encompass the broad and multifaceted effects of genes—it proves advantageous to delve into molecular genetics through the lens of specific neurobiological markers, known as endophenotypes. These endophenotypes act as intermediary traits, bridging the gap between genes and the intricate behaviors or symptoms characterizing a disorder. As such, they offer a more immediate insight into the genetic predispositions that render individuals susceptible to psychiatric conditions like alcoholism (Criado et al, 2012; Dubreuil-Vall et al, 2020).

Findings suggest that deficiencies in frontal theta and posterior delta EROs might be a strong marker for the development of alcoholism and serve as potential endophenotypes for studying the disorder. This is corroborated by research that has employed cognitive paradigms like the visual oddball task (Jones et al, 2006b; Andrew and Fein, 2010) and Go/NoGo task (Pandey et al, 2016). Rangaswamy et al (2006) found that these theta and delta decreases were present in adolescent offspring of alcoholics, indicating these EROs may present a viable biomarker for susceptibility to alcoholism. Notably, parietal theta oscillations have been associated with the CHRM2 (cholinergic muscarinic receptor M2) gene located on chromosome 7 (Jones et al, 2006a; Chen et al, 2009; Sanchez-Alavez et al, 2016). Identifying these biomarkers gives hope to detect individuals at risk even before they exhibit overt symptoms, crucial for preventive interventions.

These oscillatory responses, across various frequency bands, are linked to different cognitive operations (Sauseng and Klimesch 2008; Herrmann et al, 2016). For instance, delta oscillations are associated with decision-making and detecting novelty or unexpected stimuli (Güntekin et al, 2016; Basar et al, 2001). Theta oscillations are linked to recognition memory encoding and retrieval (Klimesch et al, 2001). Evoked alpha waves are associated with inhibitory processes, suppressing non-relevant brain areas for task performance, directing attentional processes, and reflecting sensory processing and encoding (Ehlers et al, 2015; Mathewson et al, 2014; Forschack et al, 2023). Evoked beta oscillations are associated with motor actions and their inhibition, anticipation of a stimulus, and sensory feedback and evaluation of outcomes (Del Campo-Vera et al, 2022). The one among many advantages of ERO's over ERP's is that they allow a detailed examination of oscillatory dynamics, aiding in understanding complex cognitive processes. It is worth noting that non-evoked delta waves are associated with deep, dreamless sleep and regenerative processes, while theta waves relate to light sleep,

dreaming, creativity and deep relaxation. Non-evoked alpha waves signify alertness, meditation and beta waves dominate during active thinking, alertness, stress, and anxiety (Harris, 2006). Even these resting brain waves are affected in alcohol consumption (López-Caneda et al, 2017)

Many of these studies focus on the EROs at the 200-500 ms mark (P300) and the effects of alcoholism on initial sensory processing within the first 100ms, and on induced activity in frequency bands like delta, theta, alpha, and beta during oddball tasks during that time is less well characterized (Li et al, 2021). Examining early post-stimulus windows and oscillatory responses will provide greater insight into the nature and time course of neural disruptions caused by chronic alcohol abuse.

This study employed publicly accessible EEG data from the UCI Learning Lab Repository, originally donated by Begleiter (1999) and previously used by Zhang et al, (1997). The latter study discerned significant ERP component differences at 240 ms for the right temporal region and at 320 ms for the frontal and occipital regions, with alcoholics exhibiting lower amplitudes than controls during nonmatching (target) tasks.

This publicly accessible dataset has not been previously explored to investigate the ERO differences between alcoholics and controls. To close this gap, we used EEG data from 20 subjects - 10 alcoholics and 10 healthy controls consisting of brain activity recorded during a delayed matching to sample task (analogous to the oddball paradigm).

EEG data were preprocessed using filtering, independent component analysis (ICA), and epoching procedures in EEGLAB (Delorme and Makeig, 2004). Time-frequency analysis was performed using Morlet wavelets to generate spectral perturbations in delta (2-4Hz), theta (4-8Hz), alpha (8-12Hz), and beta (12-30Hz) frequency bands, the definitions of which correlate with Rosenblum et al, (2020).

Power changes were examined in six brain regions - frontal, central, parietal, occipital, left temporal, and right temporal. In addition to visualizing the ERSP images, we also sought to divide the frequency bands over the 50-100 ms and 200-400 ms time zones. Differences between alcoholics and controls were statistically analyzed using linear mixed-effects modeling and nonparametric permutation tests.

We posit that alcoholism affects early sensory processing stages. Specifically, alcoholics are anticipated to exhibit divergent neural oscillatory patterns within the first 100 ms post-stimulus. We project that the impacted bands will primarily be delta and theta, given their roles in initial stimulus registration and encoding. Scrutinizing these sub-second spectral perturbations sheds insight into the immediacy and time course of neural disruptions in alcoholism and will contribute to further defining an endophenotype for those suffering from AUD.

Methods

We accessed publicly available EEG data from the UCI Learning Lab Repository (Begleiter, 1999). Our analysis centered on the SMNI_CMI_TRAIN and SMNI_CMI_TEST datasets, comprising recordings from 10 alcoholic and 10 control subjects, each undergoing 10 runs per paradigm. The experiment employed 90 unique object images sourced from the 1980 Snodgrass and Vanderwart collection. Participants were exposed to two sequentially presented images, separated by a 1.6-second interval, with each image displayed for 300 milliseconds. The trials alternated between one image or matching image (second image identical to the first), also called nontarget, and nonmatching (second image different from the first), also called target, categories, presented in a randomized sequence. Participants were tasked with identifying whether the second image corresponded to the first, using different mouse keys held in each hand to register their response. Typically, two-thirds of the trials were nontargets, and the remaining third were targets. While we downloaded both nontarget and target data, we exclusively utilized the target data, drawing from insights provided by the Zhang et al, (1997) study, which indicated pronounced differences in this segment.

The alcoholic group comprised the following individuals: co2a0000364, co2a0000365, co2a0000368, co2a0000369, co2a0000370, co2a0000371, co2a0000372, co2a0000375, co2a0000377, and co2a0000378.

There were 10 controls: co2c0000337, co2c0000338, co2c0000339, co2c0000340, co2c0000341, co2c0000342, co2c0000344, co2c0000345, co2c0000346, co2c0000347. Within the datasets associated with each participant, there were 54-60 text files, with each file encapsulating a 1-second EEG epoch. A stimulus, either a nontarget or a target was presented at the 190 ms mark.

There were 61 channels made up of: frontal area represented by FP1, FPz, FP2, AF7, AF1, AFZ, AF2, AF8, F7, F5, F3, F1, FZ, F2, F4; the parietal area, CP3, CP1, CPZ, CP2, CP4, P3, P1, PZ, P2, P4; the occipital area, PO7, PO1, POZ, PO2, PO8, O1, OZ, O2; the right temporal area, FT8, T8, CP6, P6, TP8, P8; the left temporal: FT7, T7, TP7, CP5, P7, P5 (Figure 1). The EEG data were sampled at 256 Hz, with all scalp electrodes referencing the CZ. Notably, this choice of reference influenced the polarity of the evoked related potentials, evident in the study's ERPs at 240 and 320 ms manifesting as negative deflections, contrary to the usual positive peaks.

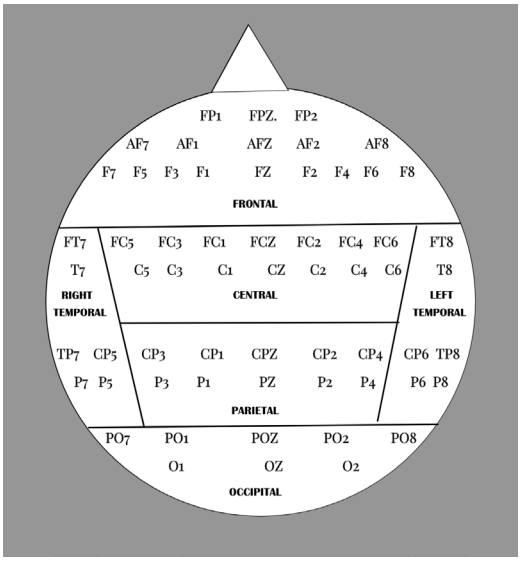

Figure1. Regional grouping of the 61-channel EEG electrodes on scalp: Frontal, Central, Parietal, Right Temporal, Left Temporal, and Occipital.

Demographic details for the specific subset of 10 controls and 10 alcoholics were not available. However, Zhang et al, (1997) indicated that the average age for the control group was all male and had a mean of 25.81 years, while the alcoholic group was also all male and had a mean age of 35.83 years. All participants underwent evaluation and diagnosis by clinical psychiatrists, adhering to the DSM-III criteria for alcohol abuse or dependence. Before the study, all alcoholic participants had a hospitalization period of at least 30 days, ensuring complete detoxification. Exclusion criteria encompassed a history of vascular, neurological, metabolic diseases, or any other significant comorbidities.

EEGLAB Analysis

Subsequently, we employed MATLAB in conjunction with the EEGLAB toolbox to facilitate the importation of the CSV files and their conversion into the '.set' format—a native file type compatible with MATLAB. This transition was achieved using the pop_importdata and pop_saveset functions. This process was uniformly applied to all 20 CSV files.

Utilizing the EEGLAB GUI, we initiated our analysis with the '.set' files, processing the data with the EEGLAB toolbox as detailed by Delorme and Makeig (2004) and Makeig et al (2004). We first processed the

data with initial band-pass filtering via a finite impulse response filter in the range of 1-30 Hz. Post-filtering, the data was subjected to ICA decomposition, segregating the EEG signal based on distinct sources. Components were labeled using the EEGLAB's ICLabel plugin. Components exhibiting a likelihood of >90% of being attributed to artifacts (muscle activity, eye blinks, cardiac signals, line noise, or channel noise) were discarded. After the ICA decomosition and filtering, the continuous EEG data was segmented into epochs spanning from -185 ms to 805 ms, with the stimulus presented at 0 ms.

Time-Frequency Transformation

We employed the newtimef() function in EEGLAB, which utilizes Morlet wavelet convolution (as discussed by Cohen, 2014; Durka et al, 2004) to decompose signals temporally and spectrally. Wavelet length varied from 1 cycle at 1 Hz to 24 cycles at 30 Hz, leading to parameter specifications of [1 0.8]. Due to the brevity of our epoch, frequencies below 3 Hz remained inaccessible. However, for our delta band analysis, we adopted a range of 2-4 Hz.

Spectral power values, represented in decibels, were automatically normalized in EEGLAB relative to a baseline period. After normalization, spectral perturbations across trials were averaged to derive an ERSP image for each of the six predefined brain regions, namely frontal, parietal, occipital, right temporal, and left temporal based on standard electrode placements.

The STUDY functions in EEGLAB enabled the creation of a study design delineating two groups (alcoholic and control) and two conditions (nontarget and target). This facilitated batch processing of EEG data, ERSP generation, and subsequent statistical evaluations. Visual comparisons between Control and Alcoholic ERSPs across brain regions revealed discernible differences, especially in the target stimuli. However, the GUI's inherent limitations precluded the quantification of amplitude values, restricting us to color-based visual interpretations.

Band Power for 50-100 ms and 200-400 ms

To address the limitations observed in our initial approach, we opted to compute the average power for each frequency band (delta, theta, alpha, beta) over two distinct time zones: 50-100 ms and 200-400 ms for both the alcoholic and control groups, followed by a permutation test. The selection of these ranges was driven by preliminary visual analyses using EEGLAB, where differences between the alcoholic and control groups appeared to be more pronounced.

The 50-100 ms epoch was specifically chosen to observe the immediate neural response post-stimulus presentation. Historically, this window has been associated with prominent alpha wave effects, especially in visual oddball tasks similar to our study.

On the other hand, the 200-400 ms window was of interest due to its potential association with the c240 and c320 ERPs, as documented by Zhang et al. in 1997. Using the same EEG data set as our study, Zhang and colleagues highlighted significant disparities between alcoholics and controls, particularly in the frontal, right temporal, and occipital regions during these ERP components. By focusing on the 200-400 ms window, our aim was to encapsulate these two ERPs and delve into the associated frequency powers.

We decided against analyzing the 100-200 ms and 400-600 ms epochs because these time windows, based on our preliminary findings, did not exhibit pronounced differences between the groups and were deemed less relevant for the specific objectives of our study.

Statistical Analysis

Two distinct statistical analyses were executed. The first aimed to contrast the time-frequency plots generated by EEGLAB between the alcoholic and control groups. To achieve this, we implemented a non-parametric

permutation-based t-test, involving 2000 permutations, subsequently adjusted for multiple comparisons using the False Discovery Rate (FDR) correction. This method was already inherent in the EEGLAB platform. This non-parametric approach refrains from making stringent assumptions about the data distribution. Through the permutation procedure, the data is systematically reshuffled and re-evaluated 2,000 times, furnishing insights into the probability of observing differences purely by random chance. The FDR correction then ameliorates the potential for Type I errors, mitigating the risk of false discoveries due to the multiple tests conducted.

For the second portion of our analysis dealing with the 50-100 ms ERSP data, we employed a three-tiered analytical approach: preliminary data exploration, linear mixed effects modeling, and permutation testing with False Discovery Rate (FDR) correction.

Preliminary Data Exploration

Before diving into advanced statistical analyses, we visually explored the data using box plots for each combination of brain regions and frequency bands for each individual. These plots revealed a pronounced intra-subject variability in ERSP measurements, where repeated measures from the same subject exhibited substantial fluctuation. This observation underscored the need for a statistical approach that could adequately account for this variability.

Initial Analysis

We initially investigated 24 distinct combinations of brain regions and frequency bands (1) Frontal Delta 2) Frontal Theta 3) Frontal Alpha 4) Frontal Beta 5) Central Delta 6) Central Theta 7) Central Alpha 8) Central Beta 9) Parietal Delta 10) Parietal Theta 11) Parietal Alpha 12) Parietal Beta 13) Right Temporal Delta 14) Right Temporal Theta 15) Right Temporal Alpha 16) Right Temporal Beta 17) Left Temporal Delta 18) Left Temporal Theta 19) Left Temporal Alpha 20) Left Temporal Beta 21) Occipital Delta 22) Occipital Theta 23) Occipital Alpha 24) Occipital Beta). Using a mixed-effects model approach, we identified significant group differences in ERSP for five combinations after the model considered the intra-subject variability: Frontal - Delta (p=0.0456); Parietal - Delta (p=0.0070); Parietal - Theta (p=0.0211); Right Temporal - Beta (p=0.0332); Left Temporal - Alpha (p=0.0431).

Subsequent analyses focused on these five combinations to further validate and understand the observed differences.

Linear Mixed-Effects Modeling

As detailed in Heise et al (2022), for each of the five identified combinations, we fitted a linear mixed-effects model where the power of ERSP was the dependent variable. The group (Alcoholic or Control) served as the fixed effect, and the individual subject was treated as a random effect. This method was selected because it effectively accounts for the observed intra-subject variability due to repeated measures within subjects and inter-subject variability among different individuals. The model can be described as:

$$ERSP_{ij} = \beta_0 + \beta_1 \times Group_{ij} + u_i + \varepsilon_{ij}$$

Where $ERSP_{ij}$ represents the ERSP power for the jth observation of the ith subject; $\beta_0$is the overall intercept; β_1 indicates the fixed effect of the group; $u_i$is the random effect for the ith subject, capturing the intra-subject variability; $\varepsilon_{ij}$is the residual error.

Permutation Test

To assess the statistical significance of the group differences while minimizing assumptions about data distribution, we employed a permutation test. For each of the five combinations, the group labels of “Alcoholic” and “Control” were randomly shuffled 1000 times, maintaining the original data structure. Then for every permutation, the mixed-effects model was fitted, and the p-value corresponding to the group effect was recorded.

Finally, the empirical p-value was subsequently determined by comparing the originally observed p-value to the p-value distribution from the permuted datasets.

Multiple Comparisons Correction

Given the multiple tests conducted across the five combinations, we implemented the False Discovery Rate (FDR) correction using the Benjamini-Hochberg procedure, ensuring robust control over type I errors.

Effect Size Estimation

To quantify the magnitude of the difference between the two groups, we calculated Cohen's d, a standardized measure of effect size. Cohen's d provides a quantitative measure of the size of the difference between two groups. While p-values indicate if a difference is statistically significant, effect sizes reveal the magnitude of the difference. Cohen's d specifically shows the standardized difference between group means. Effect sizes are less influenced by sample size compared to p-values. Therefore, Cohen's d offers a more robust estimate of the actual differences between alcoholic and control ERO power. Cohen's d was computed as the difference between the two group-means divided by the pooled standard deviation. The pooled standard deviation is a weighted average of the standard deviations of the two groups and is calculated using the formula:

$$\text{pooled standard deviation} = \sqrt{\frac{(n_1-1)\times variance_1+(n_2-1)[\times variance_2]}{n_1+n_2-2}}$$

where n_1 and n_2 are the sample sizes of group 1 and group 2, respectively, and $variance_1$ and $variance_2$ are their respective variances.

Cohen's d is then given by:

$$\text{d} = \frac{mean_1-mean_2}{pooleds\,tan\,darddeviation}$$

A Cohen's d value of around 0.2 is considered a 'small' effect size, 0.5 represents a 'moderate' effect size, and 0.8 or greater is considered 'large'.

Visualization

To effectively communicate the results, we plotted bar graphs showcasing the mean power values (with associated confidence intervals) for both the Control and Alcoholic groups across the selected regions and frequency bands. Only those combinations with statistically significant differences (after FDR correction) were included in the visualization. The color-coding was chosen to provide a clear distinction between the Control (shades of blue) and Alcoholic (shades of red) groups and among different frequency bands. Visualization aids in both the qualitative and quantitative interpretation of the results.

Confidence Intervals

95% confidence intervals were computed for the mean EEG power of both the Control and Alcoholic groups for each frequency band and region combination. This offers a range within which the true population mean is likely to lie.

Rationale for the Chosen Approach

The stepwise approach, starting with the assessment of intra-subject variability, ensured that our subsequent analyses were grounded in a thorough understanding of the data's structure and variability. By prioritizing regions and frequency bands with lower intra-subject variability, we increased the likelihood of detecting genuine group differences and reduced the noise introduced by high variability. The mixed-effects model captures the structure of the data, considering both fixed (alcoholic and control) and random effects (intrasubject variability and intersubject variability). The permutation test provides a non-parametric approach to assess the significance of the observed effects without making strong assumptions about the data distribution.

Results

The current study aimed to compare event-related oscillations (EROs) between control and alcoholic subjects in response to visual target stimuli. Based on prior work by Zhang et al. (1997), who originally collected and analyzed the EEG dataset used in the present study, the largest ERO group differences were hypothesized to occur in response to non-matching (target) stimuli. Thus, EROs time-locked to target stimuli were examined across six brain regions - frontal, central, parietal, right temporal, left temporal, and occipital - for both control and alcoholic groups across 4 different frequency bands–delta (2-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), and beta (12-30 Hz). Differences in ERO power between the two groups were statistically evaluated. By focusing specifically on target processing and key regions of interest identified by earlier research, this study sought to elucidate patterns of electrophysiological activity that may distinguish alcoholics from controls during a visual cognitive task. Examining both spatial and spectral features of EROs in response to targets allows comprehensive characterization of potential neural correlates of alcoholism.

EEGLAB and ERSP

We assessed the ERO's difference between alcoholics and controls in two different ways. One way was to use study module in the EEGLAB toolbox to generate event related spectral perturbations (ERSPs) and run the inherent EEGLAB permutation test with FDR correction to plot each region of the brain from 0-400 ms (0-600 ms for frontal region) spanning 1-30 Hz frequency bands. With the EEGLAB built-in permutation-and-FDR-correction statistical analysis, we were able to visualize where in the ERSP spectrum their significance ($p<0.05$) between the two groups was. The results are shown in figure 2.

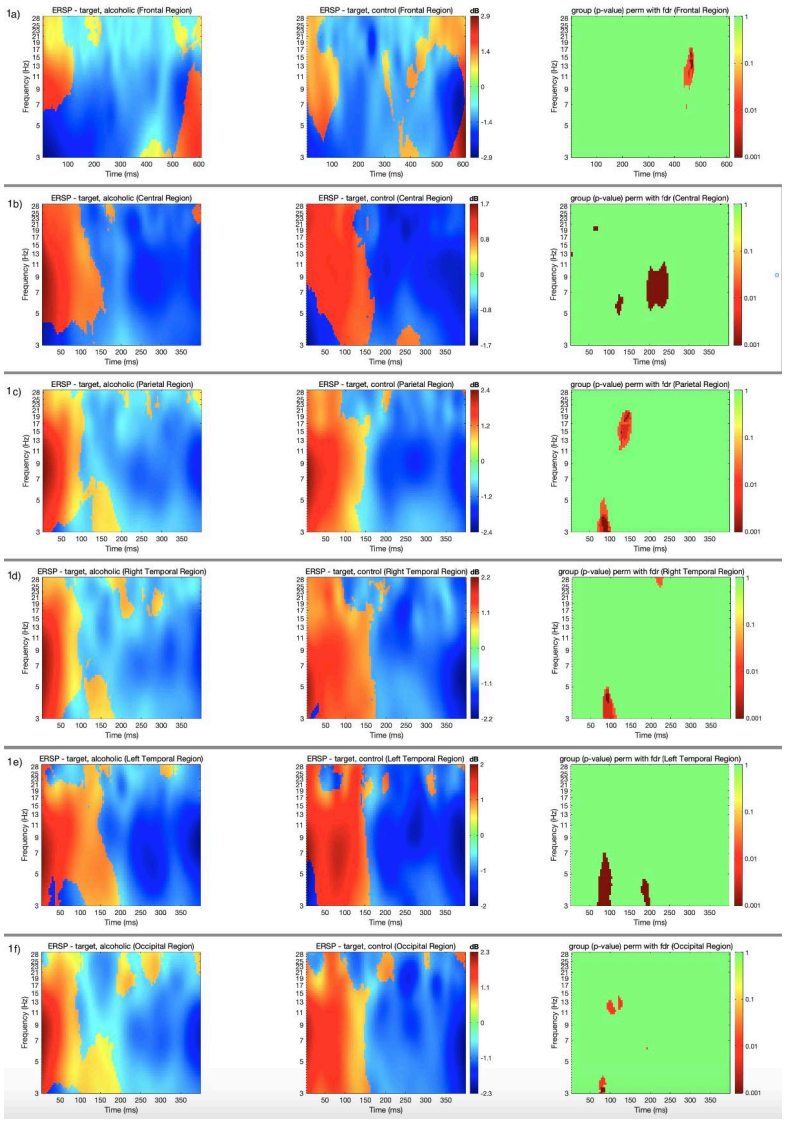

Figure 2. Time-frequency power maps (ERSP) for a visual delayed matching task with target stimuli (non-matching image) in alcoholics vs. controls. Rows represent different brain regions: Frontal (1a), Parietal (1b), Central (1c), Right Temporal (1d), Left Temporal (1e), and Occipital (1f). Data normalization is based on spectral power during a baseline period. In the ERSP maps, red indicates power increases and blue indicates decreases relative to baseline. Adjacent statistical significance maps (right) show significance after 2000 permutations and FDR correction in EEGLAB; green areas indicate non-significant regions ($p > 0.05$).

Upon examining the figures, distinct variations between the ERSP plots of the control and alcoholic groups are evident. However, only a subset of these differences reached statistical significance, as indicated by a p-value less than 0.05 after EEGLAB's permutation and FDR correction technique.

Frequency Powers During 50-100 ms and 200-400 ms

Upon initial examination, it became evident that most of the significant activity was concentrated within the post-stimulus intervals of 50-100 ms and potentially 200-400 ms. Given these observations, we sought to conduct a more in-depth analysis comparing the two groups within these time windows. As a preliminary step, we assessed the intrasubject variability for each participant, aiming to pinpoint the band powers and neural regions with the most consistent data. Figures 3 and 4 present the intrasubject variability, depicted as box plots, for the intervals of 50-100 ms and 200-400 ms, respectively.

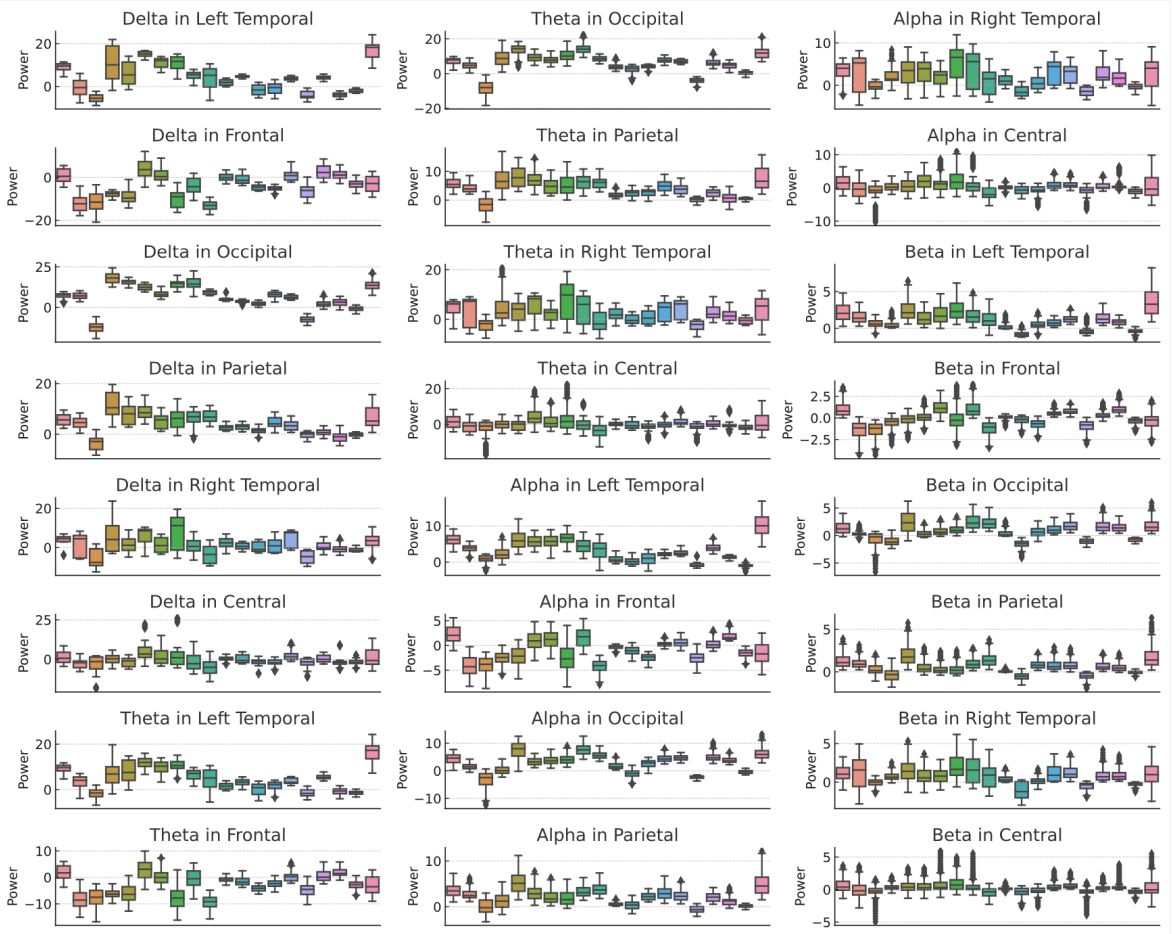

Figure 3. Individual ERSP power distributions within the 50-100ms post-stimulus interval. The y-axis delineates the power magnitude for each frequency band, while the x-axis enumerates individual participants. Controls are represented by subjects 337-347 (first ten on the x-axis) and alcoholics by subjects 364-378 (subsequent ten on the x-axis).

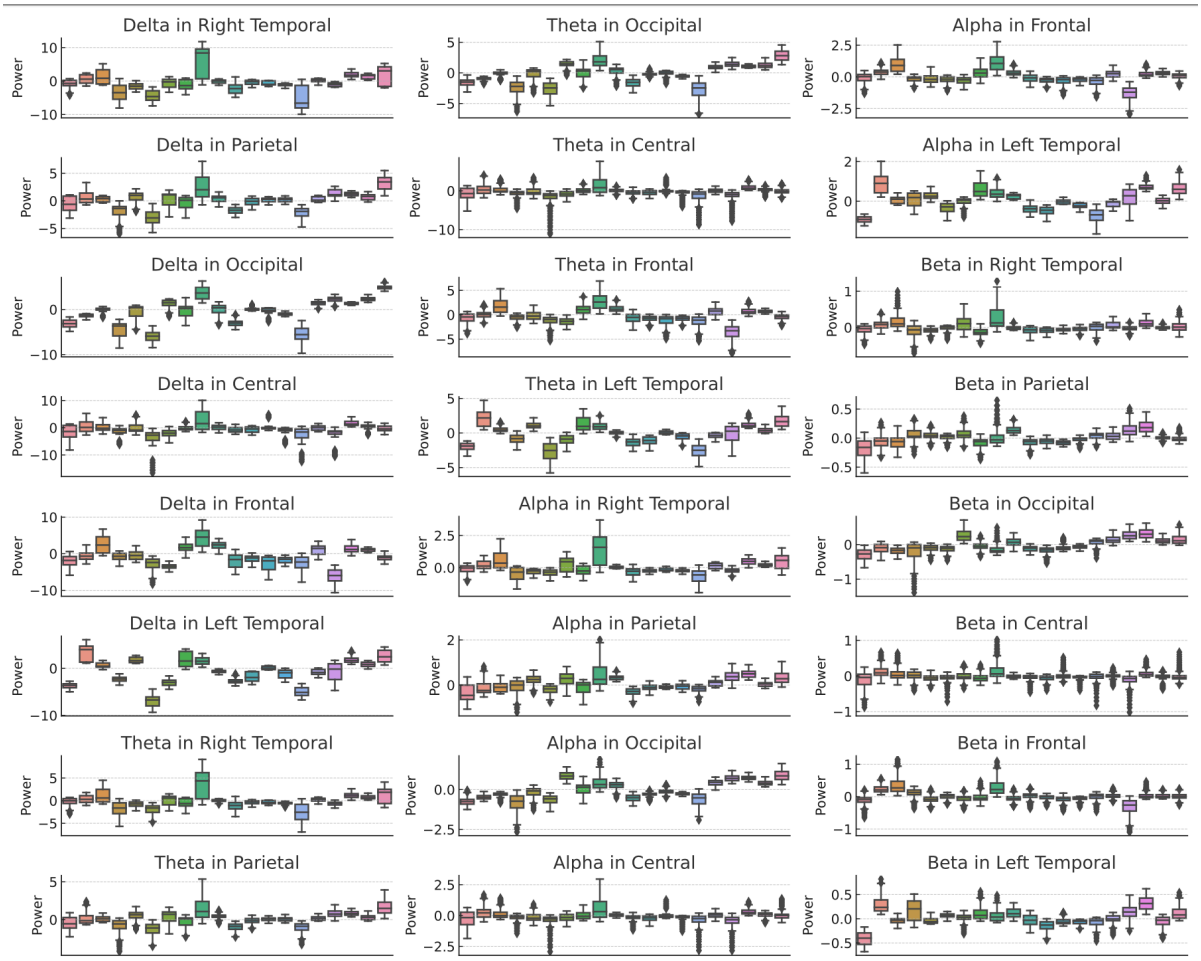

Figure 4. Individual ERSP power distributions within the 200-400 ms post-stimulus interval. The y-axis delineates the power magnitude for each frequency band, while the x-axis enumerates individual participants. Controls are represented by subjects 337-347 (first ten on the x-axis) and alcoholics by subjects 364-378 (subsequent ten on the x-axis).

Upon inspecting the boxplots representing individual ERSPs across different frequency bands and brain regions, we observed pronounced intrasubject variability during both the 50-100 ms and 200-400 ms time windows. Given the potential for this variability to generate misleading findings, it was imperative to utilize a statistical approach capable of accommodating such variability. Consequently, we adopted linear mixed-effects modeling, as elaborated in the Methods section, to discern genuine differences in specific frequency bands and regions while robustly accounting for intrasubject variability (Heise et al, 2022).

The application of linear mixed-effects modeling revealed significant group differences within the 50-100ms window in several domains: Frontal-Delta ($p=0.0456$), Parietal-Delta ($p=0.0070$), Parietal-Theta ($p=0.0211$), Right Temporal-Beta ($p=0.0332$), and Left Temporal-Alpha ($p=0.0431$) between the alcoholic and control participants. Conversely, for the 200-400 ms time window, the linear mixed-effects model did not identify any significant differences between the alcoholic and control groups across all 24 combinations once intrasubject variability was considered.

Hence, our analytical emphasis was placed on the detailed statistical examination of the frontal-delta, parietal-delta, parietal-theta, right temporal-beta, and left temporal-alpha within the 50-100 ms time window. The outcomes, obtained through non-parametric permutation tests complemented by FDR correction, alongside

bootstrapped confidence intervals and Cohen's d to quantify effect size, are tabulated in Table 1 and illustrated in Figure 5.

Table 1. This table is complementary to Figure 5 and shows comparative analysis of time-frequency power (in dB) for control and alcoholic groups across select brain regions and frequency bands during the 50-100 ms post-stimulus time window. Presented values for each group are mean power values accompanied by bootstrapped confidence intervals. Cohen's d provides a measure of effect size, with positive values indicating higher power in the control group and negative values indicating higher power in the alcoholic group. P-values are reported after correction for multiple comparisons using the False Discovery Rate (FDR) method, with asterisks (∗) denoting significance at p<0.05. Cohen's d >|0.2| denotes a small, d >|0.4| a medium, d >|0.8| a large, d >|1.2| very large effect size; Notably, the control group exhibited significant differences in the parietal region for both delta and theta bands; CI: confidence interval.

Region	Time zone	Frequency	Control Mean with CI (dB)	Alcoholic Mean with CI (dB)	Cohen's d	P-value (after FDR correction)
Frontal	50-100 ms	Delta	-6.15 +/- 0.36	-1.79 +/- 0.20	-0.79	0.05694
Parietal	50-100 ms	Delta	6.00 +/- 0.32	2.11 +/- 0.21	0.94	0.03996*
Parietal	50-100 ms	Theta	5.32 +/- 0.17	2.74 +/- 0.13	0.78	0.04995*
Right Temporal	50-100 ms	Beta	1.07 +/- 0.10	0.39 +/- 0.08	0.52	0.05694
Left Temporal	50-100 ms	Alpha	4.46 +/- 0.20	2.07 +/- 0.25	0.80	0.05694

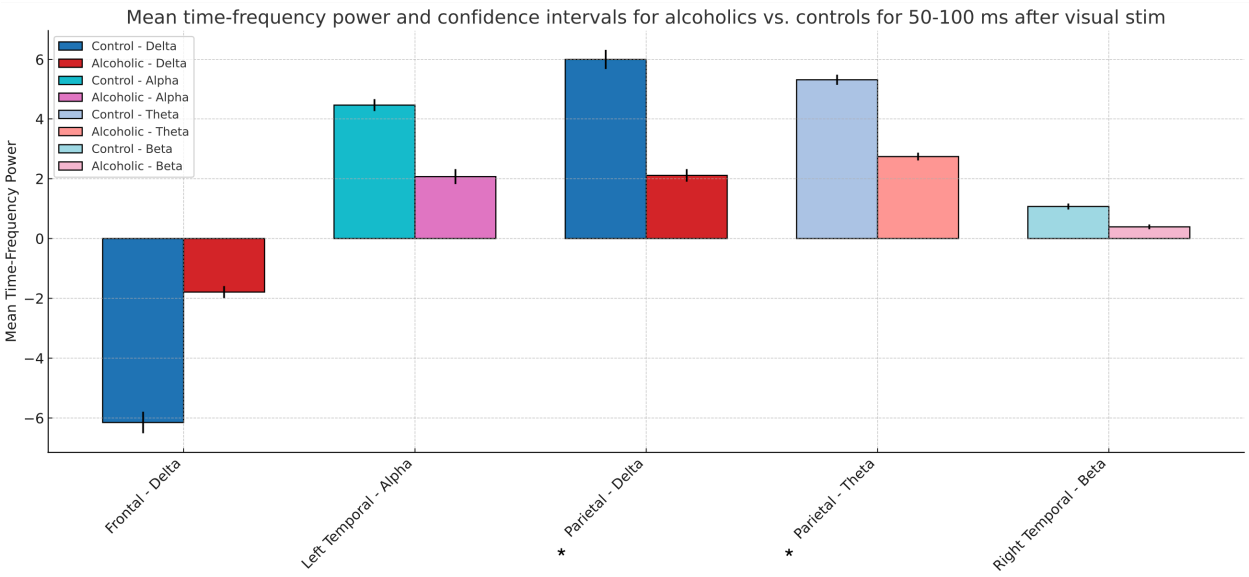

Figure 5. Comparison of mean time-frequency power (in dB) between control and alcoholic groups across various brain regions and frequency bands. The bars represent the mean power values for Delta, Theta, Alpha, and Beta frequency bands, with error bars indicating bootstrapped confidence intervals. Statistical analyses

involved the use of mixed linear models to compare power values between the groups, while accounting for individual variability. The significance of group differences was evaluated using permutation tests with 1,000 permutations. P-values have been corrected for multiple comparisons using the False Discovery Rate (FDR) method. Bars marked with asterisks denote categories significant at $p<0.05$. The control group displayed elevated frequencies in both the parietal delta and parietal theta EROs.

Delta and Theta ERO Responses

A concordance between the ERSP visualizations generated via EEGLAB and the rigorous statistical analysis of mean power within the 50-100 ms interval underscores a notable reduction in both delta and theta power within the parietal region among the alcoholic cohort relative to their non-alcoholic counterparts, following the presentation of non-matching images. While the ERSP delineations manifest these alterations predominantly between 75 ms and 110 ms, the tabulated data and graphical representations provide an aggregated perspective over the 50-100 ms duration.

We found there was a large effect size with Parietal delta power ($d\geq0.8$) and a moderate effect size with Parietal theta power ($d\geq0.5$). This means that there are pronounced differences between the groups in their neural responses within these frequency bands in the parietal region. Specifically, a large effect size in delta power suggests that this frequency band is particularly sensitive to the differences between the groups, potentially indicating substantial alterations in underlying neural mechanisms or cognitive processes. The moderate effect size observed in theta power, while not as pronounced as delta, still signifies a noteworthy difference between the groups, hinting at possible changes in attentional processing, memory encoding, or other cognitive functions associated with theta oscillations. Together, these findings underscore the importance of the parietal region and its oscillatory activity in understanding the neural and cognitive differences between the groups under investigation.

While the ERSP visual depictions indicated potential significance within the right temporal delta and theta bands, as well as the left temporal delta and theta bands, these nuances did not attain statistical significance after adjusting for intrasubject variability.

Other ERO responses

Analysis of ERSP profiles, as depicted by EEGLAB, demonstrated notable variations in alpha oscillatory activity among the alcoholic cohort. Specifically, there was a discernible attenuation of alpha power in the frontal (450-500ms), parietal (125-150ms), and occipital (100-150ms) regions. In the central region, the control group exhibited a pronounced alpha response relative to the alcoholics. An initial surge in activity around the 200 ms mark was promptly followed by a decline by roughly 250ms, showcasing greater dynamism compared to the response observed in the alcoholic cohort.

The ERSP visualizations identified a significant decline in beta activity within the frontal cortex for the alcoholic group, especially evident in the 450-500 ms window.

Due to considerations detailed in our Methods section, we opted not to delve into extended analyses for the time frames of 100-200 ms and 400-500 ms other than ERSP visualization.

Discussion

This study aimed to examine differences in event-related oscillations (EROs) between alcoholics and healthy controls using EEG data from a visual oddball task. The results reveal several key differences in spectral power within the first 100 ms after stimulus onset.

We surmised that any changes occurring during this time frame may correlate with changes seen in alcoholics and high-risk offsprings in their decreased amplitudes of an ERP called the N100, which appears roughly 100 ms after a stimulus is presented (Patterson et al, 1987; Kaseda et al, 1994). N100 is thought to represent early sensory processing and attention modulation (Steinhauer et al, 1987; Herrmann and Knight, 2001).

In terms of ERO activity near N100, there have been reports suggesting that alcoholics and those at high risk for alcoholism (HR) show impairments in early attention selection. However, the findings are not consistent across all studies. This inconsistency may be due to a phenomenon of "theta phase resetting" in those first 100 ms in alcoholics due to an already hyper-excited neuronal state of alcoholics (Fuentemilla et al, 2009).

Our results support that there indeed is an alteration in both delta and theta ERO band in the parietal region during the 50-100 ms. Even after the rigorous two step statistical method first with linear mixed effects modeling then permutation with FDR correction, we saw there was a significant ($p<0.05$) large effect ($d =0.94$) decrease in delta and moderate effect decrease ($d = 0.78$) in theta EROs in the parietal lobe of alcoholics.

The difference of almost one standard deviation d value of 0.94 for the delta power difference in the parietal lobe indicates a substantial difference between the controls and alcoholics. The large effect size suggests that the observed difference is not just statistically significant, but also practically meaningful. It indicates a real and substantial difference in brain activity between alcoholics and controls. Event-related delta oscillations arise from interactions between different cortical regions and are an outcome of the brain's extensive network system. They play a pivotal role in tasks such as signal detection and decision-making (Başar-Eroglu et al, 1992; Basar et al, 2001, Pandey et al, 2012 for review). This pronounced difference in the two groups implies significant alterations in the underlying neural mechanisms of signal detection in context of a visual task.

Similarly, the decreased parietal theta power in the alcoholic group in the 50-100ms range had a moderate effect size of 0.78 and significant p-value after mixed effect modeling and permutation. This implies that there was also substantial difference in the parietal lobe's theta activity as well in the alcoholics. Event-related theta waves stem from interactions between the cortex and the hippocampus or between the frontal region and limbic system. Theta oscillations have diverse cognitive implications, encompassing aspects like alertness, memory encoding and retrieval, selective attention, and even processes related to errors and rewards (Jacobs et al, 2006, Başar-Eroglu et al, 1992; Klimesch et al, 2001; Pandey et al, 2012 for review). This observation of moderate, significant difference in the two groups is congruent with the demands of this delayed matching visual task module, which necessitated participants to retain the memory of an image of the initial picture for subsequent comparison and click the appropriate mouse key.

The parietal lobe plays a pivotal role in sensory processing, spatial orientation, attention, and working memory data manipulation (Wang et al, 2017; Koenigs et al, 2009). Disruptions in parietal theta and delta could underlie difficulties alcoholics have with visual attention, perceptual discrimination, and context and memory updating. Neuroimaging studies have connected these initial parietal responses with the frontal lobes in a top-down control of selective attention (Tallon-Baudry et al, 1997; Corbetta et al, 2000, Giesbrecht et al, 2003, van Ede et al, 2017). This indeed may be the mechanism of how the parietal delta and theta bands have been affected.

The marked reductions in evoked delta and theta power in the parietal lobe demonstrate that chronic alcoholism disrupts early sensory processing and encoding. These neural inefficiencies likely in turn cascade into higher-order deficits in attention, memory and executive functions.

Beyond the parietal oscillations, alcoholics also showed reduced left temporal alpha power, which may reflect impairments in early perceptual grouping, binding and identification. However, this difference did not remain significant after multiple comparisons correction, so more research is needed.

Interestingly, no ERO differences remained significant in the 200-400 ms window, despite prior studies showing altered ERPs and EROs in this timeframe. Visual oddball task studies document that the centroparietal theta and parietal delta EROs are decreased in alcoholics and those at high risk for alcoholism (HR), correlating well with the timing of the P300 ERP, that is also decreased (Jones et al, 2006b, Andrew and Fein,

2010). These decreases in delta and theta oscillations are also seen in Go/NoGo tasks in the frontal lobe area in both alcoholics and HR (Kamarajan et al, 2004; Kamarajan et al, 2006). This discrepancy may have to do with the intrasubject variability and small sample size of this study and contributes to the limitation of this study.

There were many limitations to this paper. With only 10 participants in each group, the sample size is relatively small. While statistically significant results can still be observed with small sample sizes, these findings might be more susceptible to individual variability. It's essential to ensure that the results are robust and to be cautious about generalizing the findings to broader populations.

A notable limitation in our study arises from the constraints of the publicly sourced data, which provides a time epoch of only one second. This constraint adversely affects the frequency-time resolution tradeoff inherent in the time-frequency transform analysis. While our aim was to analyze the slower oscillations characteristic of delta waves, the necessity of employing lower wavelets introduced potential inaccuracies in pinpointing exact frequencies, albeit with improved temporal precision. Moreover, the restricted epoch duration impedes our ability to adequately capture slower frequencies. For instance, a 1 Hz oscillation would manifest merely as a singular cycle within this one-second window, rendering it virtually undetectable. Consequently, frequencies below 3 Hz were essentially obscured within the confines of this one-second epoch.

A further limitation of our study pertains to the absence of detailed demographic information for the 10 alcoholics and 10 controls as furnished by the SMNI_CMI_TRAIN and SMNI_CMI_TEST datasets. This omission hampers our ability to generalize our findings to broader alcoholic and control populations, particularly when our objective is to identify potential endophenotypes.

There are some confounding factors that was not screened by the original study that can affect ERPs and EROs including fatigue, caffeine intake, and sleep deprivation though they did exclude for other major confounders such as history of vascular, neurological, metabolic disease, or other comorbidities (Zhang et al, 1997). And because of the small sample size, these factors can have more impact on the results.

A further limitation of our study was the pronounced intrasubject variability within our dataset. As a result, many of our 24 combinations of frequency bands and brain regions became statistically insignificant following mixed-effects analysis. This not only constrained our ability to discern differences between the two groups but also impacted the depth and scope of our findings and interpretations. We avoided this pitfall as best as we could by employing the linear mixed-effects modeling technique.

Although our study faced certain constraints, our findings underscore a pronounced decrease in both parietal delta and theta oscillations in alcoholics when compared to controls in the early response phase of a visual stimulus.

A logical progression for future investigations would be to incorporate HR individuals into the study framework. While our research focused exclusively on chronic alcoholics, it did not encompass HR subjects. Even though frontal theta and posterior delta EROs have been posited as compelling endophenotype candidates (Jones et al, 2006b; Andrew and Fein, 2010; Pandey et al, 2016; Rangaswamy et al, 2006), the quest for identifying a diverse array of endophenotypes remains paramount. This is necessitated by the multifaceted nature of diseases, inter-individual variability, the augmentation of predictive accuracy, and potential interplay between endophenotypes. Such an approach ensures a comprehensive and rigorous methodology to both understanding and diagnosing disorders. Our findings underscore the potential of early diminished theta and delta bands in the parietal region within the 50-100ms timeframe as potential endophenotype markers. Expanding the scope of this research could pave the way for unveiling additional endophenotypes, offering invaluable insights for preemptive interventions tailored to individuals at an elevated risk of alcoholism.

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