

Induced Theta Activity as a Biomarker for a Morbid Effect of Alcoholism on the Brain in Long-Term Abstinent Alcoholics

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Abstract. Event-related, target stimulus-phase-locked (evoked) brain activity in both the time and time-frequency (TF) domains (the P3b ERP; evoked theta oscillations) has been shown to be reduced in alcoholics. Recently, studies have suggested that there is alcohol-related information in the non-stimulus-phase-locked (induced) theta TF activity. We applied TF analysis to target stimulus event-related EEG recorded during an oddball task from 41 long-term abstinent alcoholics (LTAA) and 74 nonalcoholic controls (NAC) to investigate the relationship between P3b, evoked theta, and induced theta activity. Results showed that an event-related synchronization (ERS) of induced theta (1) was larger in LTAA compared to NAC, and (2) was sensitive to differences between LTAA and NAC groups that was independent of the differences accounted for by P3b amplitude or evoked theta. These findings suggest that increased induced theta ERS may likely be a biomarker for a morbid effect of alcohol abuse on brain function.

Keywords: EEG, event-related synchronization, theta, alcoholism, time-frequency

The brain activity of alcoholics and nonalcoholics differs in several ways, and various electrophysiological methods have been used to investigate these differences. One of the most robust findings, observed in simple target detection tasks, is reduced amplitude of the P3b event-related potential (ERP) in alcoholics and in those with a genetic vulnerability to alcoholism (Begleiter, Porjesz, Bihari, & Kissin, 1984; Cohen, Wang, Porjesz, & Begleiter, 1995; Emmerson, Dustman, Shearer, & Chamberlin, 1987; Fein & Chang, 2006; Pfefferbaum, Horvath, Roth, & Kopell, 1979; Pfefferbaum, Rosenbloom, & Ford, 1987; Porjesz & Begleiter, 1979; Porjesz & Begleiter, 1990). This reduced amplitude P3b effect has also been demonstrated in those with a genetic vulnerability to externalizing psychopathology more generally (which includes alcoholism and related disinhibitory behavioral disorders; Iacono, Carlson, Malone, & McGue, 2002; Patrick et al., 2006; Porjesz et al., 2005).

Recently, time-frequency analyses have been applied to ERPs in alcoholic samples in order to determine the contributions of oscillatory activity to the P3b amplitude reduction. Time-frequency representations provide an alternative (frequency domain) characterization of brain activity to traditional (time domain) ERP measures (Pfurtscheller & Lopes da Silva, 1999). Event-related

oscillatory activity extracted with time-frequency methods represents frequency-specific event-related changes in the ongoing EEG, and is distinguished by whether or not they are phase-locked to the stimulus (Kalcher & Pfurtscheller, 1995; Pfurtscheller & Lopes da Silva, 1999). Time-frequency activity that is phase-locked to the stimulus is referred to as evoked oscillations, while non-stimulus-phase-locked activity is termed induced oscillations (Klimesch, Russegger, Doppelmayr, & Pachinger, 1998). Time-frequency activity can also be characterized by whether there is an increase or decrease in event-related power in specific frequency bands relative to the prestimulus baseline period – referred to as event-related synchronization (ERS) or event-related desynchronization (ERD), respectively (Pfurtscheller & Lopes da Silva, 1999). Work in the time-frequency domain has shown that the reduced P3b in alcoholics, abstinent alcoholics, and those with a genetic vulnerability to alcoholism (as well as externalizing, more generally) could be viewed as a reduction in evoked delta and theta activity during the P3 time window (Andrew & Fein, 2010a; Gilmore, Malone, Bernat, & Iacono, 2010; Jones et al., 2006; Kamarajan et al., 2006; Rangaswamy et al., 2007). With appropriate statistical analyses, Andrew and Fein (2010a) showed that the evoked time-frequency power measures provided a different, but

not independent representation of differences between long-term abstinent alcoholics (LTAA) and controls than did the P3 ERP measures.

Induced theta activity, however, in addition to differentiating long-term abstinent alcoholics from controls, did provide independent discriminatory power above and beyond P3b amplitude (Andrew & Fein, 2010b). Andrew and Fein (2010b) found (i) that target stimuli induced an event-related synchronization of non-phase-locked activity in the theta band that was stronger in LTAA than in controls (i.e., LTAA's induced power was *increased* relative to controls, an effect that is opposite in direction to the effect found in both P3b amplitude and in evoked theta, both of which are *reduced* in alcohol groups), and (ii) that this theta ERS provided independent discriminatory power above and beyond P3b amplitude.

Results from these studies demonstrate the importance of examining both event-related phase-locked and non-phase-locked activity. The induced theta activity was not apparent in either the time domain or the time-frequency transform of the averaged ERP data, and the effects were in the opposite direction from those in the time-domain and evoked time-frequency measures. Functional studies using different paradigms have demonstrated an association between induced theta activity and working memory and attentional processes. Using target detection, recognition memory, and n-back tasks, induced theta has been shown to be modulated by task demands, with theta ERS being stronger as a function of increased working memory load and allocation of attention (Burgess & Gruzelier, 1997; Deiber et al., 2007; Doppelmayr, Klimesch, Schwaiger, Stadler, & Rohm, 2000; Klimesch, 1996; Krause et al., 2000; McEvoy, Pellouchoud, Smith, & Gevins, 2001; Missonnier et al., 2006). While these cognitive processes have been shown to be affected by alcohol use/abuse (Beatty, Tivis, Stott, Nixon, & Parsons, 2000; Nixon & Glenn, 1995; Ratti et al., 1999; Schmidt et al., 2005), they have also been shown to resolve after long-term abstinence from alcohol (Fein, Key, & Szymanski, 2010; Fein & McGillivray, 2007). Thus, differences in induced theta activity may have implications for understanding the cognitive effects in long-term abstinent alcoholics.

The present study is a replication of the novel findings of Andrew and Fein (2010a, 2010b). To our knowledge, the induced theta effect in LTAA had not been demonstrated before. Therefore, in the present study, we applied time-frequency analysis methods that directly measure non-phase-locked event-related EEG activity (Kalcher & Pfurtscheller, 1995; Klimesch et al., 1998) to an independent group of LTAA and gender- and age-matched controls in order to investigate the hypotheses that (i) while evoked theta activity is reduced in LTAA, it does not account for independent variance in group membership beyond that of P3b amplitude, and (ii) induced theta ERS is increased in LTAA relative to controls, and induced theta accounts for independent variance in group membership above and beyond that accounted for by P3b.

Methods

Participants

Participants consisted of 74 nonalcoholic controls (NAC; 37 female; mean age = 48.4 years, $SE = 0.86$) and 41 long-term abstinent alcoholics (LTAA; 18 female; mean age = 49.0 years, $SE = 1.1$), who had abstinence durations ranging between 1.5 and 32.2 years (median = 3.5, mean = 7.5, $SE = 1.2$). Participants were recruited from the community through postings at university campuses, bus stops, bulletin boards, stores, laundromats, community centers, and health centers, Craigslist, and referrals from other participants. Alcoholic participants were also recruited from Alcoholics Anonymous (AA), substance abuse treatment centers, and clean and sober transitional houses. All alcoholic participants had attended AA sessions and/or alcohol and drug treatment programs.

Inclusion criteria for the LTAA group were: (i) met lifetime DSM-IV-R (American Psychiatric Association, 2000) criteria for alcohol dependence, (ii) did not meet criteria for dependence or abuse of any other drug (other than nicotine or caffeine), and (iii) were abstinent from alcohol and other drug use (other than nicotine or caffeine) for at least 18 months. Inclusion criteria for the NAC group were a lifetime drinking average of < 30 standard drinks per month, with no periods of drinking more than 60 drinks per month, and no lifetime history of alcohol and substance abuse or dependence (other than nicotine or caffeine).

Exclusion criteria for both groups were:

- lifetime or current diagnosis of schizophrenia or schizophreniform disorder, using the computerized Diagnostic Interview Schedule (C-DIS; Bucholz et al., 1991; Erdman et al., 1992; Levitan, Blouin, Navarro, & Hill, 1991; Robins, Marcus, Reich, Cunningham, & Gallagher, 1996),
- significant history of head trauma or cranial surgery,
- history of significant neurological disease,
- history of diabetes, stroke, or hypertension that required an emergent medical intervention,
- laboratory evidence of hepatic disease, or
- clinical evidence of Wernicke-Korsakoff syndrome.

All participants were fully informed of the study's procedures and aims, and signed consent forms prior to participation. Participants completed four sessions that each lasted between 1.5 h and 5 h, and included clinical, psychiatric, neuropsychological, electrophysiological, and neuroimaging assessments. Participants were asked to abstain from consuming alcohol for at least 24 h prior to any laboratory visit. A breathalyzer test (Intoximeters, Inc., St. Louis, MO) was administered, and a blood alcohol concentration of 0.00 was required of all participants in all sessions. A rapid screen test (Oral Fluid Drug Screen, Innovacon, San Diego, CA) was administered to all participants. A negative result was required of all participants in all sessions. Participants

were compensated for their time and travel expenses upon completion of each session. Participants who completed the entire study were also given a completion bonus.

Experimental Paradigm

The 3-condition oddball task (see below) was conducted during the EEG session on the third day. All stimuli were presented on a computer monitor, using the E-Prime software system (Psychology Software Tools Inc., Pittsburgh, PA), with a horizontal and vertical visual angle of approximately 3.7° by 1.4° . Stimuli were presented on a black screen for 200 ms, followed by a delay varying between 1,000 and 1,100 ms before the next stimulus. Three different types of visual stimuli were presented:

- standard stimuli: a small hollow white square,
- target stimuli: a small white X and
- novel rare nontarget stimuli: different shapes of various colors.

Participants responded with the index finger of their dominant hand and were instructed to press a response box button only when they saw target stimuli. Stimuli were presented in a predetermined order, with standard stimuli appearing 210 times, target stimuli appearing 35 times, and rare nontarget stimuli appearing 35 times over approximately 6.5 min. Each participant was shown an example of the target stimulus before the task began.

EEG Acquisition and Data Preprocessing

EEG was acquired using a 64-channel system that used the SynAmps2 amplifier and Scan 4.3 acquisition software (Compumedics Neuroscan, Inc., Charlotte, NC). The EEG signal was referenced to an electrode located between Cz and CPz for online recording, then re-referenced to the right ear offline. The ground electrode was placed 8 cm above the nasion. Electrode impedances were maintained below 10 kOhms. The SynAmps2 amplifier had a fixed range of $\pm 333 \mu\text{V}$ sampled with a 24-bit A/D converter where the least significant bit was $0.019 \mu\text{V}$. The sampling rate was 250 samples/sec.

EEG recordings were processed offline using the Edit program in Scan 4.3 (Compumedics Neuroscan, Inc., Charlotte, NC). Artifacts from eye movements were removed using the ocular artifact reduction algorithm (ARTCOR procedure) in Scan 4.3. Data were then band-pass filtered between 0.5 and 30 Hz using a zero-phase lag filter at 48 dB/octave. Stimulus-locked epochs for the target condition were extracted for all instances where there was a correct behavioral response. Trials consisted of 1,800 ms of data, including a 500 ms prestimulus baseline. Any epochs with voltages beyond the range of $\pm 75 \mu\text{V}$ were rejected as artifacts and excluded from further processing.

EEG Analysis

To extract P3b amplitude, epochs were averaged using the AVERAGE procedure in Scan, producing one average target waveform per electrode for each subject. P3b amplitude was quantified by calculating the mean amplitude within a latency window that was centered on each individual subject's peak P3b amplitude. A 50 ms window was chosen to capture more P3b variance than does the peak amplitude, while excluding potential influence from earlier or later ERP activity. The amplitude values for the P3b component were then extracted using the PEAK DETECT function and averaged over the 50 ms window.

Time-Frequency Measures

All time-frequency (TF) measures were computed using the Cohen's class binomial reduced interference distribution (RID) transform (see Bernat, Williams, and Gehring (2005), Williams (1996) for more detailed descriptions), the advantage of which is that it provides a uniform resolution across the TF surface. TF representations were created using the entire 1,800 ms epoch to minimize edge effects.

TF measures were extracted in two ways: (i) for evoked oscillatory activity, decompositions were performed using averaged ERP data, measuring brain activity phase-locked to the stimuli, while attenuating non-phase-locked (i.e., induced) activity, and (ii) for induced oscillatory activity, the trial-averaged ERP waveform was first subtracted from each single trial data, with the residual being transformed to the TF domain. The resultant single trial TF surfaces were then averaged across trials to produce a TF representation of the event-related non-stimulus-phase-locked TF activity. This approach for isolating the non-phase-locked activity is similar to the time-domain intertrial variance method presented in Kalcher and Pfurtscheller (1995) and the induced band power calculation in Klimesch et al. (1998) (also see Engell, Huettel, & McCarthy, 2012 for more recent application of this method). With these methods, one Evoked TF representation and one Induced TF representation were produced for each electrode site for each subject.

Based on previous findings of increased induced theta ERS in LTAA relative to controls in Andrew and Fein (2010b), and on our aim to replicate these novel results, we focused our analyses on evoked and induced activity in the theta band. Based on visual inspection of the grand-averaged Evoked and Induced TF representations, poststimulus time-frequency regions of interest (TFROIs), encompassing the theta frequency band, were selected. The TF power was averaged within each of these TFROIs. For Induced activity, in addition to the poststimulus TFROI, a corresponding prestimulus TFROI was also selected, covering the same frequency range as the poststimulus TFROI, but with a time window occurring prior to target stimulus onset. This prestimulus TFROI was utilized as a reference for comparing event-related changes in poststimulus power, that is, event-related

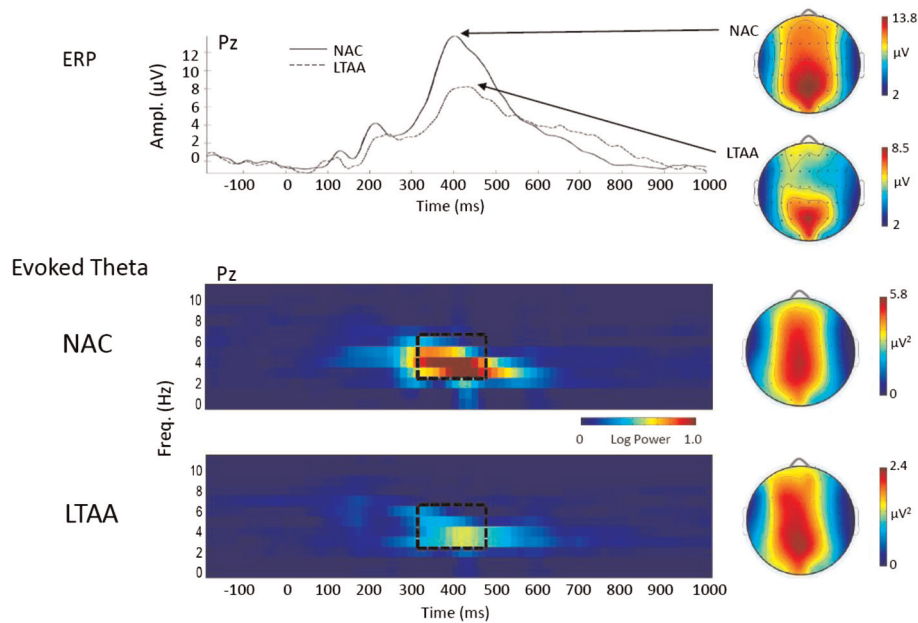


Figure 1. Evoked (stimulus phase-locked) event-related activity: At top are the grand-averaged ERPs and topographic maps of P3 peak amplitude at electrode Pz for the target stimulus for NAC and LTAA. Below are the grand-averaged Evoked time-frequency representations (TFR), bandpass filtered in the theta band (3–8 Hz) to accentuate the relevant activity, at electrode Pz for the target stimulus for NAC and LTAA, together with the topographic maps for the mean activity within the theta time-frequency region of interest (indicated by the dashed box on each TFR). The topographic maps are scaled differently so as to clearly indicate the spatial distribution of each.

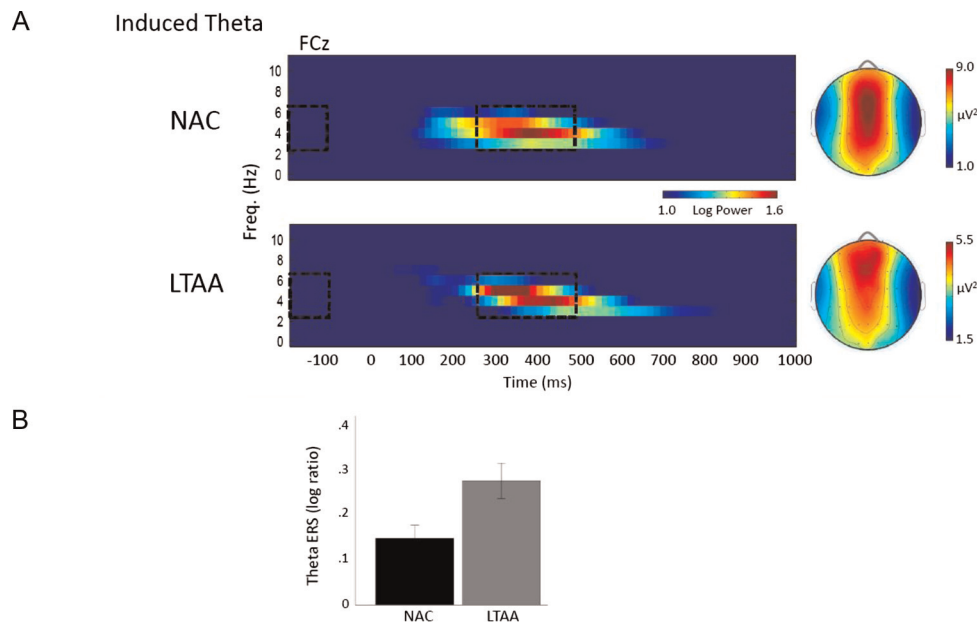


Figure 2. (A) Grand-averaged Induced (non-stimulus-phase-locked) time-frequency representations (TFR), bandpass filtered in the theta band (3–8 Hz) to accentuate the relevant activity, at electrode FCz for the target stimulus for NAC and LTAA. The poststimulus and prestimulus theta TFROIs are indicated by dashed boxes on the TFRs. Topographic maps for the mean activity within the poststimulus theta TFROI for NAC and LTAA are shown. (B) Bar graph showing the mean (with SE bars) theta event-related synchronization (ERS) values for NAC and LTAA.

synchronization/desynchronization, which was computed as the log ratio of the poststimulus power to the prestimulus power (see Andrew & Fein, 2010b for a more detailed description). Grand-averaged Evoked and Induced TF representations, and topographical maps for each, were computed for each group (see Figures 1 and 2).

Statistical Analysis

All statistical analyses were performed using SPSS (SPSS Inc., Chicago, IL). The measures submitted to statistical analysis were (i) P3b amplitude averaged over electrodes Pz and CPz, (ii) evoked theta power (log-transformed) averaged over electrodes Pz and CPz, and (iii) induced theta ERS averaged over electrodes FCz and Cz. These electrodes were those within which each of the measures was found to be maximal, both in the current study and in previous reports (e.g., Andrew & Fein, 2010a; Andrew & Fein, 2010b; Jones et al., 2006), thus were considered those best characterizing each of the measures.

To investigate the relationship between P3b, evoked theta, and induced theta in distinguishing LTAA from controls, logistic regression was performed. First, univariate regression models were performed, in which P3b amplitude, Evoked theta power, and induced theta ERS were entered as predictors, to determine each measure's relationship to LTAA. Second, bivariate regression, in which the measures were entered, pairwise, into the model (i.e., a model including P3b amplitude and Evoked theta, a model including P3b amplitude and Induced theta, and a model including Evoked theta and Induced theta), was used to test the hypotheses that (i) Induced theta ERS would account for significant variance in LTAA versus NAC group membership independent of that accounted for by either P3b or evoked theta, and (ii) evoked theta and P3b amplitude would not account for variance in group membership independent of each other. The significance of each univariate model, and of each individual measure within the bivariate model, was tested using the Wald statistic. The likelihood ratio test ($df = 1$) was used to test for a significant difference between corresponding univariate and bivariate models (e.g., univariate model with Induced theta only vs. bivariate model with P3b amplitude and Induced theta together). The likelihood ratio test is calculated as the difference between the $-2\text{Log } L$ goodness-of-fit values of corresponding univariate and bivariate models, and yields a chi-squared statistic. A significant difference indicated that the univariate model did not adequately fit the data compared to the bivariate model, thus indicating that the added variable was accounting for a significant amount of variance. If the difference was not significant, the fit of the univariate model was deemed adequate, and it was concluded that the added variable was not accounting for any additional variance.

Results

Figure 1 shows the grand-averaged ERPs and evoked TF representations at electrode site Pz for the target stimulus

for NAC and LTAA. For illustration purposes, in order to accentuate the evoked theta activity analyzed in the present study, the TF representations were filtered in the theta band (3–8 Hz). The spectro-temporal dynamics revealed in the grand-averaged TF representations show evoked theta activity that occurs from about 200 to 600 ms poststimulus. Based on visual inspection of the Evoked TF surfaces, a theta band TFROI was selected that spanned a time range of 325–470 ms and a frequency range of 3–6 Hz (indicated by boxes overlaid on the evoked TF surfaces). Figure 1 also shows topographic maps for P3 and for the mean activity within the TFROI for the NAC and LTAA groups.

Figure 2A shows grand-averaged induced TF representations at electrode site FCz for the target stimulus for the NAC and LTAA groups. These TF representations, also filtered in the theta band to accentuate the relevant activity, show a poststimulus increase in theta activity occurring between about 200 and 650 ms. Based on visual inspection of the induced TF surface, a theta poststimulus TFROI was selected that spanned a time range of 250–475 ms and a frequency range of 3–6 Hz. The corresponding prestimulus reference TFROI had the same frequency range, with a time range of -200 to -95 ms. Figure 2A also shows topographic maps for the mean activity within the poststimulus TFROI for each group. Figure 2B shows a bar graph illustrating the mean (with SE bars) theta ERS values for the NAC and LTAA groups.

Group means ($\pm SE$) for each of the measures submitted to statistical analysis were: P3b amplitude (measured in μV ; NAC: $13.52 \pm .61$, LTAA: $9.35 \pm .80$), Evoked theta (log-transformed power; NAC: $.62 \pm .05$, LTAA: $.31 \pm .07$), and induced theta ERS (log ratio of poststimulus/prestimulus power; NAC: $.15 \pm .03$, LTAA: $.28 \pm .03$). Examining the correlations (Pearson's r) between these measures revealed that, while there was a strong, significant relationship between P3b amplitude and evoked theta power ($r = .74$, $p < .001$), induced theta power was not significantly correlated with either P3b ($r = .02$, $p = .86$) or evoked theta power ($r = .08$, $p = .42$). Thus, at an overall level (without regard to LTAA vs. NAC group differentiation), P3b and evoked theta share a significant amount of variance ($r^2 = .55$), while there is no significant portion of shared variance between induced theta and either of the other two measures.

Logistic Regression

Table 1 summarizes results of the logistic regression analyses. Univariate analyses are summarized at the top of Table 1, showing the Wald statistic and portion of variance explained by each measure (represented by Nagelkerke's pseudo- R^2). Results show that each measure successfully discriminated LTAA and NAC. For the evoked measures (P3b amplitude and Evoked theta) significant discriminative ability was based on reduced amplitudes in LTAA compared to NAC. For Induced theta ERS, significant discriminative ability was based on increased amplitudes in LTAA compared to NAC.

Table 1. Results of logistic regression analyses

	Wald χ^2	Nagelkerke's R^2	Likelihood ratio test [†]
<i>Univariate models</i>			
P3b amplitude	12.26**	0.17	
Evoked theta	11.33*	0.15	
Induced theta	7.55*	0.12	
<i>Bivariate models</i>			
P3b + Evoked theta		0.19	
P3b	3.07		1.57
Evoked theta	1.54		3.23
P3b + Induced theta		0.28	
P3b	12.47**		10.91**
Induced theta	7.77*		15.60**
Evoked theta + Induced theta		0.27	
Evoked theta	12.58**		12.16**
Induced theta	8.28*		15.19**

Notes. * $p < .01$, ** $p < .001$. $df = 1$ for all Likelihood ratio tests.

[†]A significant result indicates that component accounted for a significant amount of variance in the bivariate model, independent of that accounted for by the other component. A nonsignificant result indicates that component added no significant discriminative information above that contained in the univariate model.

The bottom of Table 1 summarizes results of the bivariate analyses and of the likelihood ratio tests comparing the corresponding univariate and bivariate models. When combining P3b amplitude and Evoked theta into the model, group discrimination was not significantly improved, indicating that the addition of the second variable into the model offered no significant additional discriminative value over either the P3b or Evoked theta univariate models. Further, neither Evoked theta nor P3 was a better discriminator; neither accounted for significant additional variance in the presence of the other (as indicated by the nonsignificant Wald statistic associated with each of these measures in the bivariate model).

When induced theta was included in the bivariate model, the improved group discrimination over the corresponding univariate model was significant (see significant Likelihood ratio tests in Table 1). The bivariate model including P3b amplitude and Induced theta ERS, and the model including Evoked theta and Induced theta ERS, significantly improved group discrimination compared to the corresponding univariate models. Further, each of the measures accounted for a significant amount of variance in group membership that was independent of that accounted for by the other measure (see significant Wald statistics for each measure in the bivariate regression models in Table 1).

Discussion

Results of the present study demonstrate that, within the overall target ERP variance, (1) a phase-locked (evoked)

theta time-frequency component is accounting for alcoholism-related variance that is, however, essentially equivalent to that accounted for by P3b amplitude, while (2) a non-phase-locked (induced) theta component is sensitive to differences between LTAA and NAC groups that is independent of the differences accounted for by P3b amplitude (or evoked theta). P3b amplitude, evoked theta power, and induced theta ERS were each able to differentiate long-term abstinent alcoholics from gender and age-comparable nonalcoholic controls. When combined, however, neither P3b nor evoked theta accounted for significant variance in group membership that was independent of that accounted for by the other. Induced theta ERS, on the other hand, did account for a significant amount of variance in group membership independent of that accounted for by either P3b or evoked theta (as did both of these measures account for variance independent from that of induced theta).

Reduced amplitude P3b and evoked theta to target stimuli have been associated with genetic vulnerability to alcoholism (and to externalizing psychopathology, more generally; e.g., Begleiter et al., 1984; Iacono et al., 2002; Patrick et al., 2006; Pfefferbaum et al., 1987; Porjesz & Begleiter, 1990). The increased induced theta ERS effect has, to our knowledge, only been demonstrated in long-term abstinent alcoholics versus nonalcoholic controls (in the current report and in Andrew & Fein, 2010b). P3b and evoked theta share a significant amount of variance, while induced theta does not share a significant amount of variance with either P3b or evoked theta. These findings, taken together with the aforementioned results concerning amounts of independent variance in LTAA versus NAC group membership accounted for by each of the three measures, suggest that increased induced theta ERS may likely be a biomarker for a morbid effect of alcohol abuse on brain function, per se, rather than an endophenotypic marker for genetic vulnerability to alcoholism.

In abstinent alcoholics, however, the effects of preexisting factors (e.g., genetic vulnerability), effects of exposure to alcohol, and effects of recovery from alcoholism are confounded. Further, there were no associations (based on nonsignificant results of correlation analyses) within LTAA between induced theta ERS and (1) severity of alcohol abuse (measured by Lifetime Alcohol Dose (standard number of drinks/month during active drinking periods over the person's life): $r = .06$, $p = .69$, Lifetime Alcohol Use (Lifetime Dose \times Length of active drinking periods over the person's life, excluding periods of sobriety): $r = .13$, $p = .41$, Peak Alcohol Dose (standard drinks per month during the course of the peak drinking phase): $r = .12$, $p = .44$, and Peak Alcohol Use (Peak Dose \times Length of the peak drinking phase): $r = .23$, $p = .16$), (2) duration of abstinence ($r = -.17$, $p = .28$), or (3) density of family history of alcohol problems (the proportion of first-degree relatives who had alcohol problems: $r = .15$, $p = .36$). Therefore, we cannot unequivocally state that induced theta is a biomarker for alcohol use/abuse. In total, however, these findings suggest that higher than normal induced theta ERS in a simple target detection task may be an effect of chronic alcohol abuse that may not fully recover even with multiyear abstinence. Future studies could disentangle these effects by examining induced

theta in alcohol naïve relatives of alcoholics, individuals who have been abstinent from alcohol for a short period of time, and actively drinking, treatment naïve alcoholics.

Functionally, the amount of induced theta activity (i.e., the extent to which an ERS occurs) has been associated with working memory and attentional processes, with stronger theta ERS reflecting increased memory load and allocation of attention to task demands (Burgess & Gruzelier, 1997; Deiber et al., 2007; Doppelmayr et al., 2000; Klimesch, 1996; Krause et al., 2000; McEvoy et al., 2001; Missonnier et al., 2006). While these neurocognitive processes have been shown to be affected by alcohol use/abuse (Beatty et al., 2000; Nixon & Glenn, 1995; Ratti et al., 1999; Schmidt et al., 2005), they have also been shown to resolve after long-term abstinence from alcohol (Fein & McGillivray, 2007; Fein et al., 2010). Greater induced theta ERS in LTAA suggests that they are engaging working memory and attentional processes more strongly than are control participants in order to successfully perform the target detection task. Thus, a persistent difference in brain activity, indexed by larger induced theta oscillations, combined with normal cognitive functioning in LTAA, suggests (1) possible functional reorganization of the brain systems used by abstinent alcoholics while engaged in these tasks (cf. Pfefferbaum et al. (2001)) and/or (2) that alcoholics may (explicitly or implicitly) utilize compensatory mechanisms, as indexed by increased theta ERS in the current study, to overcome fundamental problems in brain activity to successfully perform these tasks – compensatory mechanisms that may break down as task demands increase. Given these possibilities, and given theta ERS's relationship with memory and attentional processes, it will be necessary for future research to more systematically examine the association between induced theta ERS and neurocognitive deficits seen in alcoholism in order to refine our understanding of alcohol-related brain changes.

Some important questions arise from the current results regarding (1) the degree to which genetic vulnerability to alcoholism (and related externalizing disorders) modulates the induced theta ERS effect, (2) the trajectory of the induced theta ERS effect as a function of alcohol exposure, age, gender, and cognitive factors, and (3) the extent to which cognitive function is associated with the induced theta ERS effect. Future studies addressing these questions will help gain a more complete understanding of the induced theta ERS effect, and significantly contribute to our understanding of its potential role as a sensitive biomarker for the effects on the brain of alcohol abuse.

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