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Alcoholism is a disinhibitory disorder: neurophysiological evidence from a Go/No-Go task

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Abstract

Response inhibition is considered a core dimension in alcoholism and its co-existing disorders. The major objective of this study is to compare the magnitude and spatial distribution of ERP components during response activation and inhibition in alcoholics ($N = 30$) and normal controls ($N = 30$) using a visual Go/No-Go task. The results indicate that alcoholics manifest a decreased P3(00) amplitude during Go as well as No-Go conditions. The difference between Go and No-Go processing was more evident in controls than in alcoholics. The topography of current source density in alcoholics during the P3 response was found to be very different from that of normals, suggesting that alcoholics perhaps activated inappropriate brain circuitry during cognitive processing. The significantly reduced No-Go P3 along with the relatively less anteriorized CSD topography during No-Go condition suggests poor inhibitory control in alcoholics. It is proposed that the No-Go P3, the electrophysiological signature of response inhibition, can be considered as an endophenotypic marker in alcoholism.

Keywords: Event-related potentials; P3; Go/No-Go; Alcoholism; Disinhibitory disorders; Inhibitory control; Endophenotype

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1. Introduction

The event-related potentials (ERPs) using Go/No-Go tasks have been widely examined to elucidate the possible neural correlates of response activation and inhibition in normals as well as in clinical groups (Jodo and Inoue, 1990; Falkenstein et al., 1995, 1999; Shibata et al., 1999; Weisbrod et al., 2000; Kaiser et al., 2003). These tasks require the subjects to respond to one type of stimuli (Go condition), but to withhold the response to the other (No-Go condition). In the No-Go condition, two major ERP components have been identified as the markers for response inhibition: first, the N2, a negative deflection with a frontocentral maximum around 200–300 ms, and second, referred to as ''No-Go P3'', an augmented positive-going peak usually peaking between 300 and 600 ms (Pfefferbaum et al., 1985; Eimer, 1993; Jodo and Inoue, 1990; Jodo and Kayama, 1992; Kopp et al., 1996). However, the N2 and P3 components during the No-Go condition may represent different processing of response inhibition and hence the dysfunction in either or both of these components in different mental disorders may suggest the deficiency of inhibitory control (Kaiser et al., 2003).

Response inhibition requires the activation of the executive system of the frontal lobes (Barkley, 1997; Weisbrod et al., 2000; Kaiser et al., 2003). On the other hand, the neural basis of this executive system is thought to be a distributed network involving the prefrontal areas and anterior cingulate gyrus (Posner and DiGirolamo, 1998; Smith and Jonides, 1999). However, theories based on the findings of lesion studies stressed the importance of the orbitofrontal cortex in inhibitory control (i.e., Mishkin, 1964; Fuster, 1989). Consistent with the distributed activations that underlie most of the cognitive processes, neuroimaging studies have revealed cerebral activation beyond ventral frontal regions during response inhibition (Brown et al., 1999; Garavan et al., 1999, 2002). The distributed network thought to underlie inhibitory control, as observed with neuroimaging studies, includes the dorsal and ventral prefrontal regions (Kawashima et al., 1996; Tsujimoto et al., 1997; Smith et al., 1998; Konishi et al., 1998; Watanabe et al., 2002), anterior cingulate cortex (Casey et al., 1997; Liddle et al., 2001; Menon et al., 2001; Garavan et al., 2002; Durston et al., 2002), premotor and supplementary motor areas (Ullsperger and von Cramon, 2001; Garavan et al., 2002; Sylvester et al., 2003), and parietal regions (Garavan et al., 1999; Watanabe et al., 2002; Durston et al., 2002).

A robust finding in ERP studies on alcoholism is that alcoholics as well as individuals at high risk to develop alcoholism have been shown to have low P3 amplitude in various task paradigms (Begleiter et al., 1984; Porjesz et al., 1987; Porjesz and Begleiter, 1990, 1991, 1996; Rodriguez Holguin et al., 1999; Hada et al., 2000; Prabhu et al., 2001; Cohen et al., 2002; Suresh et al., 2003). In Go/No-Go tasks, the anteriorly distributed No-Go P3 potential has a markedly reduced amplitude in alcoholic subjects as well as in high-risk individuals, indicating impaired inhibitory control in these individuals (Pfefferbaum et al., 1991; Cohen et al., 1997a, 1997b). However, the deficits in inhibitory control have been reported in a variety of behavioral disorders, which share disinhibitory psychopathology in common, including OCD and Tourette syndrome (Schall et al., 1996; Johannes et al., 2001, 2003), ADHD (Frank et al., 1998; Rubia et al., 1998; Pliszka et al., 2000; Brandeis et al., 2002), ASP and conduct disorder (Bauer and Hesselbrock, 1999a, 1999b; Kiehl et al.,

1999, 2000), schizophrenia (Weisbrod et al., 2000; Fallgatter and Muller, 2001), and drug use (Kouri et al., 1996; Bauer, 2001; Kaufman et al., 2003). Based on the patterns of comorbidity, it was suggested that the common psychiatric and substance use syndromes may be divisible into two broad groups of internalizing and externalizing disorder (Kendler et al., 2003). Despite the fact that the addictive disorders inclusive of alcoholism would also involve very specific aspects of disinhibition such as drug incentive salience, drug expectation or craving, and compulsive drug intake, the electrophysiological markers of response inhibition specific to alcoholism, as distinct from other disinhibitory disorders, are poorly understood. Nevertheless, it is important to determine not only the magnitude but also the topographic distribution of averaged brain potentials as well as the estimated surface Laplacian in alcoholism, as this might explain the cortical dynamics and networks during cortical processing.

In the present study, along with ERPs, we have therefore attempted to examine the spatial distribution of current source density (CSD) which may give distinct topographic features specific to alcoholism during response inhibition. The CSD is a method which applies an estimate of surface Laplacian and can provide differential topographic features of cortical surface potentials devoid of volume conduction effects (Nunez, 1995; Srinivasan et al., 1998; Wang and Begleiter, 1999). Although the CSD has successfully differentiated alcoholics and controls in terms of topographic differences (Hada et al., 2000, 2001), this method has not been studied in a Go/No-Go paradigm in alcoholics. The objective of the present study was to examine the ERP as well as CSD correlates of response inhibition in alcoholics and control subjects using a Go/No-Go task. By comparing the magnitude, spatial and temporal characteristics of these measures in alcoholic subjects and healthy controls, it may be possible to elucidate the specific neurocognitive abnormalities related to response inhibition in alcoholics. Further, recent advances in understanding the brain mechanisms involved in inhibitory control, impulsivity, motivation, reward, and decision-making might permit a discussion of neural circuitry underlying the pathology of addiction.

2. Methods

2.1. Subjects

The demographic and clinical characteristics of the sample are presented in Table 1. A sample of 30 alcoholics (16 males, 14 females) with an age range of 19–42 years and 30 gender-matched healthy controls aged between 18 and 35 years were selected. Control subjects were recruited through newspaper advertisements and notices. The alcoholic group comprised diagnosed alcoholic patients from the de-addiction centers of the hospitals in New York, primarily from Kings County Hospital Center at Brooklyn. A team consisting of psychiatrists and psychologists diagnosed the patients according to the DSM-IIIR or DSM-IV criteria for alcohol dependence. The Bard/Porjesz Adult Alcoholism Battery (BAAB), a semi-structured clinical assessment schedule was used to obtain the clinical data related to alcohol dependence and alcohol-related medical problems. The patients who were receiving treatment medication such as antabuse and psychoactive drugs

Table 1
Demographic and clinical characteristics of the sample

Variable	Alcoholics ($N = 30$)			Controls ($N = 30$)		
	Mean	S.D.	Range	Mean	S.D.	Range
Age (years)	34.34	4.68	19–42	24.06	5.46	18–35
Education (years)	12.03	1.83	5–15	14.73	3.06	4–20
Age of onset of drinking (years)	15.00	3.90	12–26	NA	NA	NA
No. of drinking days per month[a]	19.97	10.41	0–30	2.07	2.65	0–10
No. of drinks[b] per drinking day[a]	7.87	4.78	0–16	1.60	1.75	0–6

NA: not applicable.
[a] Data are for the 6 months prior to the treatment in alcoholic group.
[b] One drink = one shot glass of hard liquor; one glass of wine; one bottle of beer.

were excluded from the study to avoid the possible interaction of drugs with the EEG profile. Although neuroradiological investigations were not performed, the individuals with severe cognitive deficits based on their score on the mini mental state examination (MMSE; Folstein et al., 1975) were excluded from the study. The control subjects did not have any personal and/or family history of major medical or psychiatric disorders and substance-related addictive illnesses. However, subjects with present history of substance use and/or ASP as co-existing conditions and with a past history of conduct disorder, ADHD, and oppositional defiant disorder (ODD) were also included in the alcoholic sample. Subjects who had positive findings (for their recent drug use) in the urine screen and Breathalyzer test were excluded from the study. Subjects with hearing or visual impairment, liver disease, or head injury were also excluded from the study. Experimental procedures and ethical guidelines were in accordance with approval from the institutional review board (IRB).

2.2. Experimental paradigm

There were three visual stimuli in the task: (i) a cross (fixation stimulus), (ii) a circle (Go or No-Go stimulus), and (iii) a dollar sign (reinforcement sign). These stimuli subtended a visual angle of approximately 1°, and were presented on a computer monitor. The Go and No-Go stimuli were always preceded by a fixation stimulus that appeared at the center of the monitor. The circles that appeared at the top right and bottom left corners served as Go stimuli, to which the subjects had to respond by pressing a button as quickly as possible. The No-Go stimuli, to which the subjects were asked to withhold their response, appeared at the top left and bottom right corners. The dollar sign appeared whenever there was a correct button-press response to indicate a reward. The inter-trial intervals (ITI) for the Go condition with and without the dollar sign (i.e., correct and incorrect Go trials) were 2100 and 1550 ms, respectively; the ITI for the No-Go trails was 1550 ms (as the dollar sign never appeared in the No-Go trials). The probabilities of occurrence of Go and No-Go stimuli were equal (50/50), and the order of these stimuli was randomized.

The experiment consisted of a practice phase and a recording phase. The practice phase consisted of twenty Go and No-Go trials, respectively. The subjects were instructed to press

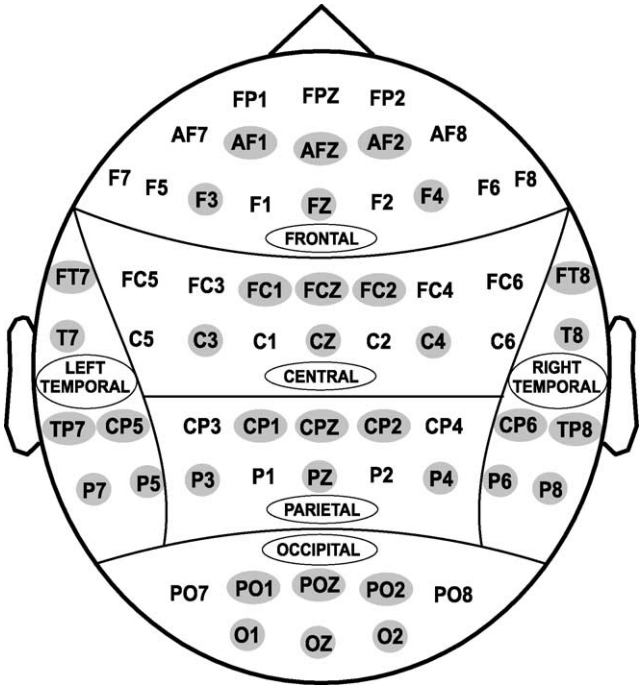

Fig. 1. Regional grouping of electrodes: (1) frontal, (2) central, (3) parietal, (4) occipital, (5) left-temporal, and (6) right-temporal. The representative electrodes included for statistical analysis are highlighted.

a button as quickly as possible whenever they saw a circle in either the top right or bottom left corner. The speed of response was stressed, as the subjects had to respond within 400 ms, and responses beyond this window were deemed incorrect. A feedback signal (a beep) was given whenever the subject's button-press response was wrong; the practice phase did not accrue any reward. The EEG activity was recorded only during the recording phase which consisted of 100 trials (50 Go and 50 No-Go stimuli). The appearance of a dollar sign in this phase indicated a reward of 25 cents for each correct button-press response, while there was no feedback signal provided for the incorrect responses. The total amount gained as reward was not displayed during the stimulus presentation. The subjects received the full amount at the end of the experiment without deductions for errors, although they were not informed of this while performing the experiment. The task characteristics are identical to our earlier study using this paradigm (see: Kamarajan et al., 2004).

2.3. ERP data acquisition and analysis

The subjects were seated in a comfortable, reclining chair located in a dimly lit sound-attenuated RF-shielded room (IAC, Industrial Acoustics, Bronx, NY) and were instructed regarding the task requirements. EEG activity was recorded on a Neuroscan system

(Version 4.1) (Neurosoft, Inc., El Paso, TX) using a 61-channel electrode cap (Electro-cap International, Inc., Eaton, OH), which included 19 channels of the 10–20 International System and 42 additional electrode sites (Electrode Position Nomenclature, American Electroencephalographic Association, 1991) as shown in Fig. 1. The electrodes were referenced to the tip of the nose and the ground electrode was at the forehead (frontal midline). Eye movements were monitored with a supraorbital vertical lead and a horizontal lead placed 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 sampling rates of either 256 or 512 Hz, and were resampled at 256 Hz during the signal analysis for the sake of uniformity.

The continuous EEG was digitally low-pass filtered at 32 Hz and then segmented into epochs of 100 ms pre-stimulus to 750 ms post-stimulus. The mean EEG activity for 100 ms prior to stimulus onset served as the pre-stimulus baseline. All segments exceeding ±75 μV threshold were automatically excluded from further processing. After excluding eye-movement artifacts, the averaged segments for each individual were screened visually for further artifact rejection. The artifact detection was done on all the channels including the electroocculogram (EOG) channels. The trials with reaction times greater than 400 ms (for Go trials) were considered as error responses and therefore were rejected. Only the trials with correct response (button-press) for the Go condition and correct inhibition (no button-press) for the No-Go condition were averaged. The P3 amplitude was measured as the voltage difference between the pre-stimulus baseline and the largest positive going peak in the latency window 300–600 ms after stimulus onset. For each individual, the amplitude and latency measures were calculated using a semi-automatic peak-picking program, wherein the time window for each component was manually selected in the computer while the peak within the window was automatically detected, measured, and tabulated for each channel. However, operator intervention was possible during the process to ensure that the computer did not make anomalous peak selections. Each subject had a minimum of 20 good trials in each condition with a mean number of about 35 good trials in each group for the purpose of averaging. The grand averages were computed and plotted to determine the components and time windows. The amplitude and latency values of the P3 component obtained separately for Go and No-Go conditions for each subject were used in statistical analyses.

For statistical comparison, the electrodes were grouped into six scalp regions, and six representative electrodes from each region were taken for analysis as shown in Fig. 1. The demographic and behavioral data (i.e., age, education, MMSE score, reaction time, and error rates) were analyzed using *t*-test. The comparison of P3 amplitude and latency between the control and alcoholic group were performed using a multivariate analysis of covariance (MANCOVA). Age was used as a covariate in the MANCOVA model for two reasons: the alcoholics were significantly older than the controls in the sample, and age as a factor is known to have an effect on ERP parameters. On the other hand, the comparison between Go and No-Go trial conditions within each group was performed using repeated measures analysis of variance (RMANOVA). The *P*-values were adjusted using Bonferroni correction for multiple comparisons during the region-wise statistical analysis of P3 amplitude.

2.4. CSD mapping

The voltage at each electrode is a voltage difference between the recording electrode and the reference electrode. Spatial resolution of these scalp-recorded potentials can be severely limited by (i) reference electrode effects, (ii) ''blurring'' effects due to the tissue between electrode and sources, and (iii) large electrode spacing (Nunez, 1981). The recorded potential at each electrode thus represents integrated contributions from several sources between the reference and recording electrode and thus provides a blurred picture of the electrical activity that generates the observed field. The CSD, derived using the surface Laplacian method, acts as a spatial filter and provides an estimate of the local radial current density rather than distant/deep (neural) sources (Hjorth, 1975; Nunez, 1981; Nunez and Pilgreen, 1991). The CSD presents a more differentiated picture emphasizing the local components in the electrical state of the scalp surface. These components theoretically represent the primary activity entering the surface from below before it has been integrated into the more smeared potential field (Hjorth, 1991). In the present study, in order to examine the topographic changes in the Laplacian transformed data, the CSD maps were constructed separately for controls and alcoholics using the grand mean values as described by Wang and Begleiter (1999).

The CSD maps were compared using Efron's bootstrap technique as described by Srebro (1996). Based on this method, two sets of data were initially created by selecting randomly from the control group and alcoholic group, respectively. Then, another two sets of data were obtained from the pooled sample consisting of both alcoholic and control subjects. These random assignments to all four sets of data were repeated 200 times, so that each set would have 200 items (or subjects). Pearson correlation (R) was performed for the sets of controls versus alcoholics and pool-1 versus pool-2. The Fisher Z transform of Pearson R (Fisher and Yates, 1957) was computed and the two sets of Z estimates were compared using F-tests. If the F-value was significantly large, then the maps would be considered to be different from each other.

3. Results

3.1. Demographic and behavioral data

The behavioral and cognitive performance scores between control and alcoholic subjects are shown in Table 2. The alcoholics were significantly older than the controls ($t = 7.832$; $P = 0.000$), and age as a variable has been included in the MANCOVA model for group comparison. Although the control subjects were relatively more educated than the alcoholics ($t = 4.147$; $P = 0.000$), education was not included in the MANCOVA model, as this variable has not been consistently shown to affect the electrophysiological profile. Although MMSE scores of alcoholics were significantly lower than that of controls, the difference was very minimal. The MMSE score was also not included in the MANCOVA model, as it was assumed that the lower score in alcoholics could have been the direct result of alcoholism per se. However, there was no significant difference in the reaction time between controls and alcoholics. Although alcoholics committed more errors

Table 2
Performance scores between control and alcoholic subjects

Variable	Control		Alcoholic		t	P
	Mean	S.D.	Mean	S.D.		
MMSE[a] score	28.87	1.20	27.80	2.23	2.305	0.025*
Reaction time (ms)	291.38	22.37	293.04	23.48	0.281	0.780
Error[a] (Go)	4.93	3.54	6.90	6.21	1.508	0.138
Error[a] (No-Go)	1.10	1.35	3.30	7.39	1.605	0.119
Error[a] (total) (Go + No-Go)	6.03	4.00	10.20	10.42	2.044	0.048*

[a] Scores represented in absolute values.
* $P < 0.05$.

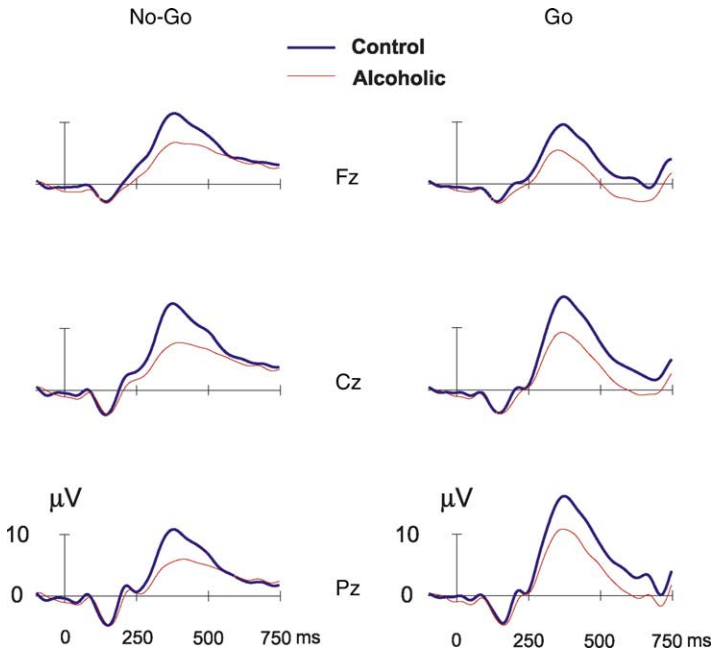

Fig. 2. ERP waveforms of control vs. alcoholic groups during No-Go and Go condition.

during the button-press responses of Go and No-Go condition separately, this difference was not statistically significant. On the other hand, the total response error (both Go and No-Go errors put together) was significantly higher in alcoholics than in controls.

3.2. ERP data

The Go/No-Go paradigm used in the present study elicited robust P3 components and also yielded significant statistical differences between groups and between trial conditions as illustrated in Figs. 2 and 3 and Tables 3–6. Other components in the ERP waveforms did

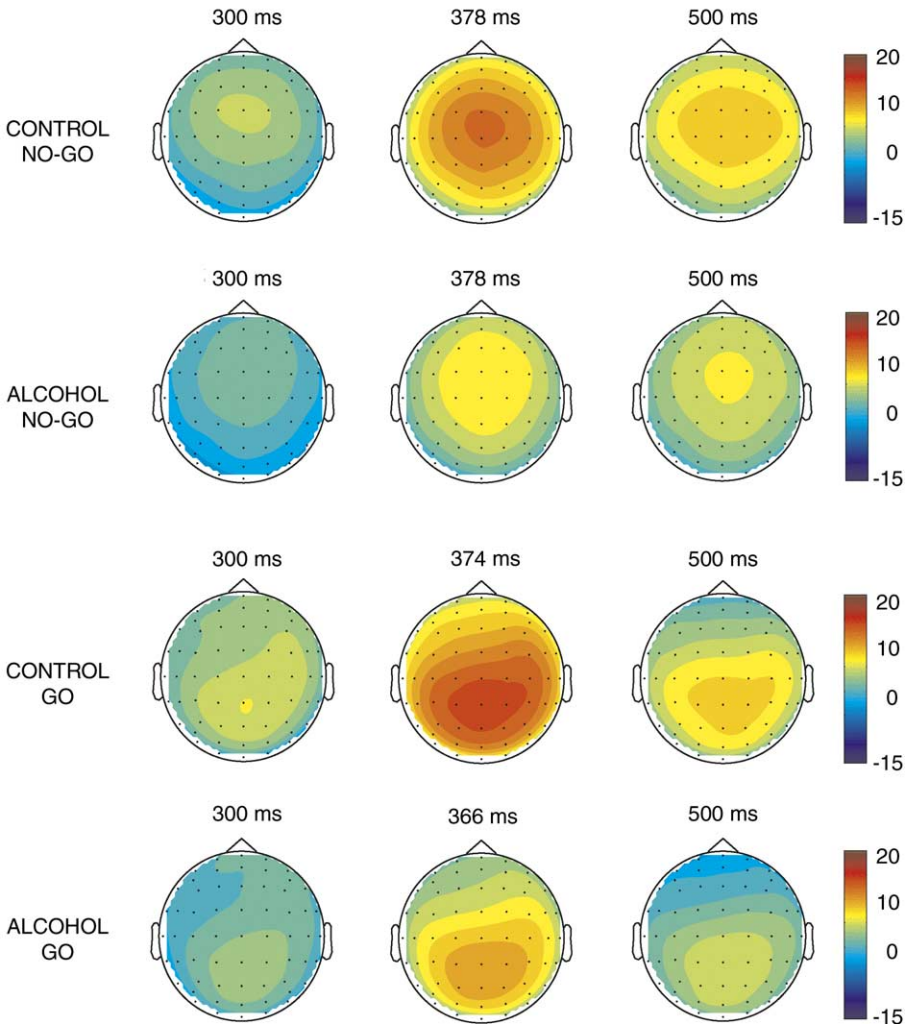

Fig. 3. The spatial distribution of ERP amplitudes (μV) at three time intervals of the P3 component in control and alcoholic groups during No-Go and Go condition.

not elicit observable differences and hence were not analyzed. There were no significant differences observed in P3 latency and therefore only the findings on P3 amplitude are reported here.

3.3. P3 amplitude: between-group comparisons

The ERP waveforms and topography of P3 amplitude in control and alcoholic subjects during the No-Go as well as the Go condition are illustrated in Figs. 2 and 3, respectively. In the No-Go condition, the maximum amplitude was observed in the central region, whereas

Table 3
Comparison of P3 amplitude (μV) between control and alcoholic groups during the No-Go condition (using MANCOVA)

Region	Control		Alcoholic		F (d.f. = 1, 58)	P[a]
	Mean	S.E.	Mean	S.E.		
Frontal	12.115	0.660	9.142	0.827	3.948	0.003**
Central	15.347	0.883	10.195	0.916	3.899	0.003**
Parietal	12.895	0.800	8.784	0.819	2.416	0.039*
Occipital	8.097	0.643	5.692	0.669	1.241	0.301
Left-temporal	7.992	0.613	5.450	0.606	2.951	0.015*
Right-temporal	9.309	0.614	5.955	0.545	3.439	0.006**

S.E. = standard error.
[a] Bonferroni corrected.
* $P < 0.05$.
** $P < 0.01$.

Table 4
Comparison of P3 amplitude (μV) between the control and alcoholic groups during the Go condition (using MANCOVA)

Region	Control		Alcoholic		F (d.f. = 1, 58)	P[a]
	Mean	S.E.	Mean	S.E.		
Frontal	10.350	0.756	6.354	1.072	1.354	0.251
Central	14.713	1.058	9.348	1.345	0.676	0.670
Parietal	16.989	1.038	11.965	1.407	2.388	0.041*
Occipital	13.412	1.004	9.418	1.197	1.089	0.381
Left-temporal	11.176	0.873	6.848	1.037	1.012	0.428
Right-temporal	11.503	0.893	7.456	0.989	1.061	0.398

[a] Bonferroni corrected.
* $P < 0.05$.

the Go condition showed a parietal maximum. Alcoholics were found to have significantly lower amplitude in both the No-Go and Go conditions (Tables 3 and 4). The frontal and central regions showed a significant difference between groups in the No-Go not in the Go condition. In the Go condition, only the parietal region showed the significant effects. Post-hoc comparisons (adjusted for multiple comparisons) between controls and alcoholics showed that the significance was more robust in the No-Go condition as compared to the Go condition at each of the electrodes.

3.4. P3 amplitude: within-group comparisons

In the within-group comparisons of ERP waveforms, while central electrodes showed higher P3 amplitude for the No-Go condition than Go condition in both groups, parietal electrodes displayed higher amplitude for the Go condition. Both groups showed

Table 5
Comparison of P3 amplitude (μV) between the No-Go and Go conditions in the control group (using RMANOVA)

Region	NO-GO		GO		F (d.f. = 1, 29)	P[a]
	Mean	S.E.	Mean	S.E.		
Frontal	12.115	0.660	10.350	0.756	4.616	0.040*
Central	15.347	0.883	14.713	1.058	0.439	0.513
Parietal	12.895	0.800	16.989	1.038	21.278	0.000***
Occipital	8.097	0.643	13.412	1.004	35.656	0.000***
Left-temporal	7.992	0.613	11.176	0.873	15.798	0.000***
Right-temporal	9.309	0.614	11.503	0.893	9.692	0.004**

[a] Bonferroni corrected.
* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

Table 6
Comparison of P3 amplitude (μV) between No-Go and Go conditions in the alcoholic group (using RMANOVA)

Region	NO-GO		GO		F (d.f. = 1, 29)	P[a]
	Mean	S.E.	Mean	S.E.		
Frontal	9.142	0.827	6.354	1.072	9.201	0.005**
Central	10.195	0.916	9.348	1.345	0.696	0.411
Parietal	8.784	0.819	11.965	1.407	7.297	0.011*
Occipital	5.692	0.669	9.418	1.197	10.647	0.003**
Left-temporal	5.450	0.606	6.848	1.037	2.237	0.146
Right-temporal	5.955	0.545	7.456	0.989	2.989	0.094

[a] Bonferroni corrected.
* $P < 0.05$.
** $P < 0.001$.

significant condition effects at frontal, parietal, and occipital regions (Tables 5 and 6). However, at the temporal regions, only the control group showed significant condition effects. The post-hoc comparison at each of the electrodes showed that the differences between trial conditions were more robust in the control group than in the alcoholic group.

3.5. CSD maps

The CSD maps for control and alcoholic groups during No-Go and Go conditions at three time points are shown in Fig. 4. The sources were found to be more anterior in the No-Go condition as compared to the Go condition. The current density of the P3 component spread from 300 to 500 ms and the CSD plots were created for every 10 ms interval. It was found that within the latency window of the P3 (i.e., 300–500 ms) the alcoholic subjects exhibited a 20 ms delay in the overall peak amplitude for both Go and No-Go conditions. The analysis of sources and sinks in the CSD topography clearly differentiates the groups and experimental conditions. In the No-Go condition, the controls have a strong centrally focused source whereas the alcoholics have a diffused and weak source. A smaller prefrontal sink observed in the controls was absent in alcoholics. On the other hand, during the Go condition, the controls manifested three distinct posterior sources at left parietal,

right centro-temporal, and occipital regions, while the alcoholics showed a single parieto-occipital source. The negative sink was more pronounced in alcoholics than in controls. Srebro's bootstrap method revealed that the correlation coefficients of CSD values obtained from control–alcoholic pairs were significantly different from those of the pairs of random pools in each region as shown in Table 7. This result suggests that the CSD maps of controls and alcoholics were significantly different from each other in both Go and No-Go conditions.

4. Discussion

The amplitude and topographic features of ERPs and CSD were assessed in alcoholic subjects and in healthy controls using a visual Go/No-Go task. The main objective of this study was to examine P3 characteristics between alcoholics and controls during response inhibition (No-Go condition) as well as response activation (Go condition). The results yielded four important findings: (1) alcoholics manifested significantly lower P3 amplitudes during the No-Go as well as Go conditions, implying deficient processing of both response inhibition and response activation, (2) the statistical difference between the No-Go and Go conditions was more robust in controls than in alcoholics, suggesting poor differentiation of task conditions in alcoholics, (3) relatively less anteriorization of CSD polarity in alcoholics during No-Go processing indicates an impaired/decreased frontal lobe contributions, and (4) the topographic patterns (involving sources and sinks) of CSD in alcoholics are significantly different from controls, implying that the network systems associated with cognitive processing are perhaps different between alcoholics and control subjects.

Using experiments of both equiprobable and non-equiprobable stimuli, Eimer (1993) suggested that the frontocentrally distributed No-Go P3 was related to response inhibition while the parietally distributed Go P3 was related to response activation. Our finding that alcoholics displayed significantly lower P3 amplitude during Go as well as No-Go conditions, therefore, suggests that both response activation and response inhibition are dysfunctional in alcoholic individuals. However, in our study, we have not found any group effects in No-Go N2, which is considered to be an important index of response inhibition. We argue that the absence of N2 effect does not exclude the presence of response inhibition deficits in alcoholics. In the literature on Go/No-Go tasks, it has been widely reported that both No-Go N2 and No-Go P3 have been considered to be the electrophysiological signatures of response inhibition. In our study, we do get a trend that there is a greater N2 on No-Go relative to go trials, although this was not statistically significant. Further, in our study, there is also a trend that alcoholics have reduced N2 in No-Go condition at FZ and CZ electrodes, but this reduction was not statistically significant, as against the robust reduction in the P3 component. Further, in an equiprobable Go/No-Go task, P3 has been found to reflect response inhibition in alcoholics and in individuals at risk for alcoholism (Cohen et al., 1997a, 1997b). Therefore, as suggested by many researchers, both No-Go N2 and No-Go P3 may index response inhibition (Cohen et al., 1997a, 1997b; Weisbrod et al., 2000; Kaiser et al., 2003), though they may represent different stages of cognitive processing and may underlie different neural generators. Further, the paradigm used in our

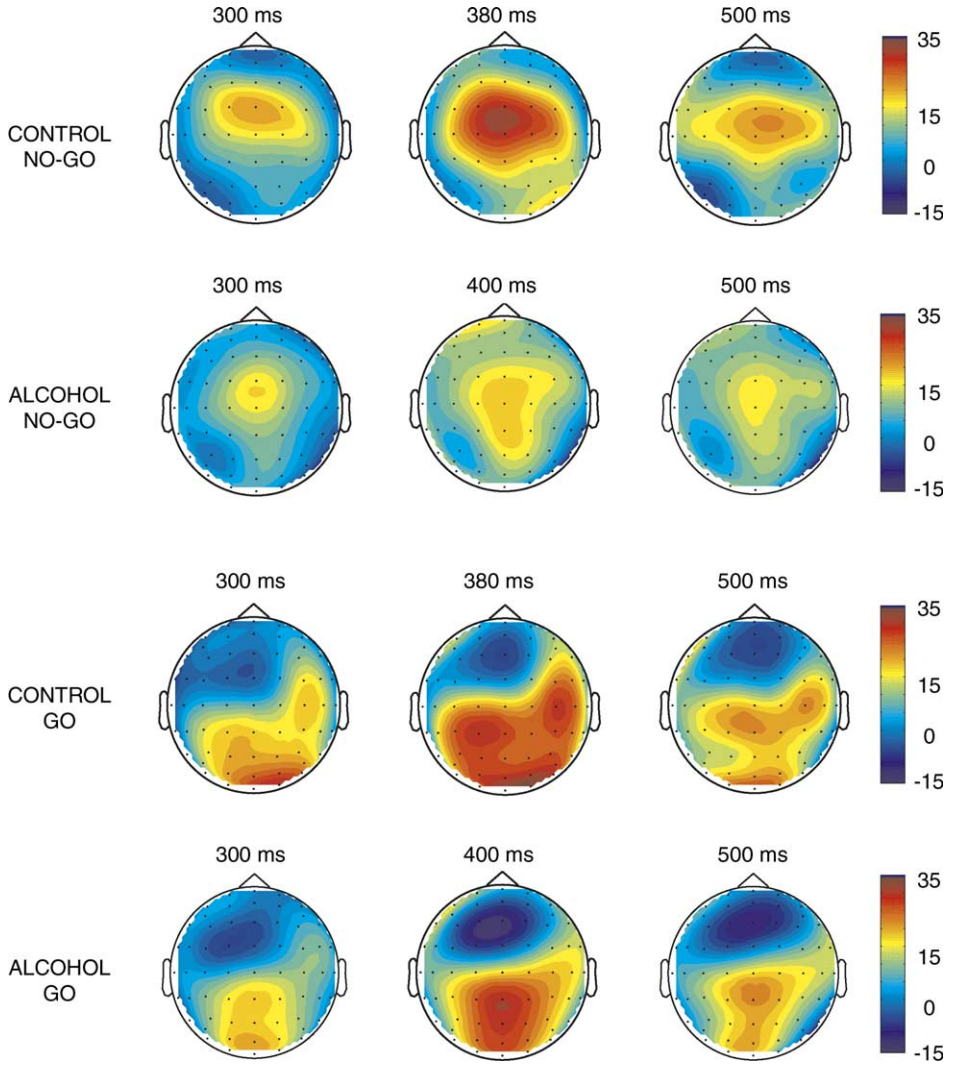

Fig. 4. The spatial distribution of CSD ($\mu V/r^2\,cm^2$, where r = head radius) at three time intervals of the P3 component in control and alcoholic groups during No-Go and Go conditions.

study was unique and required speeded reaction time less than 400 ms; in this paradigm, the N2 was perhaps camouflaged by the early P3.

It is also possible that the ERP index that underlies response inhibition might be different in different clinical groups. For example, schizophrenic patients showed normal activation in No-Go N2, but a lack of lateralization in the No-Go P3 (Weisbrod et al., 2000), while depressive patients showed significantly lower activation in the No-Go N2 but normal activation in No-Go P3 as compared to controls (Kaiser et al., 2003). Our finding is identical to the study by Cohen et al. (1997a) who reported that alcoholics showed lower P3

Table 7
Comparison of the Fisher *Z* transform (of Pearson *R*) in the No-Go and Go conditions based on bootstrap method

Region	NO-GO condition			GO condition		
	Control vs. alcoholic	Pool-1 vs. pool-2	P^a	Control vs. alcoholic	Pool-1 vs. pool-2	P^a
Frontal	0.0026	0.5258	0.0059**	1.0735	1.1685	0.0313*
Central	0.7227	1.1119	0.0000***	0.8501	1.3562	0.0000***
Parietal	0.8491	1.2457	0.0000***	0.1895	0.8303	0.0000***
Occipital	0.1559	0.9807	0.0000***	1.0930	1.5684	0.0000***
Left-temporal	−0.0552	0.4194	0.0000***	0.8384	1.0592	0.0003***
Right-temporal	0.0798	0.4194	0.0000***	1.0478	1.0592	0.0024**
Overall	0.0599	0.5835	0.0000***	0.8230	1.0147	0.0000***

[a] Based on *F*-values (d.f. = 1, 398).
* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

amplitudes in Go as well as No-Go conditions, with the absence of group effects in No-Go N2. The differences in findings could also be due to the fact that some studies reported larger amplitudes in the Go condition (Pfefferbaum et al., 1980, 1984, 1985; Pfefferbaum and Ford, 1988), while other studies observed larger P3 amplitudes in the No-Go condition (Karlin et al., 1970; Simson et al., 1977; Roberts et al., 1994). The diverse task characteristics in Go/No-Go paradigms including stimulus probability, induction of prepotency of response, and speed-accuracy trade off could have also contributed for the differential findings. It is to be noted that the paradigm used in our study involves the emphasis of speed in response and therefore the response time was shorter compared to other Go/No-Go tasks.

At the behavioral level, the dysfunction in response inhibition can also be evidenced by the finding that alcoholics committed more commission errors than controls during No-Go conditions. Response inhibition is considered to be a behavioral measure (encompassing sensory, cognitive and motor components) subserved by cortical inhibition and frontal executive processes which could be elicited by a neurophysiological index such as No-Go P3. Although the P3 component as elicited from different task paradigms has been shown to be associated with cortical inhibition, the No-Go P3 as an electrophysiological index of response inhibition, is considered to involve more than generalized cortical inhibition; it reflects activity at the cortical network subserving executive control involving prefrontal areas, anterior cingulate, and left premotor cortex (Kiefer et al., 1998). Our results showed that alcoholics had decreased amplitude in the parietally distributed Go-P3 which was related to response activation, as well as in the fronto-centrally distributed No-Go P3 that was associated with response inhibition, implying that alcoholics have dysfunctions in both cortical inhibition and frontal inhibitory mechanisms. This view can be supported by the evidence that alcoholics manifest abnormality in inhibition-based rhythms and in inhibition-related receptor mechanism like GABA at the physiological level (Volkow et al., 1993; Behar et al., 1999; Lingford-Hughes et al., 1998, 2000) and impairment in frontal executive functions at the cognitive level (Giancola and Moss, 1998; Kamarajan et al., 2004).

The topography of ERP and CSD potentials clearly delineated the controls from alcoholics. The No-Go anteriorization in the surface potential, as reported by other studies (e.g., Nativ et al., 1992; Fallgatter et al., 1998), has been observed in controls as well as in alcoholics. However, in the CSD topography, alcoholics, as compared to controls, showed less anteriorization effect in the No-Go condition and thus a reduced frontal lobe contribution during response inhibition. Further, in consensus with earlier P3 findings on alcoholism, our finding that lower P3 amplitude in the Go condition in alcoholics suggests a processing deficit during response activation as well. The processing deficits attributed to lower P3 amplitude mostly include attentional, executive, and working memory systems (e.g., Coull, 1998; Noldy et al., 1990; Perchet et al., 2001). Prefrontal cortex is recruited when there is a need to select between competing responses (Bunge et al., 2002). The executive control system regulates response selection in situations where routine mechanisms are unavailable or inadequate for task performance (Norman and Shallice, 1986; Posner and Dehaene, 1994). In an fMRI study, Pfefferbaum et al. (2001) demonstrated that alcoholics showed diminished activation of frontal cortical systems compared with controls during a task involving executive control. Further, Rangaswamy et al. (2004) reported that a dysfunctional fronto-parietal circuit involving the rehearsal component of the working memory system may underlie the low P300 responses seen in subjects who were at high risk to develop alcoholism. Therefore, our finding that alcoholics have lower P3 during response activation and inhibition perhaps indicates impaired executive control in alcoholic subjects and further suggests an insufficient input from the prefrontal cortex or circuitry.

As noted earlier, inhibitory control is considered to be an important executive function (Barkley, 2001; Collette and Van der Linden, 2002), and thought to be subserved by prefrontal circuits (Casey et al., 2002). The cognitive control model provided by Casey et al. suggests the involvement of fronto-striatal circuits during behavioral inhibition (Casey et al., 2001, 2002). Specific to addiction behavior, various neuro-cognitive models have been proposed to explain the vulnerability, genesis, and maintenance of alcohol/drug dependence. Giancola and Moss (1998) theorized that executive cognitive functioning (ECF) was an important determinant in the etiology of alcoholism and comorbid disinhibitory pathology, and proposed a cognitive-neurobehavioral model of alcoholism by implicating the fronto-striatal system. According to Begleiter and Porjesz (1999), the genetic predisposition to develop alcoholism primarily involves a state of CNS disinhibition/hyperexcitability which is reflected by the electrophysiological and cognitive anomalies in alcoholics as well as in the offspring of alcoholics. Goldstein and Volkow (2002) conceptualized alcohol/drug addiction as a syndrome of impaired response inhibition and salience attribution, and summarized the involvement of the fronto-subcortical circuits in addiction disorders. Chambers et al. (2003) proposed that the primary motivation circuitry involving cortical–striatal–thalamic-cortical loops were putatively involved in impulsivity, decision-making and alcohol/drug addiction. Recently, we proposed the prefrontal network systems (PNS) model of alcoholism based on available evidence on compromised frontal function in alcoholism and on our finding that the brain oscillatory responses during inhibitory processes (No-Go condition) were attenuated in alcoholics (Kamarajan et al., 2004).

It is often discussed that the electrophysiological deficits observed in alcoholics could have been a trait variable rather than drinking-related state variable. By documenting the

evidence from the collaborative study on the genetics of alcoholism (COGA), Porjesz et al. (1996, 1998) demonstrated that P3 amplitude meets all the criteria to be considered as a phenotypic marker for alcoholism. Further, the P3 amplitude has been consistently proposed to be a trait marker in alcoholism as the decreased P3 amplitude has also been frequently identified in children of alcoholics compared to normal controls (e.g., Begleiter et al., 1984; Porjesz and Begleiter, 1990, 1991; Polich et al., 1994; Porjesz et al., 1998). Moreover, many researchers have proposed that ERP features and EEG oscillations are highly heritable (Begleiter et al., 1998; van Beijsterveldt and Boomsma, 1994; van Beijsterveldt et al., 1996, 1998, 2001; van Beijsterveldt and van Baal, 2002; Almasy et al., 1999a; Anokhin et al., 2001; Hesselbrock et al., 2001; Porjesz et al., 2002a, 2002b; Winterer and Goldman, 2003). In the face of these observations, our finding that alcoholics display anomalies during response activation and inhibition may also suggest an impaired genetic mechanism in alcoholics, which could have perhaps led to deficient cognitive processing.

In conclusion, the results of the present study indicate that alcoholics manifest deficient cognitive processing mechanisms as evidenced by suppressed P3 amplitude during response activation and inhibition. The topographic pattern of alcoholics was found to be different from that of normals, suggesting the possibility that alcoholics activate different/inappropriate brain circuitry during cognitive processing. The relatively weaker No-Go P3 in surface potential and less anteriorization in CSD topography are suggestive of poor inhibitory control in alcoholics. Evidence suggests that the spectrum of disinhibitory or externalizing disorders, that includes alcoholism, share common inherent causality and external manifestations of symptoms. It is suggested that the No-Go potential can be considered as an endophenotypic marker in alcoholism and related disinhibitory disorders. However, future studies should attempt to elucidate the relative as well as interactive contributions of genetic and environmental factors.

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