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Spatial-anatomical mapping of NoGo-P3 in the offspring of alcoholics: evidence of cognitive and neural disinhibition as a risk for alcoholism

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Abstract

Objective: The concept of disinhibition as a behavioral and biological trait has been considered to be involved in the etiology of alcoholism and its co-existing disorders. The magnitude and functional mapping of event-related potential P3(00) components were analyzed, in order to examine the possible response inhibition deficits in the offspring of alcoholics.

Methods: The P3 components were compared between 50 offspring of alcoholics (OA) and a matched normal control group (NC) using a visual Go/NoGo task. The low-resolution electromagnetic tomography (LORETA) was used to analyze the functional brain mapping between groups.

Results: The results indicated that the OA group manifested decreased P3 amplitude during the NoGo but not the Go condition compared to the NC group. The voxel-by-voxel analysis in LORETA showed group differences at several brain regions including prefrontal areas during the processing of NoGo but not Go signals.

Conclusions: The decreased NoGo-P3 suggests that cognitive and neural disinhibition in offspring of alcoholics may serve as a neurocognitive index for a phenotypic marker in the development of alcoholism and related disorders.

Significance: Dysfunctional neural and response inhibition in the offspring of alcoholics perhaps provides an endophenotypic marker of risk for the development of alcoholism and related disorders.

Keywords: P300; Go/NoGo; Inhibitory control; Offspring of alcoholics; LORETA; Endophenotype

1. Introduction

Alcoholism is a complex and heterogeneous disorder with genetic and environmental variability. Genetic vulnerability for alcoholism is associated with collective variations in many different genes, which, along with interaction with the environment, can cause the risk for the disorder. In order to understand the risk factors involved in alcoholism, research has been directed at identifying the characteristic traits and behaviors (i.e. phenotypes) in affected alcoholics and their pedigrees. A phenotype generally represents the observable characteristics of an organism, which are the joint product of both genotypic and environmental influences (Gottesman and Gould, 2003). As the genetic complexity of alcoholism involves various phenotypes including electroencephalograms (EEGs), event-related potentials (ERPs), and event-related oscillations (EROs), the analysis of such electrophysiological data in alcoholics and their pedigrees is essential to identify and quantify the phenotypic markers for alcoholism and other co-existing disinhibitory disorders (Begleiter and Porjesz, 1990, 1999; Iacono et al., 2000; Limosin et al., 2000; Porjesz and Begleiter, 1991; Porjesz et al., 1996, 1998; Reich, 1996).

The ERP techniques offer a unique approach for assessing the level of brain functioning, as they permit a non-invasive and simultaneous observation of brain signaling and cognition. Further, the ERP is sensitive to sensory,

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cognitive, and motor aspects of information processing, and it can be a valuable tool in studying the genetics of alcoholism (Porjesz and Begleiter, 1991). In the ERP literature on alcoholism, the reduced P3 amplitude is a consistent finding that seems to characterize people at risk for alcoholism and may serve as a phenotypic marker for alcoholism and related disorders (Begleiter and Porjesz, 1999; Porjesz et al., 1998). Begleiter et al. (1984) reported that the sons of alcoholic fathers, who had no prior exposure to alcohol, showed lower P3 amplitudes without an alcohol challenge. This finding has been replicated in many different experimental conditions in male as well as female offspring of alcoholics (Begleiter et al., 1987; Benegal et al., 1995; Berman et al., 1993; Cohen et al., 1997b; Ehlers et al., 2001, 2003; Hill and Shen, 2002; Hill et al., 1990; Hill and Steinhauer, 1993; Hill et al., 1995, 2000; O'Connor et al., 1986, 1987; Porjesz and Begleiter, 1990a; Ramachandran et al., 1996; Ratsma et al., 2001; Rodriguez Holguin et al., 1999; Van der Stelt et al., 1998; Whipple et al., 1991).

This reduction in P3 amplitude is not only observed in alcoholism, but for a spectrum of disinhibitory disorders, such as conduct disorder (CD), attention-deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), and antisocial personality disorder (ASPD) (e.g. Bauer et al., 1994; Carlson et al., 1999; Iacono et al., 2002; Justus et al., 2001; Kiehl et al., 1999, 2000; Kim et al., 2001). In recent years, alcohol/drug dependence is considered to be part of the disinhibitory/externalizing spectrum (Kendler et al., 2003) as these disorders co-exist in their clinical presentation, and share similar electrophysiological indices (i.e. reduced P3 amplitude) (Bauer, 2001; Kuperman et al., 2001; Lewis and Bucholz, 1991; Myers et al., 1995; Reebye et al., 1995; Sher and Trull, 1994). Further, it has been suggested that the production of P3, irrespective of the task and modality, is associated with widespread cortical inhibition (Coenen, 1995; Elbert and Rockstroh, 1987; Nash and Fernandez, 1996; Nash and Williams, 1982; Roberts et al., 1994; Rockstroh et al., 1992; Tomberg and Desmedt, 1998; Woodward et al., 1991), and hence the low P3 amplitude would indicate a state of disinhibition (Begleiter and Porjesz, 1999; Iacono et al., 2002; McGue et al., 2001). Genetically mediated CNS disinhibition as indexed by such electrophysiological anomalies formed the core of the model for alcoholism as proposed by Begleiter and Porjesz (1999).

It has been suggested that the electrophysiological features, especially the ERP components, during a Go/NoGo task could provide direct measures of frontal inhibitory control and thus could serve as biological markers for cognitive and/or neural disinhibition in several disorders including alcoholism (Bokura et al., 2001; Eimer, 1993; Falkenstein et al., 1999, 1995; Filipovic et al., 2000; Kamarajan et al., in press; Kok, 1986; Kopp et al., 1996; Schroger, 1993; Yamanaka et al., 2002). The ERP studies of the Go/NoGo paradigm mainly focus on the NoGo condition, as it involves active inhibition of prepared responses, whereas the Go condition accounts for the response execution processes. These studies have identified two major markers (during the NoGo condition) for response inhibition: (1) the N2, a negative deflection with a frontocentral maximum around 200–300 ms, and (2) the NoGo-P3, an augmented positive-going peak usually peaking between 300 and 600 ms (Eimer, 1993; Jodo and Inoue, 1990; Jodo and Kayama, 1992; Kopp et al., 1996; Pfefferbaum et al., 1985). This anteriorly distributed NoGo-P3 has markedly reduced amplitude in alcoholic subjects (Cohen et al., 1997a; Kamarajan et al., in press) as well as in individuals at high risk to develop alcoholism (Cohen et al., 1997b), indicating impaired inhibitory control in such populations.

Although these electrophysiological signatures contain valid functional information in the time domain, they do not provide adequate spatial resolution. In other words, one fundamental limitation of these extracranial measurements of EEG/ERPs is that they do not contain sufficient information on the three-dimensional (3D) distribution of neuronal electric activity (Pascual-Marqui et al., 2002). Therefore, the localization of one or more generators of these brain potentials (i.e. the inverse problem) is possible only by using additional (neuroanatomical) constraints (Luck and Girelli, 1998; Winterer and Goldman, 2003). The recently developed method of low resolution electromagnetic tomography (LORETA) (Pascual-Marqui et al., 2002) overcomes these problems by incorporating the neurophysiological observations that measurable EEG-fields on the scalp reflect synchronized neuronal mass activity while close but opposing sources produce no scalp EEG. Therefore, combining ERP mapping with LORETA can characterize the type, timing, and source configuration of neural processing. LORETA has been applied to study different task-related cognitive processing in normal subjects (Bokura et al., 2001; Hamm et al., 2002; Schairer et al., 2001;) and in various disorders (Berg et al., 2001; Brandeis et al., 2002; Gallinat et al., 2002; van Leeuwen et al., 1998) including alcoholism (Prabhu et al., 2001; Saletu et al., 2002). Further, this method has also been employed to examine the phenotype–genotype relationship of gene variants in association with event-related activity (Winterer et al., 2000).

In our laboratory, using ERP measures of a Go/NoGo paradigm, we demonstrated that alcoholics as well as individuals who were at high risk for alcoholism showed impairments in response inhibition as well as response production (Cohen et al., 1997a,b; Kamarajan et al., in press). We also studied brain oscillations during the Go/NoGo task, and found that alcoholics had lower band power in delta and theta activity during a NoGo condition, indicating poor inhibitory mechanisms (Kamarajan et al., 2004). In the present study, along with ERPs, spatial–anatomical mapping using LORETA has been implemented in order to study the inhibitory processes in the offspring of alcoholics (OA) as compared to normal controls (NC). Moreover, as the genetics

of alcoholism is strongly associated with the concept of disinhibition (Begleiter and Porjesz, 1999), the present study is an attempt to elucidate the magnitude, temporal and spatial characteristics of the ERP features related to response inhibition in both groups. We hypothesized that if the OA group showed processing dysfunctions associated with response inhibition, this could possibly reflect cognitive and neural disinhibition as a risk marker for the development of alcoholism. We also expected that the functional imaging (through LORETA) would exhibit a lower activation in OA subjects in several brain regions (including frontal lobes) during response inhibition.

2. Methods

2.1. Subjects

A sample of 50 offspring of alcoholics (OA) consisting of 29 males and 21 females with an age-range of 18–25 years (Mean = 20.72; SD = 2.06), and 50 normal controls (NC) matched for age (Mean = 20.34; SD = 1.93), gender, and education were selected. All subjects were right-handed and were recruited through newspaper advertisements and notices. The OA subjects had at least one of their biological parents diagnosed to have alcohol dependence. The initial screening was done using a questionnaire that included the details of alcohol and drug use, medical and psychiatric histories of the subject and his/her relatives. The individuals with major medical, neurological, and psychiatric conditions inclusive of alcohol/drug dependence, and/or with concurrent psychotropic medications were excluded from the study. However, the OA subjects with concurrent or past history of externalizing disorders (such as CD, ASPD, ODD, ADHD) were included in the study. All the subjects were screened for organicity (gross brain damage), using the Mini Mental State Examination (MMSE; Folstein et al., 1975). The subjects were also excluded for their recent (i.e. past few days) drug/alcohol use, based on Breath-analyzer and urine screen. No subjects had hearing or visual impairments. Informed consent was obtained from each individual, and the experimental procedures and ethical guidelines were in accordance with the Institutional Review Board (IRB).

2.2. Experimental paradigm

The experimental paradigm is identical to our previous studies (Kamarajan et al., 2004, in press). The stimulus features of the Go/NoGo task are illustrated in Fig. 1.

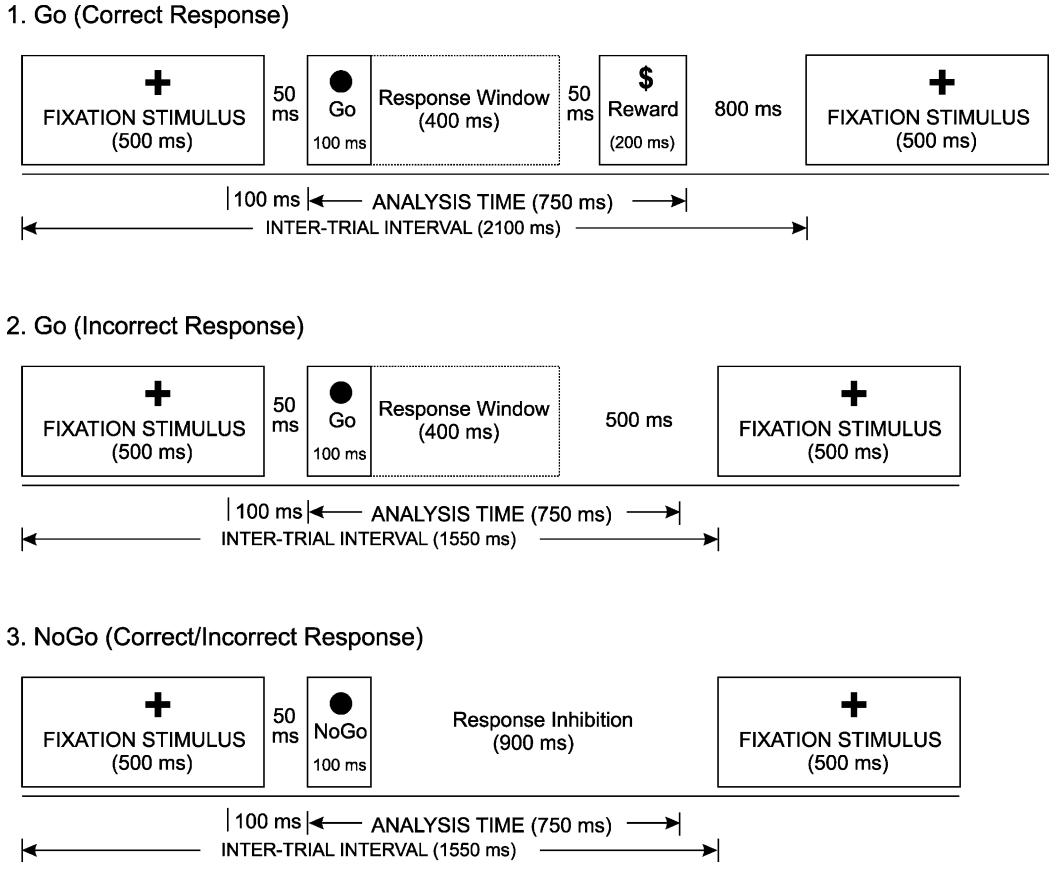

Fig. 1. Illustration of Go/NoGo task, showing (1) Correct response for the Go condition, (2) Incorrect response for the Go condition, and (3) Correct/incorrect responses for the NoGo condition.

There were 3 visual stimuli in the task: (i) a cross (fixation stimulus), (ii) a circle (Go or NoGo 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 NoGo 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 NoGo 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 probabilities of occurrence of Go and NoGo 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 20 Go and NoGo trials, respectively. The subjects were instructed to press a button as quickly as possible whenever they saw a circle in either the top right or bottom left corner. A feedback signal (i.e. 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 NoGo 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.[1]

2.3. EEG data acquisition and signal analysis

The subjects were seated in a comfortable, chair located in a dimly-lit sound-attenuated RF-shielded room (IAC, Industrial Acoustics, Bronx, NY) in front of the task computer placed 1 m away. 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 electrodes of the 10–20 International System and 42 additional electrode sites (Electrode Position Nomenclature, American Electroencephalographic Association, 1991) as shown in Fig. 2. The electrodes were referenced to the tip of the nose and the ground electrode was at the forehead (frontal midline). A supraorbital vertical lead and a horizontal lead on the external canthus of the left eye recorded the eye movements. 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

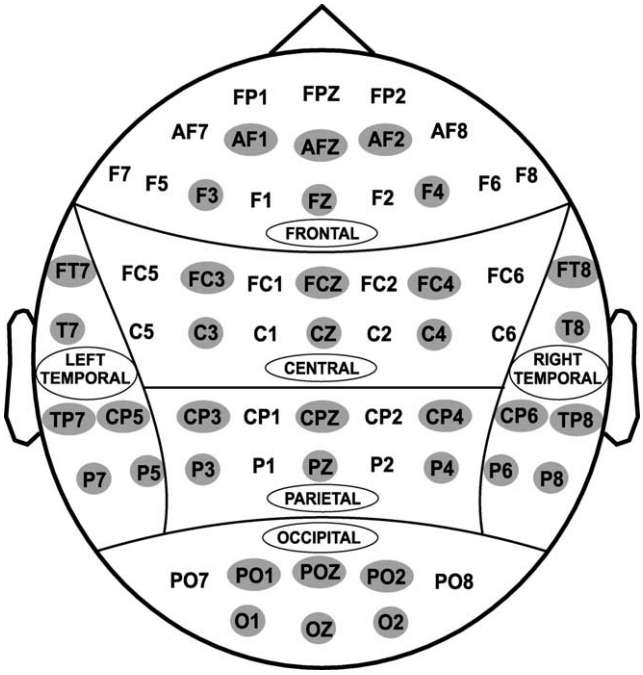

Fig. 2. Regional grouping of electrodes: (1) Frontal, (2) Central, (3) Parietal, (4) Occipital, (5) Left-temporal, and (6) Right-temporal. The representative channels in each region are highlighted.

(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 segmented into epochs of 100 ms pre-stimulus to 750 ms post-stimulus after digital low-pass filtering at 32 Hz. All segments exceeding $\pm$ 75 μV threshold were rejected as artifacts. After excluding the trials with eye-movement, the averaged segments for each individual were screened visually for further artifact rejection. Only the trials with correct response (button press) for the Go condition and correct inhibition (no button press) for the NoGo condition were averaged. Using a semi-automatic peak-picking program, the P3 amplitude was measured as the voltage difference from the pre-stimulus baseline to the largest positive going peak in the latency window 300–600 ms after stimulus onset. A minimum of 20 trials was available for each subject in both conditions. The statistical analyses were performed on the P3 amplitude and latency data that were derived separately for Go and NoGo conditions for each subject.

2.4. Statistical analyses

All 61 electrodes were grouped into 6 scalp regions for the statistical analyses as shown in Fig. 2. The behavioral data were analyzed using *t* test. Initially, the Repeated Measures Analysis of Variance (RMANOVA) was performed by having regions, electrodes, and task condition as within-subject variables and group and gender as between-subject variables. Only 6 representative electrodes

[1] However, based on ethical considerations, the subjects received the full amount (without deductions for incorrect responses) at the end of the experiment, although they were not informed of this while performing the experiment.

from each of the regions were taken into analysis (Fig. 2). As a second stage of analysis, the Multivariate Analysis of Variance (MANOVA) for between groups was performed for each of the regions separately by including all the electrodes of the specific region. The Bonferroni correction for multiple comparisons was implemented by adjusting the resulting P values.

2.5. LORETA analyses

The LORETA is a functional imaging method based on certain electrophysiological and neuroanatomical constraints (Pascual-Marqui, 1999; Pascual-Marqui et al., 2002). The cortex has been modeled as a collection of volume elements (voxels) in the digitized Talairach atlas provided by the Brain Imaging Center, Montreal Neurological Institute (MNI). The LORETA algorithm solves the inverse problem by assuming related orientations and strengths of neighboring neuronal sources (represented by adjacent voxels). LORETA has been identified as an efficient tool for functional mapping, since it is consistent with physiology and capable of correct localization (Pascual-Marqui et al., 2002). Along with a comprehensive experimental validation, independent validation of the localization properties of LORETA has been replicated by Yao and He (2001) and by Phillips et al. (2002). The version of LORETA employed here to study the current density and source localization (of the generators of ERP components) was made available at http://www.unizh.ch/keyinst/NewLORETA/LORETA01.htm.

Initially, the voxel-based (2394 voxels per time frame with a spatial resolution of 7 mm) data were created from the ERP data from 61 scalp electrodes for a single time frame that corresponded to the peak value of P3 in each group for both Go and NoGo conditions. The current density (at each voxel) was computed as a linear, weighted sum of the scalp electric potentials scaled to amperes per square meter (A/m^2). The current density data created for each of the individuals in both groups were statistically analyzed using the built-in voxelwise independent t tests with 5000 permutations and corrected for multiple comparisons (Holmes et al., 1996). The voxels with significant differences ($P<0.01$) between NC and OA groups were identified in terms of specific brain regions and Brodmann areas (BA) as provided at http://www.unizh.ch/keyinst/NewLORETA/Software/Software.htm.

3. Results

The focus of the current study is to compare ERP features in NC and OA subjects. Therefore, we report the statistical as well as LORETA results only for between-group comparisons.

3.1. Behavioral data

The behavioral performance scores between NC and OA have been shown in Table 1. It was observed that the subjects in OA group tended to commit more errors and have longer reaction times than subjects in the NC group, that approached significance ($P<0.10$) on both measures.

3.2. ERP data

The Go/NoGo paradigm used in the present study elicited robust P3 components and also yielded significant statistical differences between groups. Other components of the ERP waveforms (i.e. N1, P2, and N2) did not elicit observable differences and hence were not analyzed. All 61 electrodes were included in the analyses. The RMANOVA model included 2 conditions (Go and NoGo), 6 regions and 6 representative electrodes (Fig. 2) as within-subject factors, and group and gender as between-subject factors. It was found that Group main effect ($F=36.09$; $P=0.0000$) and Group×Condition interaction ($F=13.278$; $P=0.0004$) were significant. However, the Gender main effect ($F=1.092$; $P=0.2985$), the Gender×Group interaction ($F=0.481$; $P=0.4896$), and the Gender×Condition interaction ($F=0.318$; $P=0.5744$) were not significant. Further, significant main and interaction effects were also observed in Region ($F=98.19$; $P=0.0000$), Electrode ($F=41.96$; $P=0.0000$), Group×Region ($F=3.33$; $P=0.0083$), Group×Electrode ($F=2.81$; $P=0.0208$), Condition×Region ($F=56.70$; $P=0.0000$), Condition×Electrode ($F=38.50$; $P=0.0000$), Region×Electrode ($F=27.56$; $P=0.0000$), Condition×Region×Electrode ($F=19.83$; $P=0.0000$). Other interactions were not significant. There were no significant differences observed in P3 latency.

Table 1
The performance scores between NC and OA group

Variable	NC		OA		t value	P value
	Mean	SD	Mean	SD		
MMSE score	28.74	1.94	28.10	2.04	1.608	0.111
Reaction time	301.69	27.89	311.68	31.35	−1.683	0.096
Error (Go)	4.56	2.49	6.04	5.07	−1.852	0.067
Error (NoGo)	1.70	1.59	1.94	1.77	−0.713	0.477
Error (Total)	6.26	2.97	7.98	5.45	−1.958	0.053

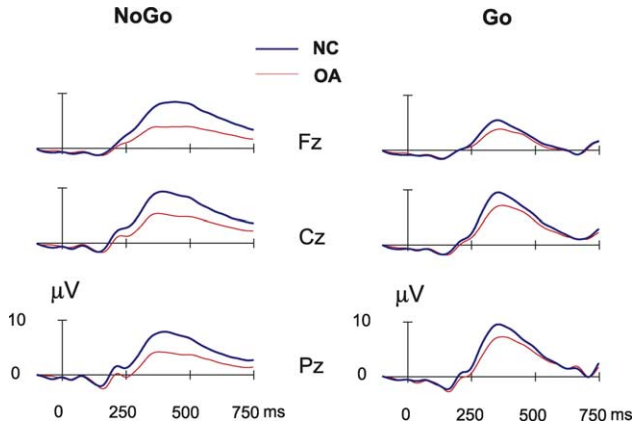

Fig. 3. The ERP waveforms of NC versus OA groups during NoGo and Go conditions.

The ERP waveforms and the topography of P3 amplitude in NC and OA groups during NoGo as well as Go conditions are illustrated in Figs. 3 and 4 respectively. In the NoGo condition, the maximum amplitude was observed in the central region, whereas the Go condition showed a parietal maximum. The region-wise analysis (of MANOVA) showed that the OA group had significantly lower amplitudes in each region during the NoGo but not in Go condition (Table 2). The post-hoc comparison (adjusted for multiple comparisons) between NC and OA groups showed that the significance was more robust in the NoGo condition as compared to Go condition for each of the electrodes (Fig. 5).

3.3. LORETA findings

The LORETA images comparing NC and OA groups for Go and NoGo conditions are illustrated in Figs. 6 and 7. Statistical analyses revealed that the OA group manifested a significant ($P<0.05$) reduction in brain activations in 136 areas (voxels), which also involved 34 specific regions of bilateral frontal lobes such as bilateral anterior cingulate, right inferior frontal gyrus, right middle frontal gyrus, bilateral medial frontal gyri, rectal gyrus (area 11), subcallosal gyrus and left precentral gyrus. These differences in frontal activity were more evident in the right than in the left hemisphere. Other brain regions that showed weaker activations included the bilateral temporal,

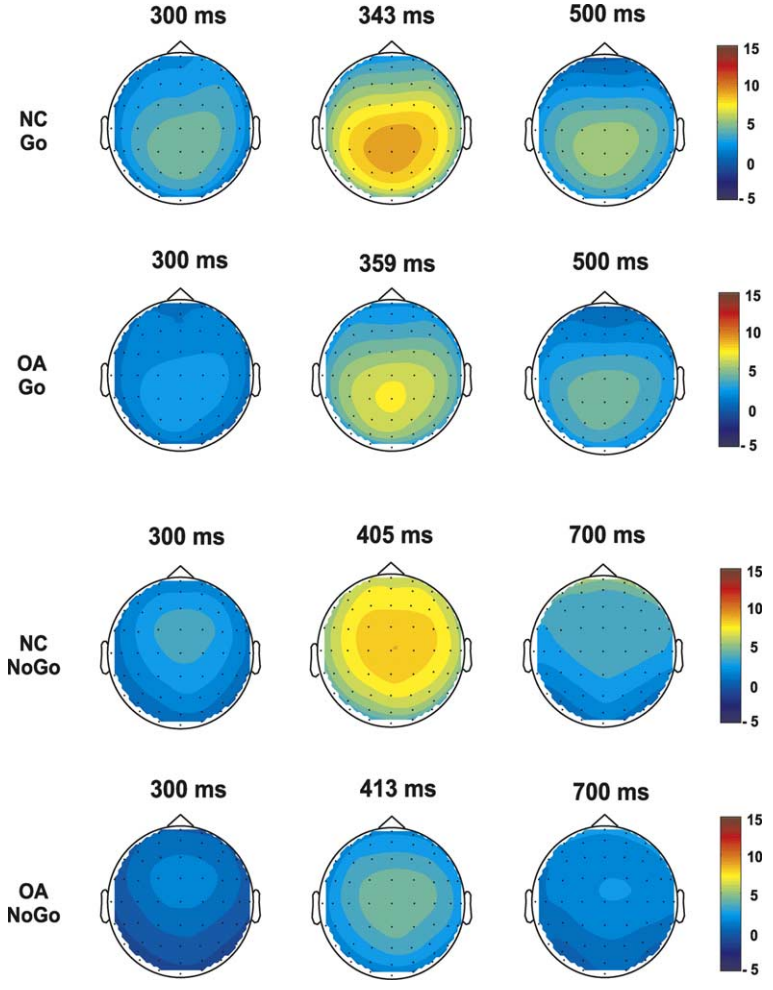

Fig. 4. The spatial distribution of ERP amplitudes (in μV) at 3 time intervals of P3 component in NC and OA groups during NoGo and Go conditions.

Table 2
The comparison of P3 amplitude (in μV) between NC and OA groups during the NoGo condition (using MANOVA)

Region	NC		OA		F value (df = 1, 98)	P value[a]
	Mean	SD	Mean	SD		
Frontal	11.04	7.49	5.80	3.66	3.396	0.0006***
Central	10.45	4.34	6.04	2.64	3.639	0.0006***
Parietal	9.68	3.82	5.42	2.62	4.628	0.0002***
Occipital	7.25	3.65	3.78	2.22	5.103	0.0002***
Left-temporal	7.82	4.11	4.00	2.20	6.450	0.0001***
Right-temporal	8.18	3.91	4.32	2.20	8.603	0.0000***

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

left parietal, right occipital, limbic, sub-lobar, and hippocampal areas. Visual inspection of LORETA images confirms the findings that OA subjects exhibit reduced activation in frontal, anterior cingulate and tempero-parietal regions during the NoGo condition. On the other hand, there was no significant difference observed in the Go condition in any of the 2394 voxels at the P3 peak, either in the statistical analysis or in the qualitative analysis of LORETA images.

4. Discussion

In the present study, the ERP and current density were analyzed in NC and OA groups. In the region-wise analysis, it was found that OA subjects manifested significantly decreased P3 amplitude in the NoGo but not in the Go condition. This finding was further confirmed by the LORETA analyses which revealed that the OA group exhibited a lower activation during the NoGo (but not Go) processing at several brain regions, including frontal and prefrontal areas. These dysfunctions of inhibitory response control in OA group are explained in terms of cognitive and neural disinhibition that is perhaps genetically mediated in causing alcoholism and related disinhibitory disorders. The discussion of the results focuses around 3 key topics: (1) P3(00) and cognitive processes in the offspring of alcoholics and the genetic implications, (2) different perspectives on the concept of inhibition, and the correlates of disinhibition (especially the electrophysiological indices), and (3) the NoGo-P3 as a potential endophenotypic marker in alcoholism.

4.1. P3 correlates in offspring of alcoholics

Electrophysiological aberrations, using diverse ERP paradigms, have been widely studied in abstinent alcoholics (for reviews, Porjesz and Begleiter, 1983, 1985, 1990b, 1993, 1996). Among the ERP features, the component most frequently studied in alcoholism research is P3(00), a positive going peak that occurs around 300 ms after the stimulus onset (e.g. Porjesz and Begleiter, 1993). The finding that the children of alcoholics have a decreased P3 amplitude has been widely reported, and a meta-analysis of P3 studies in high-risk individuals concluded that the P3 can be a useful investigative tool as an index of vulnerability for alcoholism (Polich et al., 1994). These findings strengthened the view that P3 amplitude can serve as a phenotypic marker for alcoholism. The finding of the present study that the OA group (which also had subjects with co-existing disinhibitory disorders) displayed significantly lower P3 amplitude as compared to that of the (age, gender, handedness, and education matched) NC group is supportive of the notion that P3 amplitude is an index of genetic vulnerability towards the development of alcoholism and related disinhibitory disorders. While P3 amplitude of the Go condition is larger in the NC than OA group, the absence of a significant group difference in the present paradigm may require further explanation, as the Go stimulus cannot be equated with the target stimulus of the Oddball paradigm, where many authors have reported effects of a family history of alcoholism. There are several differences between the target stimulus of the Oddball paradigm and the Go stimulus of the Go/NoGo task used in this study. In general, the task characteristics and instructions are different for the Oddball paradigm and the Go/NoGo task. In the oddball paradigm, attention is directed to the target stimulus, whereas in the Go/NoGo paradigm

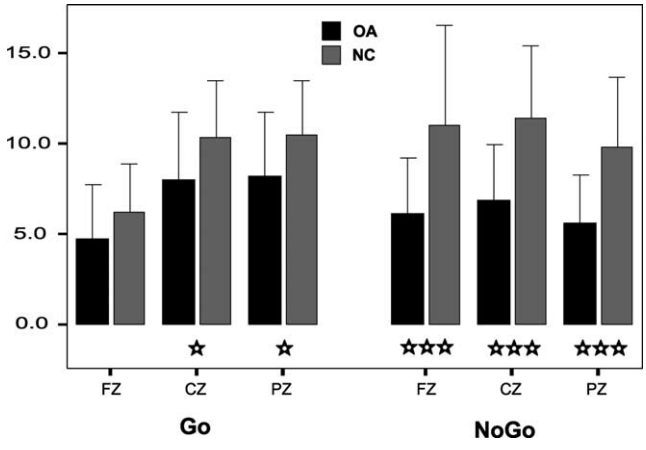

Fig. 5. The mean P3 amplitude (in μV) between NC and OA groups during NoGo and Go trails at FZ, CZ, and PZ electrodes (error bars represent 1 SD). The significance levels represented by star marks are based on independent t-values corrected for multiple comparisons (*$P < 0.05$; ***$P < 0.001$).

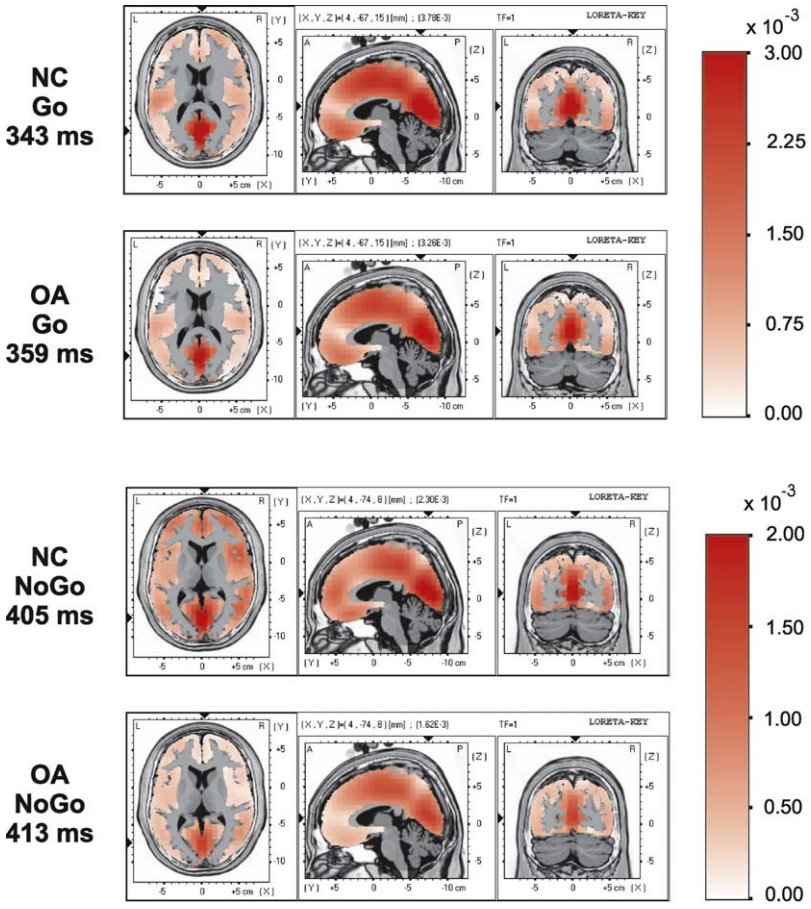

Fig. 6. The LORETA images of 3 orthogonal (axial, saggital, and coronal) views showing the current density (in amperes per square meter, A/m^2) during the peaks of the P3 component in NC and OA groups during the NoGo and Go conditions (NC, normal controls; OA, offspring of alcoholics).

additional emphasis is placed on inhibiting the NoGo stimuli. Further, in the oddball paradigm, the standard stimuli act as passive signals, whereas in the Go/NoGo task, the NoGo condition involves the active inhibition or suppression of prepotent/prepared responses. While the stimulus probability of Go and NoGo stimuli can vary within paradigms, typically in the 'oddball' paradigms the Go (target) is rare and the NoGo is frequent (standard); in the Go/NoGo task they are equiprobable or the NoGo is rare and the Go is frequent. Because probabilities are different, NoGo is more active in Go/NoGo task than oddball where 'Go' is a rare occurrence.

Our finding on functional mapping (through LORETA) demonstrated that OA subjects showed less activation only during the NoGo condition in many brain regions including the areas of the prefrontal cortices such as anterior cingulate, orbitofrontal cortex and medial frontal gyri. This reduced activity was more prominent in the right hemisphere than in the left. The possible explanations may include the hypothesis and findings that the right hemisphere is more affected than the left in alcoholics (Ellis and Oscar-Berman, 1989). Imaging studies (e.g. Konishi et al., 1999) as well as ERP studies (e.g. Fallgatter et al., 1998) have shown more prominent right hemispheric activation during the NoGo condition. Taken together, these findings suggest that the cognitive dysfunction in high-risk individuals may be attributable to a dysfunctional response inhibition mechanism which is perhaps genetically mediated. This finding is also supportive of the prefrontal network systems model that was proposed to explain the neuro-cognitive and genetic aspects in the development of alcoholism (Kamarajan et al., 2004, in press). In an fMRI study, Rangaswamy et al. (2004) reported that a dysfunctional fronto-parietal circuit may underlie the low P3 responses seen in children of alcoholics. In addition, the findings of neuropsychological deficits in high risk individuals (Drejer et al., 1985; Knop et al., 1993; Peterson et al., 1992; Schaeffer et al., 1984; Tarter et al., 1989) may serve as valid evidence for the hypothesis that the cognitive deficits may have preceded their alcohol use. Further evidence for the genetic hypothesis of alcoholism came from the observation that the cognitive functions of prefrontal lobe are highly heritable (for a review, Winterer and Goldman, 2003), including that of frontal executive functions (Ando et al., 2001; Swan and Carmelli, 2002; Winterer and Goldman, 2003) and attentional networks (Fan et al., 2001; Fossella et al., 2002). Therefore, it can be suggested that the findings of the present study are suggestive of strong genetic

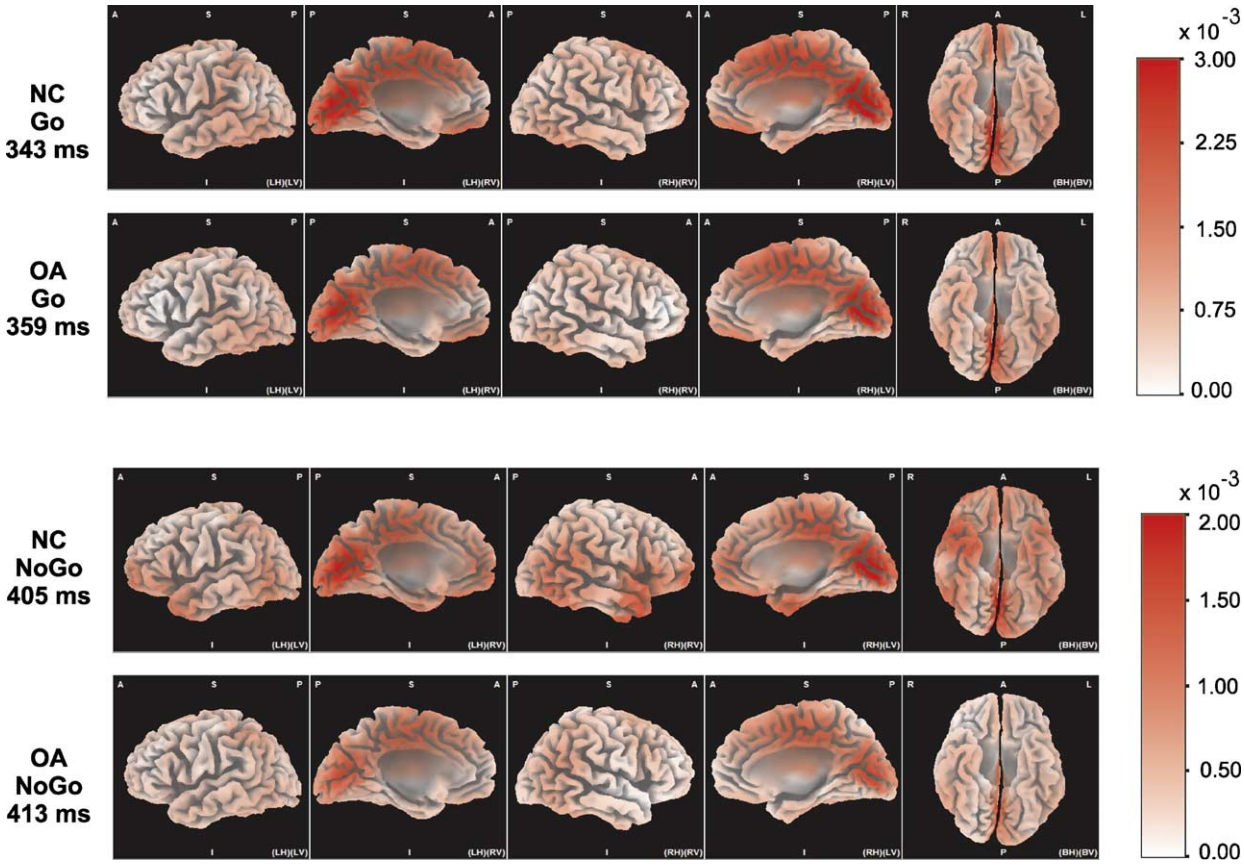

Fig. 7. The LORETA images of 3-dimensional views showing the current density (in A/m^2) during the peaks of the P3 component in NC and OA groups during the NoGo and Go conditions (NC, normal controls; OA, offspring of alcoholics; LH, left hemisphere; RH, right hemisphere; bH, both hemispheres; A, anterior; P, posterior; S, superior; I, inferior; LV, left view; RV, right view; BV, bottom view).

mediation in predisposing the risk to develop alcoholism, as evidenced by cognitive and neurophysiological dysfunctions that are elicited by decreased P3 amplitude and weaker activation of brain areas during response inhibition in OA subjects.

4.2. Inhibition/disinhibition: concepts and correlates

At the behavioral level, however, inhibitory control refers to the ability of the organism to withhold a planned response, to interrupt a response that has been started, to protect an ongoing activity from interfering activity, and to delay a response (Rubia et al., 1998). On the other hand, various neuro-cognitive models suggest that inhibitory control is subserved by the frontal lobe circuits (Casey et al., 2001, 2002; Chambers et al., 2003; Giancola and Moss, 1998; Goldstein and Volkow, 2002; Kamarajan et al., 2004). However, the central concept of inhibition–excitation shares a parallel with Gray's theory of Behavioral Activation and Inhibition systems (BAS and BIS respectively; Gray, 1972, 1987, 1990). The BAS and BIS are construed as bio-behavioral traits representing the psychobiological systems responsible for arousal/inhibition in humans (Carver and White, 1994; Gray, 1988, 1994), and are linked to frontal activity levels (Coan and Allen, 2003; Harmon-Jones and Allen, 1997; Sutton and Davidson, 1997) and to various forms of child psychopathology (Kooijmans et al., 2000). Further, Finn et al. (1994) found that the subjects who are at high-risk to develop alcoholism had significantly smaller skin conductance responses to the conditioned stimulus for punishment, possibly reflecting weak behavioral inhibition system processes.

It has been theorized that disinhibition as a cognitive and neural construct is involved in predisposing to alcoholism (Begleiter and Porjesz, 1999) and other disinhibitory disorders (Iacono et al., 1999, 2002, 2003). It has been reasoned that the production of P3, irrespective of the task and modality, is associated with widespread cortical inhibition (e.g. Nash and Williams, 1982; Roberts et al., 1994; Tomberg and Desmedt, 1998). Further, the P3 amplitude was found to be significantly decreased in various externalizing disorders (Kendler et al., 2003) such as ASPD (Costa et al., 2000; Hesselbrock et al., 1993; Iacono et al., 2002; Justus et al., 2001; Kiehl et al., 1999, 2000), CD (Bauer and Hesselbrock, 1999a,b, 2003; Iacono et al., 2002), ADHD (Banaschewski et al., 2003; Jonkman et al., 1997; Overtoom et al., 1998; Steger et al., 2000; van der Stelt et al., 2001) and alcohol/drug dependence

(e.g. Begleiter and Porjesz, 1999; Hill et al., 1999; Iacono et al., 1999, 2002). Fallgatter and Herrmann (2001) explain that features of the NoGo-P3 are valid measures of the brain electrical basis of impulsive behavior and cognitive response control, and hence the impaired NoGo-P3 may also indicate 'emotional disinhibition'. In this context, alcoholism is considered to be a part of the disinhibitory spectrum, owing to the suppressed P3 amplitude in alcoholics and individuals at risk. Our finding that the OA group showed lower P3 amplitude as well as lower activation of brain regions including frontal areas during response inhibition strongly supports the notion that disinhibition is perhaps the core feature in the predisposition for the development of alcoholism and other disinhibitory disorders.

4.3. NoGo-P3 as an endophenotypic marker for alcoholism

An endophenotype-based approach can facilitate the process of genetic analyses of psychiatric disorders (Gottesman and Gould, 2003). A heritable biological endophenotype could identify those individuals at genetic risk in the absence of overt manifest symptoms (Begleiter and Porjesz, 1999). By citing evidence, Porjesz et al. (1996, 1998) demonstrated that P3 amplitude meets all the criteria to be considered as a phenotypic marker for alcoholism. Since the ERP features and EEG oscillations are highly heritable (e.g. Begleiter et al., 1998; Porjesz et al., 2002; van Beijsterveldt et al., 1996, 1998, 2001; Winterer and Goldman, 2003), dysfunction in these measures in clinical groups, especially in high-risk individuals, suggests a genetic vulnerability for the disorder(s).

In the present study, we observed that the OA group displayed lowered activation in several brain regions during P300 processing of the NoGo (but not Go) condition as elicited by functional imaging through LORETA, reflecting a weaker neural inhibition system in the vulnerable population. This dysfunction may have been genetically mediated, as reported by Jones et al. (2004) who found that the frontal theta band elicited during the P300 time window (300–700 msec) target condition of the visual oddball task was associated with single nucleotide polymorphisms (SNPs) in the cholinergic muscarinic receptor gene *(CHRM2)* on chromosome 7. Further, this fronto-centrally focused theta activity was reportedly deficient in both alcoholics (Kamarajan et al., 2004) and their offspring (Kamarajan et al. in preparation). The phenomenon of reduced 'NoGo-P3', along with poorer brain activation during NoGo processing, has therefore been supported with considerable evidence to suggest a genetic mediation of inhibition/disinhibition in causing predisposition to develop alcoholism and other disinhibitory disorders in high risk individuals. Thus it can be concluded that the 'NoGo-P3' can be considered to be a potential endophenotypic marker for alcoholism and other co-existing disinhibitory disorders, which can be elicited in high-risk individuals even before the onset/manifestation of the disorder. However, further studies using different task paradigms to measure inhibition/disinhibition in different disinhibitory disorders are essential in order to replicate and confirm the findings of the present study.

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