Reduced Frontal Lobe Activity in Subjects With High Impulsivity and Alcoholism

Andrew C. H. Chen, Bernice Porjesz, Madhavi Rangaswamy, Chella Kamarajan, Yongqiang Tang, Kevin A. Jones, David B. Chorlian, Arthur T. Stimus, and Henri Begleiter

Objective: Impulsivity is an important characteristic of many psychiatric disorders, including substance-related disorders. These disinhibitory disorders have a similar underlying genetic diathesis, with each disorder representing a different expression of the same underlying genetic liability. This study assessed whether there is a relationship between impulsivity and alcohol dependence, and their correlations with P3 (P300) amplitude, a proposed endophenotype of alcoholism.

Methods: Healthy control subjects ($n = 58$) and subjects with DSM-IV diagnosis of alcohol dependence ($n = 57$) were assessed with a visual oddball task. Event-Related Potentials (ERPs) were recorded from 61 scalp electrodes and P3 amplitudes measured. Barratt Impulsiveness Scale (BIS), version 11, was used to evaluate impulsivity. Source localization of P3 was computed using low-resolution brain electromagnetic tomography (LORETA).

Results: Alcoholic subjects manifested reductions in target P3 amplitudes ($p < 0.0001$). Using LORETA, significantly reduced activation was mapped in the cingulate, medial, and superior frontal regions in alcoholic subjects and highly impulsive subjects. Alcoholic subjects had significantly higher scores on the BIS ($p < 0.0001$) than nonalcoholic individuals. There were significant negative correlations between total scores on BIS and P3 amplitude ($r = -0.274$, $p = 0.003$, on Pz; $r = -0.250$, $p = 0.007$, on Cz).

Conclusions: Our results demonstrate a strong frontal focus of reduced activation during processing of visual targets in alcoholic subjects and individuals with higher impulsivity. The findings suggest that impulsivity may be an important factor that underlies the pathogenesis of alcohol dependence. Studies are underway to examine the relationship between impulsivity and ERPs in offspring of alcoholic subjects, and to identify genes associated with the underlying predisposition involved in disinhibitory disorders.

Key Words: P3, Disinhibition, Impulsivity, LORETA, Endophenotype.

ALCOHOLISM IS A complex and heterogeneous disorder with both genetic and environmental determinants. In recent decades, research has been directed at identifying the characteristic traits (i.e., phenotypes) in affected alcoholic subjects as well as their pedigrees to understand the factors underlying the pathogenesis of the disorder. A phenotype represents the observable characteristics of an organism, the joint product of the influences of genetic and environment factors. However, it became clear that using "diagnoses" as phenotypes may not be optimal for genetic dissection of complex diseases such as psychiatric diseases because these diseases have complex genetic underpinnings (Gottesman and Gould, 2003). Therefore, it is valuable to analyze electrophysiological data, such as electroencephalograms (EEGs), event-related potentials (ERPs), and event-related oscillations (EROs), in alcoholic subjects and their pedigrees to identify and quantify the endophenotypic markers for studying the molecular genetics of alcoholism and other coexisting disinhibitory disorders (Begleiter and Porjesz, 1999; Porjesz et al., 1998). It is believed that these endophenotypes are closer to gene action than diagnostic categories, and that they provide a more powerful strategy in searching for genes involved in producing psychiatric diagnoses (Porjesz et al., 2005).

Measuring ERPs provides a valuable tool for assessing dynamic brain processes: it is noninvasive and allows an exquisite temporal observation of brain signaling and cognition. In addition, the ERP is highly sensitive to sensory, cognitive, and motor aspects of information processing in the brain, and it has been shown to be of great value in studying the genetics of alcoholism and other psychiatric

From Henri Begleiter Neurodynamics Laboratory, Department of Psychiatry, SUNY Downstate Medical Center, Brooklyn, New York.

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Reprint requests: Bernice Porjesz, Henri Begleiter Neurodynamics Laboratory, Department of Psychiatry, SUNY Downstate Medical Center, Box 1203, 450 Clarkson Ave., Brooklyn, NY 11203; Fax: 718-270-4081; E-mail: bp@cns.hscbklyn.edu

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disorders (Porjesz et al., 2005). There is solid evidence for considering the P3 amplitude of the ERP as an endophenotype for the risk of alcoholism (Porjesz et al., 1998, 2005). Of particular note is the initially reported finding by Begleiter et al. (1984) regarding reduced P3 amplitudes in the sons of alcoholic fathers, who had no prior exposure to alcohol. This finding has been replicated in many different paradigms in both male and female offspring of alcoholic subjects (e.g., Berman et al., 1993; Ehlers et al., 2003; Van der Stelt et al., 1998; Whipple et al., 1991). Furthermore, this reduction in P3 amplitude is not only observed in alcoholism, but in a spectrum of disinhibitory disorders, such as conduct disorder (CD), attention-deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), and antisocial personality disorder (ASPD) (Iacono et al., 2002; Kiehl et al., 1999).

It has been suggested that production of the P3 component of the ERP, irrespective of the task and modality, is associated with an inhibition of neuron assemblies involved in perceptual processing of the attended sensory input, thereby achieving a "closure" of the cognitive operations dealing with the currently attended sensory input (Iacono et al., 2002; Nash and Williams, 1982). In addition, an association of reduced P3 amplitudes with high sensation-seeking, particularly with high disinhibition, has been identified in adult children of alcoholic subjects (Ratsma et al., 2001). Data from the Minnesota Twin Family Study showed that a low P3 amplitude is associated with externalizing psychopathology in adolescents (Carlson et al., 1999). Thus, a low P3 amplitude would indicate a state of disinhibition (Iacono et al., 2002; Porjesz et al., 2005; Tomberg and Desmedt, 1998).

Gorenstein and Newman (1980) proposed that behavioral phenomena such as psychopathology, antisocial, and impulsive traits, and alcoholism should be viewed as variable expression of a generalized disinhibitory complex. Recently, substance dependence, such as alcohol dependence, has been considered part of the disinhibitory/externalizing disorder spectrum (Kendler et al., 2003), as these disorders coexist in their clinical presentation; they co-occur with externalizing traits in both children and adults (Kuperman et al., 2001; Reebye et al., 1995), and share similar electrophysiological indices such as a reduced P3 amplitude (Sher and Trull, 1994). Clinically, altered impulsiveness is one of the most common manifestations of these disinhibitory disorders. Impulsivity, which is mostly defined as action without planning or behavior that is prematurely executed and has maladaptive consequences, is a complex behavioral construct (Barratt et al., 1999; Evenden, 1999; Moeller et al., 2001). It appears to be associated with a failure of behavioral filtering processes outside of consciousness and with compromised capacity to use appropriate judgment to reflect on impending acts (Moeller et al., 2001). The prevalence of increased impulsivity among substance abusers has been widely discussed or speculated upon. Recent studies indicate that alcoholic subjects have higher levels of impulsivity, particularly those with cluster B personality disorders (Dom et al., 2006a) or early-onset type alcoholism (Dom et al., 2006b). However, an earlier report showed that impulse control disorders in alcoholic subjects were related only to sensation seeking but not to impulsivity, as neither the total score nor the subscale scores on the BIS showed significant differences between alcohol-dependent subjects (with or without impulse control disorders) and control subjects (Lejoyeux et al., 1998).

In the present study, we investigated the correlation between impulsivity and the phenotypic marker, P3 amplitude of the ERP, in control subjects and subjects with alcohol dependence. To further study the differences in source localizations of neuronal activities in the brain during processing of visual targets among controls, alcoholic subjects, and subjects with extreme high or low impulsivity, we used the recently developed method of low-resolution electromagnetic tomography (LORETA; Pascual-Marqui et al., 2002), which overcomes limitations of earlier EEG/ERP techniques in 3-dimensional distribution of neuronal electric activity. The LORETA technique is able to compute a functional brain image of source localizations by incorporating the following neurophysiological observations: (a) measurable EEG-fields on the scalp reflect synchronized neuronal mass activity, and (b) close but opposing sources produce no scalp EEG. Low-resolution electromagnetic tomography has been applied to study task-related cognitive processing in normal subjects (Schairer et al., 2001) and in various disorders (Gallinat et al., 2002) including alcoholism (Kamarajan et al., 2005b). It has also been used to examine the phenotype–genotype relationship of gene variants in association with event-related activity, and the results have demonstrated good reliability (Winterer et al., 2000).

We hypothesize that subjects with alcohol dependence exhibit increased impulsivity and that this is correlated with cognitive deficits, as reflected in reduced P3 amplitudes. In addition, we predict that source localization of P3 (using LORETA) will reveal a lower activation in the frontal lobes, the brain regions that are thought to be involved in inhibition, in subjects with alcoholism or high impulsivity during response inhibition such as processing target visual signals.

METHODS

Subjects

The sample included the adults who met the Diagnostic and Statistical Manual of Mental Disorders, DSM-IV (American Psychiatric Association, 1994) criteria for alcohol dependence but no other Axis I diagnoses ($n = 57$) and healthy adult controls ($n = 58$). Alcoholic subjects were recruited from several treatment centers for alcohol dependence in and around New York City. Before testing, they had been detoxified in a 30-day treatment program and none of the subjects was in the withdrawal phase. Control subjects were recruited through newspaper advertisements and notices. Informed consent

Table 1. Demography of Subjects Included in the Study ($N = 115$)

	Controls	Alcohol dependence
N (number)	58	57
Gender[a] M/F	29/29	47/10
Age[b] (mean ± SEM)	23.7 ± 1.0	38.5 ± 0.8

[a]Gender is significantly different between groups.
However, among subjects within the same group, there were no significant correlations between gender and BIS scores ($p = 0.53$, $r = 0.083$ in controls; $p = 0.54$, $r = -0.082$ in alcoholic subjects, respectively) or P3 amplitudes on the leads we analyzed.

[b]Age is also significantly different between groups.
However, among subjects within the same group, there were no significant correlations between age and BIS scores ($p = 0.86$, $r = 0.023$ in controls; $p = 0.34$, $r = 0.13$ in alcoholic subjects, respectively). In addition, age was treated as a covariate in MANOVA and RMANOVA.

BIS, Barratt Impulsiveness Scale; MANOVA, multivariate analysis of variance; RMANOVA, repeated measures analysis of variance.

was obtained from each individual, and the experimental procedures and ethical guidelines were in accordance with the Institutional Review Board (IRB).

Subjects, both healthy controls and alcoholic subjects, were excluded if they manifested any of the following: uncorrected sensory deficits, hepatic encephalopathy/cirrhosis of the liver, significant head injury, history of seizures or neurosurgery, other acute/chronic medical illness, were on medication known to influence brain functioning, or tested positive for HIV. The subjects were also excluded for their recent (i.e., 5 days) substance and alcohol use, based on self-report as well as breath analyzer and urine screen. In addition, all subjects were screened for organicity, using the Mini Mental State Examination (MMSE, Folstein et al., 1975). The demography of subjects in this study is shown in Table 1.

Assessment of Impulsivity

Impulsivity was measured using a self-report questionnaire, BIS, version 11 (Patton et al., 1995). It consists of 30 items measuring 3 aspects of impulsivity: nonplanning (NP, lack of future orientation), motor impulsivity (MI, impetuous action), and cognitive impulsivity (CI, attention deficits, rapid, unstable thoughts, and lack of cognitive patience, or labeled as "attentional impulsiveness"). Barratt Impulsiveness Scale scores have recently been shown to be elevated in subjects with cocaine abuse (Moeller et al., 2002) and alcoholic subjects with cluster B personality disorders (Dom et al., 2006a).

Event-Related Potential Data Acquisition and Signal Analysis

Details of the visual oddball paradigm used in the present study have been previously described (Porjesz et al., 1998). It consists of presentation of 3 types of visual stimuli ($n = 280$), 60-ms duration, subtending a visual angle of 2.5°, with an interstimulus interval of 1.625 seconds. The rare target stimulus ($n = 35$) was the letter X, to which the subject was required to press a button as quickly as possible; the responding hand was alternated across subjects to counterbalance any laterality effects due to responding. Speed was emphasized, but not at the cost of accuracy. The frequently occurring nontarget stimuli ($n = 210$) were squares, and the novel stimuli ($n = 35$) consisted of colored geometric polygons that were different on each trial; the subject was not required to respond to the nontarget and novel stimuli. The probabilities of occurrence of the trials were 0.125 for the target trials, 0.75 for the nontarget trials, and 0.125 for the novel trials. The stimuli were presented pseudo-randomly with the constraints that neither targets nor novels could be repeated consecutively.

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 computer monitor placed 1 m away. Electroencephalogram 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 previously (Kamarajan et al., 2005b). 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 to 100 Hz and amplified 10,000 times using a set of amplifiers (Sensorium, Charlotte, VT).

The continuous EEG was digitally low-pass filtered at 32 Hz and then segmented into epochs of 100 ms prestimulus to 750 ms poststimulus. The mean EEG activity for 100 ms before stimulus onset served as the prestimulus baseline. All segments exceeding ± 75 μV threshold were automatically excluded from further processing. After correcting eye-movement artifacts, the averaged segments for each individual were screened visually for further artifact rejection. The artifact detection was performed on all channels including the electro-occulogram (EOG) channels. The visual P3 (VP3) amplitude was measured as the voltage difference between the prestimulus baseline and the largest positive going peak in the latency window 300 to 600 ms after stimulus onset. For each individual, the amplitude and latency measures were calculated using a semiautomatic 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. The grand averages were computed and plotted to determine the components and time windows (Kamarajan et al., 2005a).

LORETA Analyses

The LORETA is a functional source imaging method based on certain electrophysiological and neuroanatomical constraints (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 (Talairach and Tournoux, 1988). The LORETA algorithm solves the inverse problem by assuming related orientations and strengths of neighboring neuronal sources (represented by adjacent voxels). Low-resolution electromagnetic tomography has been identified as an efficient tool for functional mapping, as it is consistent with physiology and capable of correct localization. Along with a comprehensive experimental validation of the initial designers, many independent studies have replicated the validation of the localization properties of LORETA (Pascual-Marqui et al., 2002). The version of LORETA used 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 (2,394 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. 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 voxel-wise independent *t*-tests with 5,000 permutations and corrected for multiple comparisons (Holmes et al., 1996). The voxels with significant differences ($p<0.05$) between groups were identified for specific brain regions and Broadmann areas (BA) as provided at the website http://www.unizh.ch/keyinst/NewLORETA/Software/Software.htm.

Statistical Analyses

The demographic data were analyzed using a *t*-test (e.g., age) or chi-square test (e.g., gender) when applicable. All 61 electrodes were grouped into 6 scalp regions for the statistical analyses. Details of the localization of electrodes and graph were described in our previous study (Kamarajan et al., 2005a). The grouping of electrodes into 6 scalp regions was based on the lobe-wise divisions of the cerebral cortex. Several previous studies have used this lobe-wise grouping (e.g., Cohen et al., 2002; de Bruin et al., 2004), which may help in interpreting the findings for the functional significance of different lobes of the cortex. Initially, the repeated measures analysis of variance (RMANOVA; full-factorial model) was performed on the mean P3 amplitudes by having regions and electrodes as within-subject variables and group (diagnosis) as a between-subject variable. Greenhouse–Geisser correction was carried out for the within-subject factors and interactions wherever applicable. Only 6 representative electrodes from each of the regions were taken into analysis as described previously (Kamarajan et al., 2005a). Having equal numbers of electrodes in each region makes the comparisons among regions more viable and meaningful, and this fits well with the RMANOVA design. The *p*-values were adjusted using Bonferroni correction for multiple comparisons during the region-wise statistical analysis of P3 amplitude. Then, a second stage of analysis was performed: the mean P3 amplitude values were compared between the control and alcoholic groups using a multivariate analysis of variance (MANOVA) for each of the regions separately by including all the electrodes of the specific region. Age and gender were treated as covariates in the RMANOVA and MANOVA models for 3 reasons: (1) there were significantly more male subjects in the alcoholic sample, (2) the alcoholic subjects were significantly older than the controls in the sample, and (3) age as a factor is known to have an effect on ERP parameters (Kamarajan et al., 2005a). The behavioral data (BIS scores) were analyzed using *t*-tests as well as MANOVA, in which both age and gender were treated as covariates. The association of P3 amplitudes with BIS scores was assessed by the Pearson 2-tailed correlation with the bivariate model.

RESULTS

Target VP3 Amplitudes Are Reduced in Alcoholic subjects

This study replicated previous data showing that alcoholic subjects had widespread reductions in visual P3 amplitudes during processing of the target stimuli. For example, the mean P3 amplitudes at the parietal electrode in the midline (Pz) were 18.43 ± 1.03 (SEM) μV in controls and 12.85 ± 0.83 (SEM) μV in alcoholic subjects, respectively ($p<0.0001$ by MANOVA); at the frontal electrode in the midline (Fz), P3 amplitudes were 13.62 ± 0.95 (SEM) μV in controls and 9.26 ± 0.89 (SEM) μV in alcoholic subjects ($p<0.001$), as shown in Fig. 1. The difference is statistically more pronounced in the posterior regions (e.g., $p<0.0001$ at the parietal electrode, Pz; $p<0.001$ at the frontal electrode, Fz; and $F=12.044$, $p=0.000018$ for the group-by-region 2-way interaction analysis by RMANOVA).

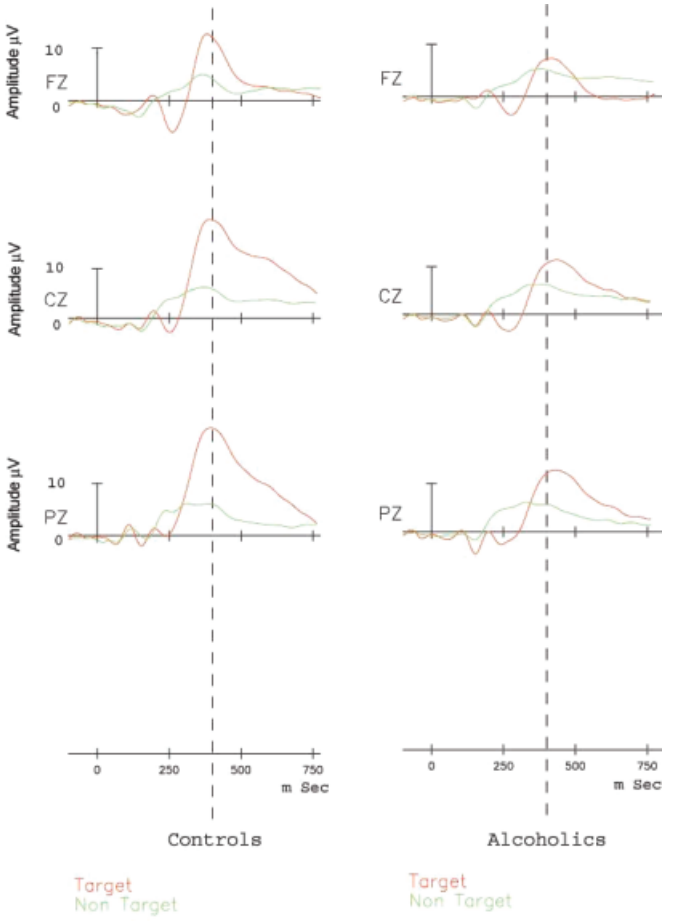

Fig. 1. Grand means of the event related potentials in control and alcoholic subjects at 3 representative (midline) electrodes, Fz, Cz, Pz. Note the lower P3 amplitude in alcoholic subjects in response to target visual stimuli (in red curves).

We also analyzed the VP3 amplitudes elicited by novel stimuli. Although the novel P3 amplitudes were reduced in alcoholic subjects, the difference was not statistically significant. For example, the mean P3 amplitudes at the parietal electrode in the midline (Pz) were 11.98 ± 0.76 (SEM) μV in controls and 10.16 ± 0.73 (SEM) μV in alcoholic subjects, respectively ($p=0.018$ by *t*-test; $p=0.285$ by MANOVA in which age was treated as a covariate); at the frontal electrode in the midline (Fz), P3 amplitudes were 9.95 ± 0.71 (SEM) μV in controls and 8.84 ± 0.88 (SEM) μV in alcoholic subjects ($p=0.323$ by *t*-test; $p=0.184$ by MANOVA).

Alcoholic Subjects Show Higher BIS Scores

The BIS scores between controls and subjects with alcohol dependence are shown in Fig. 2. Alcoholic subjects had significantly higher scores on all 3 subscores (nonplanning, motor impulsivity, cognitive impulsivity) as well as the

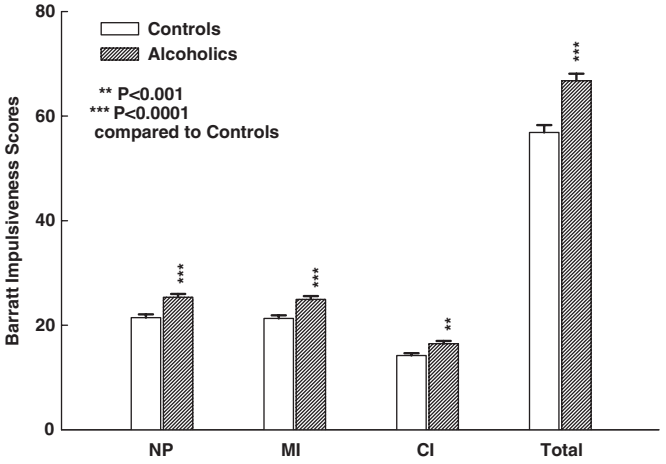

Fig. 2. Mean scores on Barratt Impulsiveness Scale in control and alcoholic subjects. Alcohol-dependent subjects show a significantly increased overall level of impulsivity trait, as well as for each of the subscales (NP, nonplanning score; MI, motor impulsiveness score; CI, cognitive impulsiveness score, or attentional impulsiveness).

total score of BIS ($p<0.0001$ by t-test; $p=0.004$ by MANOVA).

Correlations Between VP3 and Impulsivity

There were significant negative correlations between VP3 and the total BIS scores for all 115 subjects in this study (Fig. 3). These correlations varied topographically: they were statistically more prominent in the posterior/parietal region (Pz: $r=-0.274$, $p=0.003$; Cz: $r=-0.250$, $p=0.007$; Fz: $r=-0.148$, $p=0.115$) and at the left temporal lobe (T7: $r=-0.252$, $p=0.007$; T8: $r=-0.215$, $p=0.021$).

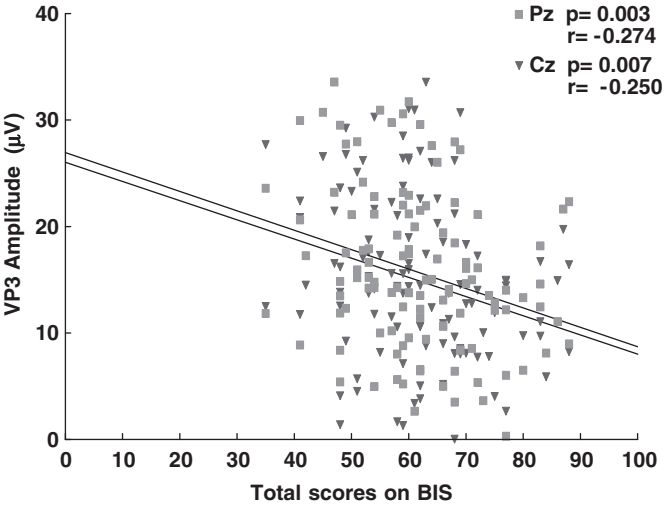

Fig. 3. Figure shows the linear correlation between VP3 amplitudes at Cz and Pz leads of all subjects and their respective total scores on Barratt Impulsiveness Scale. Significant negative correlations between VP3 and impulsivity were found. These correlations varied topographically, and were statistically more pronounced in the posterior region.

Functional Image (LORETA) Findings Demonstrate Reduced VP3 Activity in Both Alcoholic Subjects and Subjects With High Impulsivity in Similar Areas in the Frontal Lobe

The LORETA images comparing controls and alcoholic groups for target visual P3 of ERP are illustrated in Figs. 4A and 4B. Statistical analyses revealed that the alcoholic group manifested significant ($p<0.05$) reductions in brain activations in 35 adjacent voxels ($7\times7\times7$ mm), which involved 5 specific regions (BA 6, 8, 24, 32, 33) of bilateral brain exclusively in the frontal lobes, such as bilateral anterior cingulate, cingulate gyrus, medial frontal gyrus, and superior frontal gyrus (Table 2).

To further investigate the localization of sources of activity that may underlie impulsivity, we compared subjects with "high impulsivity," i.e. 30 subjects on the top quartile of distribution of total BIS scores regardless of diagnoses, and those with "low impulsivity," i.e., 33 subjects on the bottom quartile of the distribution of total BIS scores regardless of diagnoses, for target visual P3 of the ERP using LORETA images. Details of the composition of the subjects are shown in Table 3. Statistical analyses demonstrated that the high-impulsivity group manifested a significant ($p<0.05$) reduction in brain activations in 49 voxels ($7\times7\times7$ mm), which involved 5 specific regions (BA 6, 8, 24, 31, 32) of bilateral brain in the frontal lobes comprising cingulate gyrus, medial frontal gyrus, and superior frontal gyrus (Table 4). The regions are similar to those showing reduced activities in alcoholic subjects (Table 2), but appear to involve larger areas (49 vs 35 voxels) and are located more posterior and superior.

DISCUSSION

The present study demonstrated that alcoholic subjects showed increased impulsivity as evidenced by their significantly higher scores on the BIS. This study also replicated previous data showing that alcoholic subjects show widespread reductions in P3 amplitudes. Furthermore, there were significant negative correlations between total scores in BIS and visual P3 amplitude. Functional imaging of sources using LORETA showed a significant reduction in activation in both alcoholic subjects and subjects with high impulsivity in the bilateral frontal lobe areas, such as cingulate gyrus, medial frontal gyrus, and superior frontal gyrus.

P3 Deficits in Alcoholics and Its Implication for Impulsivity and Disinhibitory Disorders

Studies over the last few decades have replicated that the P3 (P300) amplitudes in response to task-relevant target stimuli (e.g., visual stimuli) are significantly lower in abstinent alcoholic subjects than controls. The P3 amplitude decrements are most prominent over the parietal regions, and do not recover with prolonged abstinence (e.g.,

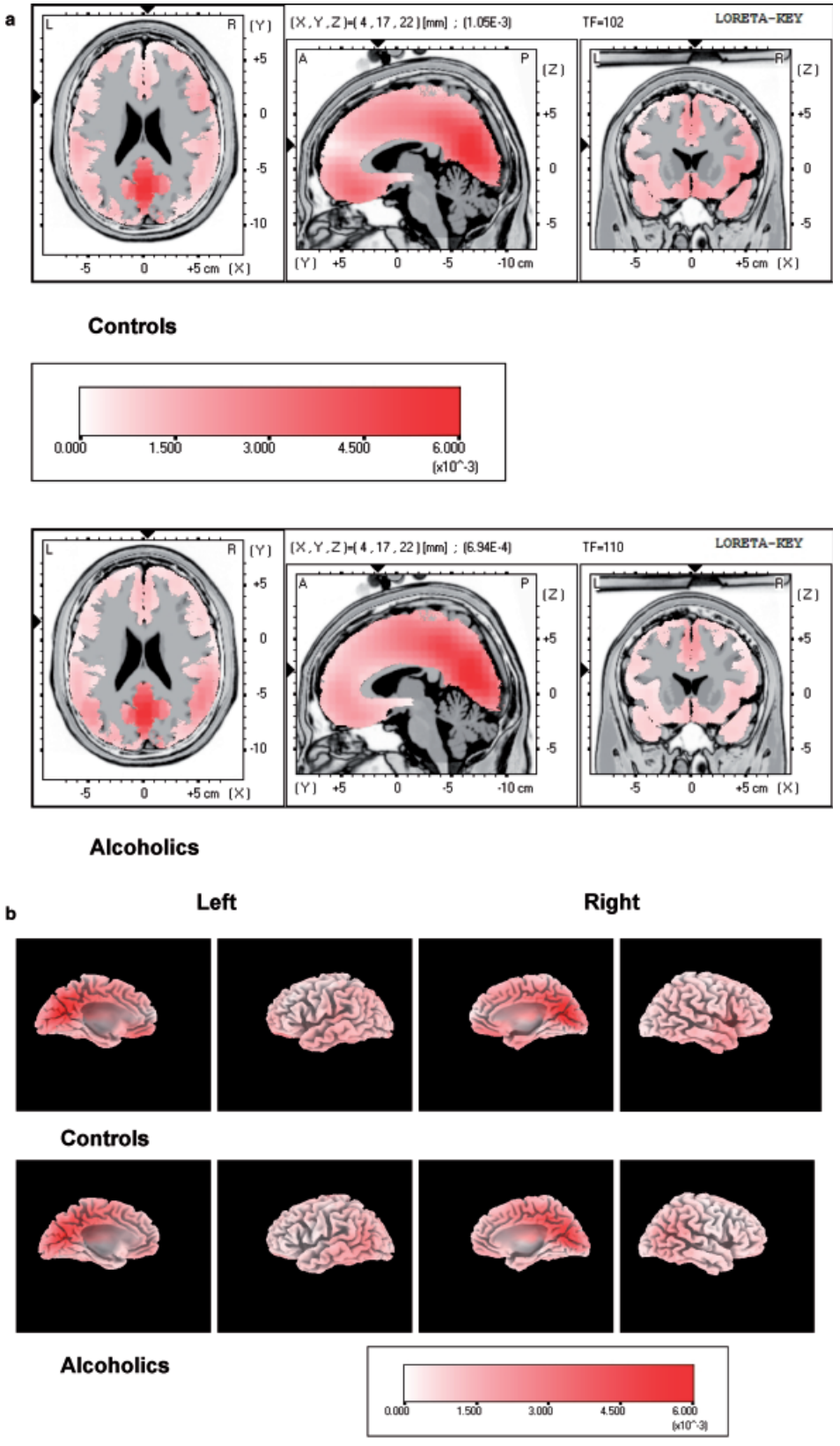

Fig. 4a. Panels show the 2-dimensional low-resolution brain electromagnetic tomography (LORETA) images of 3 orthogonal (axial, saggital, and coronal) views showing the current density (in amperes per square meter, A/m^2) during the peaks of the P3 component of event related potential (ERP) in controls (top) and alcoholic subjects (bottom). Alcoholic subjects showed significantly reduced activation during the processing of the target visual signal in the anterior cingulate, cingulate gyrus, medial, and superior frontal gyrus in LORETA.
b. Panels (upper: controls, lower: alcoholics) show the 3-dimensional LORETA images during the peaks of P3 component of ERP.

Table 2. Brain Areas Showing Statistical Differences ($p < 0.05$) in VP3 Activity Between Controls and Alcoholic Subjects According to Voxel-by-Voxel Analysis With Low-Resolution Brain Electromagnetic Tomography (LORETA)

t-Value	*x*-mm	*y*-mm	*z*-mm	Brodmann area	Anatomical locations
3.636	4	17	22	Brodmann area 33	Anterior cingulate
3.615	−3	17	22	Brodmann area 33	Anterior cingulate
3.5974	4	17	29	Brodmann area 24	Cingulate gyrus
3.5785	−3	17	29	Brodmann area 24	Cingulate gyrus
3.5576	4	10	43	Brodmann area 32	Cingulate gyrus
3.5387	11	10	43	Brodmann area 32	Cingulate gyrus
3.5351	−3	10	43	Brodmann area 32	Cingulate gyrus
3.5298	11	10	36	Brodmann area 32	Cingulate gyrus
3.5229	4	10	50	Brodmann area 6	Medial frontal gyrus
3.522	4	10	29	Brodmann area 33	Anterior cingulate
3.5168	−10	17	29	Brodmann area 32	Cingulate gyrus
3.5059	4	17	43	Brodmann area 32	Cingulate gyrus
3.5054	4	10	36	Brodmann area 24	Cingulate gyrus
3.5043	−3	10	50	Brodmann area 6	Medial frontal gyrus
3.4998	4	17	50	Brodmann area 8	Medial frontal gyrus
3.489	−3	10	29	Brodmann area 33	Anterior cingulate
3.483	−3	17	50	Brodmann area 8	Medial frontal gyrus
3.4772	11	17	36	Brodmann area 32	Cingulate gyrus
3.4761	−3	17	43	Brodmann area 32	Cingulate gyrus
3.4744	4	17	36	Brodmann area 32	Cingulate gyrus
3.4743	4	17	57	Brodmann area 8	Superior frontal gyrus
3.4585	−3	10	36	Brodmann area 24	Cingulate gyrus
3.4583	−3	17	57	Brodmann area 8	Superior frontal gyrus
3.4539	−3	17	36	Brodmann area 32	Cingulate gyrus
3.4226	−10	17	43	Brodmann area 32	Cingulate gyrus
3.4177	−10	10	36	Brodmann area 32	Cingulate gyrus
3.4169	4	3	29	Brodmann area 24	Cingulate gyrus
3.416	−10	17	36	Brodmann area 32	Cingulate gyrus
3.3982	4	10	57	Brodmann area 6	Superior frontal gyrus
3.382	4	3	36	Brodmann area 24	Cingulate gyrus
3.3801	11	3	43	Brodmann area 24	Cingulate gyrus
3.3794	−3	10	57	Brodmann area 6	Superior frontal gyrus
3.3781	−3	3	29	Brodmann area 24	Cingulate gyrus
3.371	4	3	43	Brodmann area 24	Cingulate gyrus
3.371	4	17	64	Brodmann area 6	Superior frontal gyrus

Coordinates are given in millimeters, and the origin is at the anterior commissure. For *x*, negative values represent left, positive values represent right. For *y*, negative values represent posterior, positive values represent anterior. For *z*, negative values represent inferior, positive values represent superior.

Porjesz et al., 1998, 2005). In addition, mean P3 amplitudes are also significantly lower in family members from densely affected alcoholic families, compared with mean amplitudes of control family for all comparisons, namely probands, affected and unaffected individuals, and offspring (e.g., Porjesz et al., 1998, 2005). Furthermore, recent genetic linkage analyses indicate that visual P3 amplitude is a biological phenotypic marker that has genetic underpinnings (Jones et al., 2004; Porjesz et al., 2005).

It has been proposed that P3 reflects attentional distribution and context updating processes of working memory, cognitive closure, and that it involves inhibitory processes in specific brain areas (Tomberg and Desmedt, 1998). Production of P3 is believed to be involved in inhibition of brain activities: the larger the P3 amplitude, the more the neurophysiological inhibition. Therefore, the low P3 amplitude in alcoholics is suggestive of a lack of inhibition, i.e., neurophysiological disinhibition. In the present study, the findings of increased impulsivity in alcoholic subjects and significant negative correlations between VP3 amplitudes and impulsivity provide novel evidence that links a basic neuro-electric endophenotypic marker to a multidimensional behavioral construct, impulsivity. To further substantiate our hypothesis that impulsivity indeed mediates the relation between alcoholism and the P3 amplitudes, we performed an additional MANOVA with a general linear model where the total BIS score was treated as a covariate. The results showed that the association between alcoholism and the reduced P3 amplitudes was no longer significant ($p = 0.564$ at Fz, $p = 0.431$ at Cz, and $p = 0.853$ at Pz), indicating that impulsivity indeed mediates the relationship between alcoholism and P3 amplitude. These data suggest that there is a common mechanism(s), e.g., genetic control, underlying the expression of a shared symptom, namely impulsivity, in a class of disinhibitory disorders. The results also provide evidence to support our hypothesis that the underlying dysfunctional neural and response inhibition is involved in a predisposition to alcoholism and other disinhibitory disorders as observed in the reduction in P3 amplitude not only in alcoholism, but in a spectrum of disinhibitory disorders, such as CD, ADHD, ODD, and ASPD (Begleiter and Porjesz, 1999; Kamarajan et al., 2005b; Porjesz et al., 2005).

Frontal Lobe Dysfunction in Alcoholic Subjects and Subjects With High Impulsivity

Frontal lobe pathology in alcoholism has been well documented at anatomical, physiological, and neuropsychological levels, as reviewed by Moselhy et al. (2001). Moderate neuronal loss in the frontal cortex and in the cingulate gyrus of alcoholic subjects has been reported (reviewed by Harper and Kril, 1994). Functional imaging studies using positron emission tomography (PET) report a decrease in glucose utilization, selectively affecting the bilateral medial frontal lobe such as anterior cingulate in alcoholic subjects (Gilman et al., 1996). Single photon

Table 3. Composition of the Subjects With "High Impulsivity" or "Low Impulsivity" in this Study

	Definition	Total score of BIS range	Number	Controls	Alcoholics
High impulsivity	Top quartile in total score of BIS of all subjects	69–88	$n = 30$	7 (23.3%)	23 (76.7%)
Low impulsivity	Bottom quartile in total score of BIS of all subjects	35–54	$n = 33$	27 (84.8%)	6 (18.2%)

BIS, Barratt Impulsiveness Scale.

Table 4. Summary of Brain Areas, 49 Bilateral Adjacent Voxels (7×7×7 mm), Showing Statistical Differences ($p<0.05$) in VP3 Activity Between Subjects With High Impulsivity and Those With Low Impulsivity to Voxel-by-Voxel Analysis With Low-Resolution Brain Electromagnetic Tomography (LORETA)

Brodmann area	Anatomical location
Brodmann area 32	Cingulate gyrus
Brodmann area 24	Cingulate gyrus
Brodmann area 6	Medial frontal gyrus
Brodmann area 8	Medial frontal gyrus
Brodmann area 6	Superior frontal gyrus
Brodmann area 8	Superior frontal gyrus

emission computerized tomography (SPECT) studies have shown a decrease in regional blood flow in the anterior cingulate and inferior/anterior frontal lobe (Gansler et al., 2000; O'Carroll et al., 1991). Furthermore, recent PET and functional magnetic resonance imaging (fMRI) studies demonstrated similar results of decreased activities in the frontal lobe in the high-risk offspring of alcoholic subjects (Rangaswamy et al., 2004). These findings strongly suggest that the frontal lobe and the circuitry connections to the limbic structures are vulnerable substrates in alcoholic subjects, even before the symptoms emerge, and it may be one of the indicators of a predisposition to developing alcoholism.

The impulsivity component of externalizing disorders has recently gained increasing attention for research. Imaging studies in individuals with high impulsivity, e.g. in borderline personality disorder, demonstrated similar findings of a decreased activation in the bilateral medial frontal lobes during response inhibition (Soloff et al., 2003). A recent report using diffusion tensor imaging indicated that reduced anterior corpus callosum white matter integrity is related to increased impulsivity in cocaine-dependent subjects (Moeller et al., 2005). However, there is no literature on functional brain mapping of impulsivity in alcoholism. In the present source localization study using LORETA, we demonstrated a strong frontal focus in both alcoholic subjects and subjects with high impulsivity. Voxel-by-voxel analyses revealed a great deal of similarity in the brain areas showing reduced activation between the alcoholic group and the high-impulsivity group: the voxels with significant difference ($p<0.05$) in both comparisons are located within the same Brodmann Areas (BA 6, 8, 24, 32) and 14 of the 35 voxels are identical. In addition, the LORETA results based on the trait, "high impulsivity" versus "low impulsivity" indicate greater differences than comparison of groups based on a clinical diagnosis, "alcoholic" versus "control." These findings all suggest that impulsivity may be one of the most important coexisting conditions that underlie the pathogenesis of alcoholism and perhaps other disinhibitory disorders. Neuroelectric measures, such as visual P3, which are sensitive to the underlying vulnerability to develop certain psychiatric disorders and are hence considered phenotypic markers, may more closely reflect the presence of these underlying coexisting conditions. These conditions are part of the integration of the clinical manifestations in the vast majority of alcoholic populations, and are likely genetically influenced. For molecular genetic studies of psychiatric illnesses, rather than studying the clinical endpoints, such as a dichotomous diagnosis, it is of more value to investigate the underlying quantitative biological measures of neurobiological dysfunction, e.g., visual P3 and BIS scores, in the genetic predispositions, as they reflect more proximal effects of such genes (Kendler et al., 2003; Porjesz et al., 2005).

CONCLUSIONS

This study demonstrates a reduced activation of sources in bilateral frontal lobe in both alcoholic individuals and individuals with higher impulsivity during processing of visual targets. Our data also provide evidence of a link between an index of neuronal disinhibition and a manifestation of impulsivity. The findings suggest that impulsivity may be an important factor that underlies the pathogenesis of alcohol dependence. Studies are underway in our laboratory to examine the relationship between impulsivity and ERP characteristics in offspring of alcoholic subjects, to determine whether this relationship antecedes the development of alcoholism and to identify genes associated with the underlying predisposition involved in disinhibitory disorders.

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