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Neurocognitive deficits in male alcoholics: An ERP/sLORETA analysis of the N2 component in an equal probability Go/NoGo task

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ABSTRACT

In alcoholism research, studies concerning time-locked electrophysiological aspects of response inhibition have concentrated mainly on the P3 component of the event-related potential (ERP). The objective of the present study was to investigate the N2 component of the ERP to elucidate possible brain dysfunction related to the motor response and its inhibition using a Go/NoGo task in alcoholics. The sample consisted of 78 abstinent alcoholic males and 58 healthy male controls. The N2 peak was compared across group and task conditions. Alcoholics showed significantly reduced N2 peak amplitudes compared to normal controls for Go as well as NoGo task conditions. Control subjects showed significantly larger NoGo than Go N2 amplitudes at frontal regions, whereas alcoholics did not show any differences between task conditions at frontal regions. Standardized low resolution electromagnetic tomography analysis (sLORETA) indicated that alcoholics had significantly lower current density at the source than control subjects for the NoGo condition at bilateral anterior prefrontal regions, whereas the differences between groups during the Go trials were not statistically significant. Furthermore, NoGo current density across both groups revealed significantly more activation in bilateral anterior cingulate cortical (ACC) areas, with the maximum activation in the right cingulate regions. However, the magnitude of this difference was much less in alcoholics compared to control subjects. These findings suggest that alcoholics may have deficits in effortful processing during the motor response and its inhibition, suggestive of possible frontal lobe dysfunction.

1. Introduction

Deficits in inhibitory control have consistently been reported in a variety of psychiatric disorders, such as substance use disorders, including alcohol use disorders (Bauer, 2001; Kaufman et al., 2003; Kouri et al., 1996), attention-deficit hyperactivity disorder (Brandeis et al., 2002; Frank et al., 1998; Pliszka et al., 2000; Rubia et al., 1998), antisocial personality disorder (ASPD) and conduct disorder (Bauer and Hesselbrock, 1999a, 1999b; Kiehl et al., 1999, 2000), obsessive compulsive disorder (OCD) and Tourette syndrome (Johannes et al., 2001, 2003; Schall et al., 1996), as well as in Schizophrenia (Fallgatter and Müller, 2001; Weisbrod et al., 2000).

The Go/NoGo task has been most widely used to assess response inhibition, in which an error of commission (defined as a false alarm response or a response made on a NoGo trial when it should have been withheld/suppressed) is considered to be an index reflecting a lack of adequate inhibition. The majority of studies have used a "reverse oddball" paradigm, where responses are "biased" towards the frequent "Go" trial in comparison to the rare "NoGo" (refrain response) trial, in order to establish "prepotency" of the "Go" response. Under these conditions, it is assumed that if an automatic "prepotent" (Go) response is suppressed (NoGo) successfully, this effortful suppression reflects successful response inhibition. Thus, measures associated with this effortful suppression may be regarded as correlates of response inhibition.

In electrophysiological research the majority of studies have used this "reverse oddball" paradigm and mainly investigated two time-locked (stimulus) components of the event-related potential (ERP): namely, N2 and P3. Traditionally, N2 and P3 amplitude differences have been suggested to be associated with inhibition of the prepotent response on NoGo trials (Eimer, 1993; Falkenstein et al., 1999; Jodo and Kayama, 1992). N2 and P3 latency effects have also been found, and taken to be critical indicators of active inhibitory processes for the Go/NoGo task, suggesting a pattern

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of sequential activation rather than altered activity level in key cortical structures that may mediate success in the task (see Roche et al., 2005). While the NoGo N2 has been associated with the subject's recognition of the need for inhibition (e.g., Kok, 1986), the NoGo P3 has been considered a more precise indicator of the effectiveness of motor response inhibition (Smith et al., 2007). While there is abundant literature available on the functional significance and clinical relevance of the Go/NoGo P3, there are relatively fewer studies that have evaluated the N2 component, especially in a clinical population. In the present study, we focus on studying the N2 component in more detail using a normal control sample and an alcoholic sample.

The "inhibitory" N2 is understood to tap response inhibition, particularly when prepotent response tendencies (Go responses) are present. The N2 peak is observed at frontal electrode sites about 200–350 ms post-stimulus, and its amplitude is greater on successful NoGo trials, when subjects withhold a learned response (Bokura et al., 2001; Eimer, 1993; Falkenstein et al., 1999; Jodo and Kayama, 1992; Lavric et al., 2004). However, robust frontal N2 peaks have been reported on "Go" trials as well (e.g., Davis et al., 2003; Nieuwenhuis et al., 2003). Studies evaluating trial-type frequency have reported enhanced N2 amplitude for stimuli occurring at low frequency, irrespective of whether the stimuli were associated with generating (Go) or suppressing (NoGo) a response (e.g., Nieuwenhuis et al., 2003). These authors have argued that their results are consistent with the view that the Go/NoGo N2 represents an index of response conflict monitoring on correct trials that arises from competition between execution and inhibition of a single response (Botvinick et al., 2001; Braver et al., 2001; Nieuwenhuis et al., 2003). Although few studies have interpreted the NoGo N2 "effect" as inhibitory in an equal probability paradigm (Jodo and Kayama, 1992; Lavric et al., 2004), there are a growing number of studies suggesting that it can be better explained by the conflict monitoring hypothesis (see Botvinick et al., 2001; Donkers and van Boxtel, 2004; Nieuwenhuis et al., 2003). Stimulus modality and difficulty level of discriminating between competing stimuli also have their influence on Go/NoGo N2 modulation and have been interpreted by the conflict monitoring hypothesis (Nieuwenhuis et al., 2004). Further, in a study that used response priming and evaluation of the lateralized readiness potential (LRP) to assess the effects of the motor response related contribution to brain electrical potentials, Bruin et al. (2001) concluded that P3, but not N2, is associated with response inhibition, and speculated that the traditional Go/NoGo N2 "effect" should be explained in terms of response activation instead of response inhibition. Additionally, in a review of studies that examined N2, Tucker et al. (2003) have interpreted that N2 might best be considered as an "evaluative negativity", whose psychological purpose is effortful attention and self-monitoring.

Bokura et al. (2001) have implicated the origin of the N2 to the right lateral orbitofrontal and cingulate cortex brain areas. More recent studies on source analysis of the N2 indicate a cortical generator in the frontal midline area, consistent with the position of the dorsal ACC (e.g., Nieuwenhuis et al., 2004; van Veen and Carter, 2002). The ACC is shown to be associated with self-monitoring and directed attention in conditions that require response control or conflict resolution (e.g., Botvinick et al., 1999; Luu and Pederson, 2004; for review see Botvinick et al., 2004; Ridderinkhof et al., 2004a).

Although there is debate over whether the NoGo N2 reflects inhibition of the prepotent response (e.g., Falkenstein et al., 1999; Jodo and Kayama, 1992; Kok, 1986; Kopp et al., 1996) or detection of response conflict (Botvinick et al., 2001; Nieuwenhuis et al., 2003; van Veen and Carter, 2002; Yeung and Cohen, 2006; for review see Botvinick et al., 2004; Ridderinkhof et al., 2004a), there appears to be consensus that the N2 is a marker of a general control process that operates in a variety of situations (Nieuwenhuis et al., 2004).

Taken together, on the basis of the current literature, it appears that two areas in the frontal cortex are identified as being responsible for the generation of N2 while performing a Go/NoGo task: namely, medial frontal regions including ACC, and right inferior prefrontal regions. The activation of the medial frontal region, specifically ACC, is said to be involved in conflict detection, whereas the activations of the right inferior prefrontal region is said to reflect response inhibition. The traditionally reported NoGo N2 "effect" as being due to inhibition (e.g., Jodo and Kayama, 1992) gets support from findings of substantial right dorsal and ventral prefrontal activity for NoGo trials (e.g., Bokura et al., 2001; Buchsbaum et al., 2005), whereas there is growing evidence in support of the conflict monitoring explanation (e.g., Nieuwenhuis et al., 2003) from findings of possible cortical neural generators of N2 involving ACC regions (Nieuwenhuis et al., 2004; van Veen and Carter, 2002). A related interpretation of N2 supports the notion of selecting to execute or inhibit an appropriate response (Simmonds et al., 2008), whereas the NoGo P3 "effect" is considered more likely to reflect inhibition proper (e.g., Smith et al., 2007). Deficits caused by dysfunction of any of these brain areas would eventually lead to deficits in the resultant response inhibition.

ERP studies of long term alcoholics as well as on individuals at risk for developing alcoholism, have consistently reported reduced P3 amplitude in various task paradigms (Begleiter et al., 1984; Cohen et al., 2002; Ehlers et al., 2001, 2007; Hada et al., 2000; Hill et al., 1999a; Hill and Shen, 2002; Hill et al., 1999b; Porjesz and Begleiter, 1987, 1990, 1991; Prabhu et al., 2001; Rodriguez Holguin et al., 1999; Suresh et al., 2003; for a meta-analysis see Polich et al., 1994; Porjesz et al., 2005). In Go/NoGo tasks, the anteriorly distributed NoGo P3 potentials have markedly reduced amplitudes in alcoholic subjects as well as in high-risk individuals, indicating impaired inhibitory control in these individuals (Cohen et al., 1997a, 1997b; Kamarajan et al., 2005a, 2005b; Saunders et al., 2008).

However, the findings on N2 related abnormalities have been equivocal. Realmuto et al. (1993) have reported reduced N2 amplitudes in alcoholics on an auditory oddball task. Similarly, Cristini et al. (2003) have reported reduced auditory oddball N200 in alcoholics and Go/NoGo differences between alcoholics and controls. Reduced N2 amplitude has been associated with ADHD in children on a stop-signal task (Pliszka et al., 2000) and N2 amplitude was found to be significantly lower in impulsive-violent offenders than in matched controls on a cued Go/NoGo task (Chen et al., 2005, 2008), suggesting difficulties with inhibition of prepotent behavior. Porjesz et al. (1987) have reported longer N2 latency in alcoholics in a visual discrimination oddball task. Conversely, Ridderinkhof et al. (2002) reported that the effect of alcohol leads to a substantial reduction in error-related negativity (ERN) amplitude while performing a version of the flanker task, but does not affect N2 amplitude. Recently, Crego et al. (2009) reported larger N2 amplitudes for young binge drinkers in a visual working memory task and interpreted it as a result of higher attentional efforts in this group. Similar findings of increased N2 amplitude in alcoholics have also been reported (Olbrich et al., 2000, 2002). Swick and Turken (2002) reported that a patient with a rare focal lesion of left ACC exhibited substantially reduced ERN amplitude after incorrect responses on a version of the Stroop paradigm, but greatly increased N450 amplitude on correct conflict trials. Hogan et al. (2006) reported diminished response-locked correct-response negativity (CRN) and ERN in patients with frontal white matter lesions whereas stimulus-locked ERP components (N2 and P3) were not significantly affected by the presence of lesions. Using a computational simulation model, Yeung and Cohen (2006) have replicated Swick and Turken's findings, and suggested that the

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ERN and N2 are sensitive to different aspects of task processing, where lesion-induced attentional deficits led to impaired task processing (i.e., reduced ERN amplitude) while also causing increased processing of irrelevant stimulus information (i.e., increased N2 amplitude). Thus, findings are equivocal, and there is a dearth of studies evaluating the N2 component using a Go/NoGo task in alcoholics.

Over the last decade, various hypotheses have been advanced concerning the cognitive functions affected by chronic alcoholism. This study attempts to further identify the pattern of executive function impairment in chronic alcoholism, shedding light on possible differences between specific functions related to the frontal lobe, with a focus on the source localization of the current density of ERP in the time-range of N2 component in three-dimensional space within the brain. By comparing the magnitude, spatial and temporal characteristics of the N2 component in alcoholic and control subjects in a Go/NoGo task, this study attempts to elucidate the specific neurocognitive abnormalities in alcoholics. A better understanding of underlying neurocognitive abnormalities and its possible causes/precursors would lead to better intervention strategies in dealing with a complex disorder such as alcoholism.

Due to the difficulty in interpreting the role of inhibition in ERP studies that are designed to establish "prepotency" of the Go response to enhance inhibitory efforts (namely weighted with more Go than NoGo trials), the present study was designed to remove this bias by having an equal number of Go and NoGo trials. It was reasoned that the absence of this bias (confound) would make the interpretation of the NoGo N2 "effects" more discernible. Therefore, the aim of the present study was to evaluate the N2 differences between alcoholic and normal control subjects as well as between task conditions using an equal probability Go/NoGo task. Further, an attempt was made to localize the sources of the current density occurring in the time-range of the N2 component in three-dimensional space within the brain using standardized low resolution electromagnetic tomography analysis (sLORETA). With this sLORETA technique we aimed to determine group differences as well as differential characteristics of this current density between Go and NoGo in alcoholics and controls.

2. Methods

2.1. Subjects

A total of 78 right-handed abstinent alcoholic males and 58 healthy right-handed male controls who met the criteria for inclusion were recruited. Initial screening was performed over the telephone for all participants. Control subjects were recruited through newspaper advertisements and did not have any personal and/or family history of major medical, psychiatric, or substance-related disorders. They were instructed to abstain from alcohol and other substances with CNS effects for at least five days prior to the recordings and assessments. The alcoholic subjects (Alcohol Dependence as per DSM-IV criteria) were recruited from treatment centers for alcohol dependence in and around New York City. Before testing, they had been detoxified in a 30-day treatment program and were not in withdrawal state. The Bard/Porjesz Adult Alcoholism Battery (BAAB; cited from Kamarajan et al., 2005a), a semi-structured clinical assessment schedule, was used to obtain the clinical data related to alcohol dependence and alcohol-related medical problems. Alcoholic subjects who had a family history of psychiatric disorders in their first degree relatives, as well as those with severe cognitive deficits based on their score (<21) on the mini mental state examination (MMSE; (Folstein et al., 1975)) were excluded from the study. Subjects who were found to be positive (for their recent drug use) on the urine screen and Breathalyzer test as well as those with a history of hallucinogen abuse (e.g., LSD) were excluded from the study to avoid the possible interaction of drugs with the EEG profile. However, given the nature of the disorder, subjects with a history of other substance use and/or ASPD as co-existing conditions and with a past history of CD, ADHD, and oppositional defiant disorder (ODD) were included in the alcoholic group. Only subjects who had a minimum of 20 successful trials for the Go as well as the NoGo trials were included. For both groups, subjects with hearing or visual impairment, liver disease, or head injury were also excluded. Experimental procedures and ethical guidelines were in accordance with approval from the institutional review board (IRB). Alcohol and other drug use information for the period of six months prior to detoxification for the alcoholic group is shown in Table 1.

Table 1
Alcohol and drug use profile of alcoholic subjects for last six months before detoxification.

	N	Mean	SD
Alcohol: Days/month	78	22.69	7.65
Alcohol: Drinks/day	78	10.32	5.70
Tobacco: Days/month	65	24.29	9.25
Tobacco: Times/day	65	14.59	7.16
Cocaine: times in last six months	36	65.50	67.24
Marijuana: times in last six months	21	48.52	87.35
Barbiturates: times in last six months	4	33.25	38.66
Opiates: times in last six months	3	1.67	1.16

SD = Standard Deviation

2.2. Task and procedure

Each subject was presented with four types of visual stimuli consisting of white isosceles triangles pointing in either the up, down, right, or left direction (see Fig. 1). The stimuli were presented for 100 ms at the center of a computer screen against a dark background and subtended a visual angle of approximately 1°. The minimum response time was set at 100 ms from stimulus onset so that any faster responses would be considered premature, and would not be counted.

The experiment consisted of a practice phase and an experimental phase. The practice phase consisted of 20 stimuli, 5 of each type, while the experimental phase consisted of 100 stimuli, 25 of each type. Subjects were instructed to press a key with the index finger of their right hand whenever a white triangle pointed either up or down (Go stimulus) and refrain from pressing the key whenever the triangle pointed towards the right or left (NoGo stimulus). If subjects responded correctly to the Go stimulus by pressing the key within 100–500 ms of stimulus onset, or successfully refrained from pressing the key to the NoGo stimulus within 1200 ms of stimulus onset, a dollar sign ($) appeared on the screen for 200 ms at 1200 ms after stimulus onset. However, if subjects responded incorrectly, i.e., either pressed the key for a NoGo stimulus within 1200 ms from stimulus onset or did not press the key hard enough and/or within 100–500 ms of stimulus onset for a Go stimulus, a cross sign (X) appeared on the screen for 200 ms at 1200 ms after stimulus onset. Subjects were instructed that speed and accuracy were equally important for making a correct response. The probabilities of occurrence of Go and NoGo stimuli were equal (50/50), and the order of stimulus presentation was randomized. The inter-trial interval was 2400 ms.

The EEG was recorded during the experimental phase. The subjects were informed that each correct response would earn a reward. The subjects received a predetermined fixed amount at the end of the experiment without deductions for errors, although they were not informed of this while performing the task.

2.3. Data acquisition and analysis

2.3.1. Data recording

The subjects were seated in a comfortable, reclining chair located in a dimly lit sound-attenuated RF-shielded room (IAC, Industrial Acoustics, The Bronx, NY). EEG activity was recorded on Neuroscan systems (Versions 4.1, 4.2, and 4.3; (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, Society, 1991; Fig. 2). The electrodes were nose-referenced and subjects were grounded using an electrode placed on the forehead (frontal midline, 2 cm above the nasion). Eye movements were monitored with two electrodes placed on supraorbital regions of the left eye for vertical and two electrodes placed on external canthi of both eyes for horizontal movements. Electrode impedance was maintained below 5 kΩ throughout the recording. The continuous EEG signals were recorded at sampling rates of 256, 500, and 512 Hz depending on the amplifier version, with a band pass filter set at 0.02–100 Hz and were amplified 10,000 times using a set of amplifiers (SynAmps2, Neuroscan, TX).

2.3.2. Data reduction and analysis

All recordings were digitally re-sampled offline at 256 samples per second. In order to extract the N2 component that would be independent of the effects of the initial ascending wave of the P3 and other slow deflections, a band-pass filter of 2–16 Hz was applied to the waveform (Fig. 3, Section 3). The EEG segments were divided into epochs of 1625 ms (187.5 ms pre- and 1437.5 ms post-stimulus, similar to Kamarajan et al., 2005a). The EEG activity of 125 ms prior to stimulus onset served as baseline. All epochs exceeding ±75 μV amplitude were automatically excluded from further processing. The eye blink, eye movement, and other artifacts were visually inspected and subsequently removed manually. Each subject had a minimum of 20 good (i.e., artifact-free) trials in each

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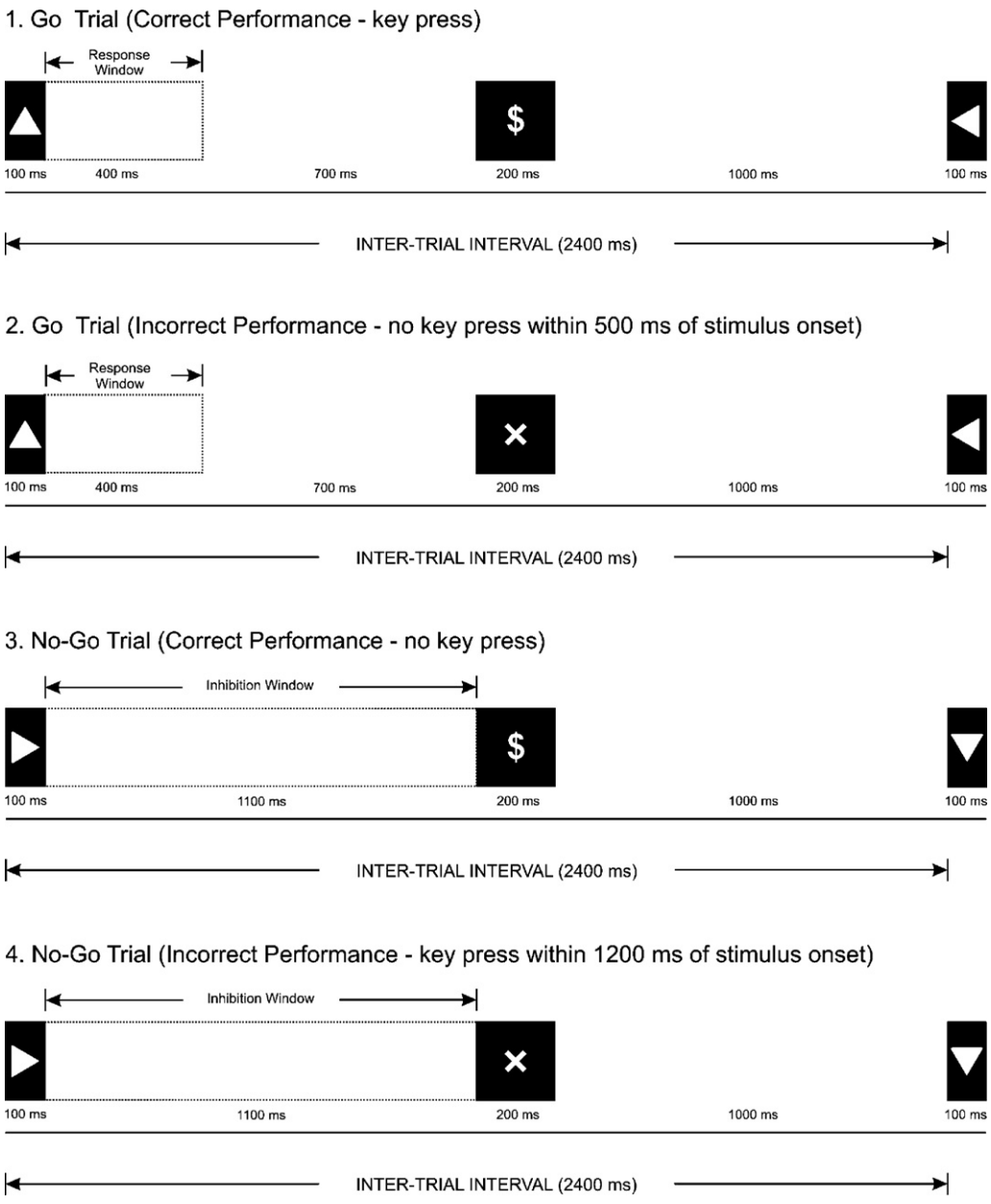

Fig. 1. Illustration of Go/NoGo task, showing correct (1, 3) and incorrect (2, 4) response.

condition (Go/NoGo). Averages were computed for each condition and subject separately.

The N2 peak amplitude was measured as the voltage at the largest negative going peak in the latency window of 180–330 ms after stimulus onset. Amplitude and latency measures were calculated using a semi-automatic peak-picking program. The time-window was manually selected for each condition and subject while the peak within the window was automatically detected, measured, and tabulated for all channels. This peak-picking method was similar to the procedure used in other studies (e.g., Kamarajan et al., 2005a) from our laboratory. The amplitude and latency values of N2 peaks for each subject were obtained for each condition and were used in statistical analyses. The grand averages for control and alcoholic groups were computed and plotted (Fig. 3a).

2.4. Statistical analysis

For statistical comparisons, the electrode sites were grouped into six scalp regions, and six representative electrodes from each region were included in the analysis; all six electrodes were included from temporal regions (Fig. 2). This is similar to the method used by Kamarajan et al. (2005a). The obtained amplitude and latency values of N2 peaks were analyzed using a linear mixed-effect model of SAS Proc Mixed Procedure (SAS 9.1, SAS Institute Inc., NC, USA). The mixed-effects model included group (controls, alcoholics), condition (Go/NoGo), region (frontal, central, parietal, occipital, left temporal, and right temporal), electrode (6 representative electrode sites nested within each region) age, age^2 and their interactions as fixed effects, where condition (Go/NoGo) and electrode coordinates (x, y, z) were treated as repeated measures. To determine direct (Kronecker) product structures based on distance between electrodes (i.e., x, y, z), a spatial anisotropic exponential (EXPA) matrix was used to model within subject covariance structure of the data. A scatter plot of the N2 peak amplitude and latency values with age showed a curvilinear trend, which was consistent with the observations of previous studies (Amenedo and Diaz, 1998; Czigler et al., 1997; Pekkonen et al., 1996; van der Stelt et al., 1998). Therefore, to model the linear and quadratic relationship, both age and age^2 were included as fixed factors. A backward stepwise method was used to remove nonsignificant effects. Further exploration of main and interaction effects were performed using Wald's tests (Kenward and Roger, 1997) for pairwise comparisons and the significance levels were adjusted with Bonferroni correction for multiple comparisons. The demographic and behavioral data (i.e., age, education, MMSE score, reaction time, and error responses) were analyzed using t-tests.

2.5. Standardized low resolution tomography analysis (sLORETA)

The sLORETA is a functional imaging method based on certain electrophysiological and neuroanatomical constraints (Pascual-Marqui et al., 2002). The

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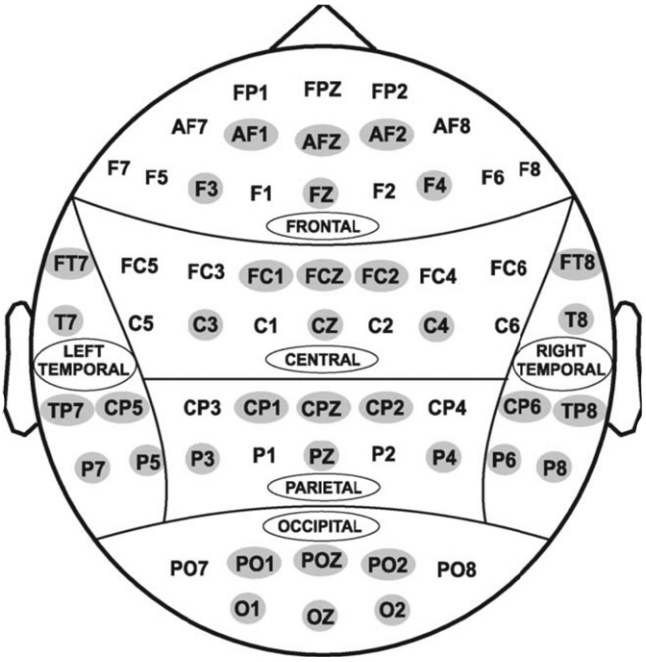

Fig. 2. 61 Electrode locations are illustrated and shown according to regional groupings. Electrodes selected for statistical analysis from each group included are highlighted.

cortex has been modeled as a collection of volume elements (voxels) in the digitized Montreal Neurological Institute (MNI) coordinates corrected to the Talairach coordinates. The sLORETA algorithm solves the inverse problem by assuming related orientations and strengths of neighboring neuronal sources (represented by adjacent voxels). It 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 comprehensive experimental validation, independent validation of the localization properties of sLORETA has been replicated by Sekihara et al. (2005), Greenblatt et al. (2005), and Wagner et al. (2004). The version of sLORETA employed here was made available at http://www.unizh.ch/keyinst/NewLORETA/LORETA01.htm

sLORETA analysis was done and images were constructed to answer two questions, i.e., "When" and "Where". The "When" question attempts to locate the differences temporally and the "Where" question attempts to localize those differences in the three dimensional space within the brain. The electrode coordinates were created from the 61 electrode locations using the original recording montage. A transformation matrix was created using the electrode coordinates. The averaged waveforms (for all 416 time-samples, i.e., 1625 ms) were converted and saved into ASCII values for each condition and subject.

To answer the "When" question, paired and independent t-tests were computed for all time-samples (3.91 ms each per sample) of the epoch to determine differences between conditions and groups, respectively. The average reference was used and 5000 random permutations (i.e., bootstrapping) were performed. The levels of significance were corrected for multiple comparisons and false positives (Holmes et al., 1996; Nichols and Holmes, 2002). For each comparison, statistically significant (<0.05, two-tailed) blocks of five time-samples within the time-range of the N2 component were selected for further analysis. Out of the five, the third time-sample in the block had the highest significance. By selecting only five instead of all time-samples those were statistically significant in the N2 time-range, this analysis was made more conservative.

sLORETA values for these time-samples were computed for each condition and subject separately using ASCII values, electrode coordinates, and the transformation matrix. To answer the "Where" question, obtained sLORETA values were subjected to paired and independent tests to find out the differences between conditions and groups, respectively. For each comparison, one single test (Log of ratio of averages) was calculated for all five time-samples for each analysis with 5000 random permutations (i.e., bootstrapping) and levels of significance were corrected for multiple comparisons and false positives. The resultant values were then plotted and evaluated for the level of significances. The maximum differences between conditions and groups at respective MNI coordinates and Brodmann areas (BA) are reported.

3. Results

3.1. Demographic, cognitive, and behavioral performance data

Comparisons of demographic details, behavioral and cognitive performances are shown in Table 2. There were significant effects for age, $t\ (134) = -24.83$, $p < 0.0001$, errors made on the Go trials $t\ (134) = -2.14$, $p = 0.034$, and reaction time $t\ (134) = -3.44$, $p = 0.0007$, indicating alcoholics were

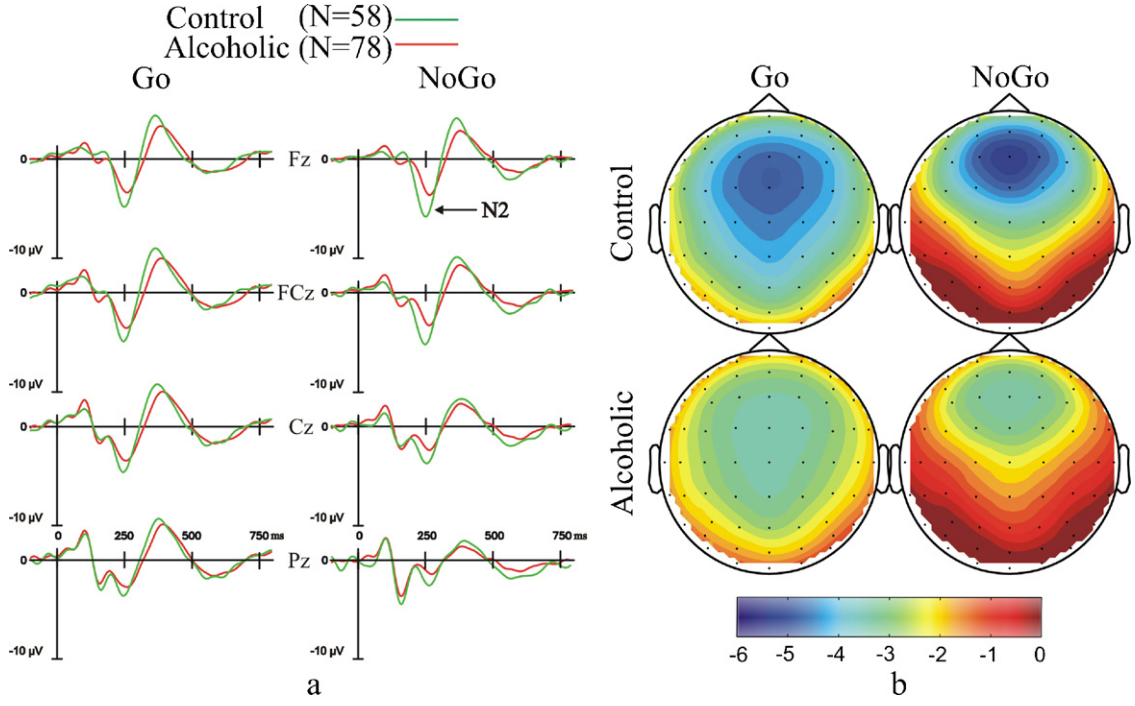

Fig. 3. (a) Grand averaged ERP waveform of N2 components in control (green line) and alcoholic (red line) subjects during Go/NoGo task. Time is shown in milliseconds where stimulus onset was at 0 with a 125 ms prestimulus baseline, and (3) 2-D maps of N2 peak surface potentials (μV) for the Go (alcoholic = 254 ms, controls = 242 ms) and NoGo (alcoholic = 262 ms, controls = 246 ms) task conditions in control and alcoholic subjects.

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Table 2
Comparison of demographic, cognitive, and behavioral performance data.

Variable	Controls ($N = 58$)		Alcoholics ($N = 78$)		t value df = 134
	Mean	SE	Mean	SE	
Age (in years)	21.14	0.33	40.71	0.72	−24.83***
Education (in years)	12.41	0.24	11.81	0.29	1.53
Go error[a] (in %)	5.04	0.96	8.42	1.16	−2.14*
NoGo error[a] (in %)	4.56	0.62	3.20	0.42	1.89
Total error[a] (in %)	4.79	0.56	5.81	0.58	−1.23
Reaction time	324.40	4.36	346.72	4.56	−3.44**

SE = Standard error, df = Degrees of freedom
[a] Absolute values.
* Significance <0.05.
** Significance <0.01.
*** Significance <0.0001.

Table 3
Main and interaction effects for the N2 amplitude and latency.

Effect	df	N2 amplitude	N2 latency
		F (Sig.)	F (Sig.)
Group	1, 132	40.46****	3.53
Condition (Go/NoGo)	1, 134	609.22****	239.01****
Region	5, 670	197.95****	5.66****
Group × Condition	1, 134	21.59****	3.22
Group × Region	5, 670	8.49****	4.36***
Condition × Region	5, 669	97.47****	4.16**
Group × Condition × Region	5, 669	2.16	0.88
Age	1, 132	0.03	21.94****
Age^2	1, 132	0.84	24.10****

df = Degrees of freedom
**** Significance <0.0001.
*** Significance <0.001.
** Significance <0.01.

older[3], made more errors, and manifested longer reaction time than control subjects. No significant effects were found for education, NoGo errors, and total number of errors committed.

3.2. Event-related potential data

The Go/NoGo paradigm used in the present study elicited a robust N2 component. An average of 37 Go trials were used to calculate the averaged waveform in both groups whereas for the alcoholic group, 36 (mean) NoGo trials and for the control group, 34 (mean) NoGo trials were used for the purpose of averaging. Fig. 3a shows the ERP averaged waveforms, indicating the N2 component at approximately 250–260 ms for Go and NoGo conditions for the two groups separately. Four midline sites, namely, Fz, FCz, Cz, and Pz are shown. As depicted in the figure, alcoholic and control groups showed maximum amplitude of Go N2 at the FCz location in the frontocentral region (Fig. 3a) whereas maximum amplitude of NoGo N2 was observed at the Fz site in the frontal region for both groups. Alcoholics were found to have lower amplitudes of N2 than controls in both Go and NoGo conditions at all electrode sites.

Fig. 3b illustrates grand averaged peak N2 amplitude surface potential maps (two-dimensional topographical distributions) for the Go and NoGo conditions. The topographical distribution showed larger surface potentials for the NoGo N2 in the frontal region and for the Go N2 in the frontocentral region in both groups. Further, the relative intensity of N2 potentials was observed to be reduced in alcoholics on both conditions.

Statistical analysis yielded significant main and interaction effects (Table 3). For the N2 amplitude, all main and interaction effects except age, age^2, and three-way interactions were found to be highly significant (Table 3). Post hoc analyses of the significant interaction effects revealed significant pair wise differences. For the Group × Condition interaction effects, alcoholics showed reduced N2 amplitudes compared to controls for both Go (t (134) = −5.22, $p < 0.0001$) and NoGo (t (134) = −7.21, $p < 0.0001$) conditions, whereas Go N2 amplitudes were larger than NoGo N2 in both alcoholic (t (134) = −22.49, $p < 0.0001$) and control (t (134) = −13.21, $p < 0.0001$) subjects, regardless of regions. Further, alcoholics showed reduced N2 amplitudes compared to controls at all six regions (F (5, 670) = 8.49, $p < 0.0001$; Group × Region), regardless of task conditions. For the Condition × Region interaction effects, the largest NoGo N2 amplitude was found at frontal regions, whereas Go N2 amplitudes were found to be largest at central regions. Further, NoGo N2 amplitudes were found to be significantly larger than Go N2 at frontal regions (t (669) = 6.56, $p < 0.0001$), whereas Go N2 amplitudes were significantly larger at all posterior regions. The central region manifested larger NoGo N2 amplitudes than Go N2; however, this difference was not statistically significant. Although the three-way interaction (Group × Condition × Region) effects were not found to be statistically significant at the <0.05 level, the F ratio value (F (5, 669) = 2.16, $p = 0.057$) was close to the significance level. In keeping with this observation, coupled with the regional specificity of the directional nature of the condition differences as well as the number of factors involved (2 × 2 × 6), post hoc exploration of the pair wise comparison was performed for the Group × Condition × Region as well. On Wald's test, the significant differences between Go and NoGo N2 amplitudes were observed at all except central regions in control and at all except frontal regions in alcoholic subjects (Table 4). The direction of the differences revealed that at the frontal regions, the NoGo N2 had larger amplitudes than the Go N2, whereas at all other regions, the Go N2 had larger amplitudes than the NoGo in both groups. However, only control subjects accounted for the significantly larger NoGo N2 amplitude than Go N2 at frontal regions (Table 4).

Fig. 4 illustrates the least-square mean values of N2 peak amplitudes for both groups. As seen in the figure, controls produced larger mean peak N2 amplitudes than alcoholics at all regions. Further,

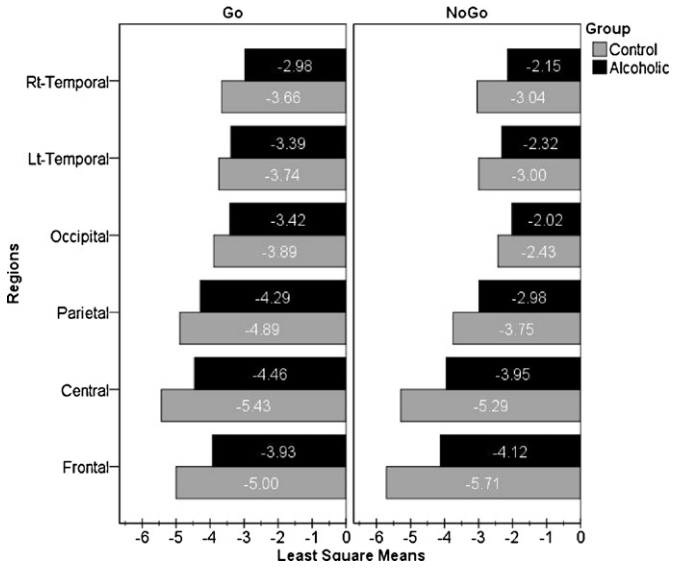

Fig. 4. Least square means of N2 peak amplitudes for control and alcoholic subjects on the Go/NoGo task.

[3] The age confound necessitated a separate identical statistical analysis on a smaller age-matched sample. The results were replicated. Detailed results can be provided upon request.

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Table 4
Least-squares mean differences of N2 amplitude by subtracting NoGo from Go condition.

Regions	Control ($N = 58$)		Alcoholic ($N = 78$)	
	Difference (SE)	Wald's t value (Sig.)	Difference (SE)	Wald's t value (Sig.)
Frontal	0.72 (0.10)	6.91****	0.18 (0.09)	2.02
Central	−0.15 (0.10)	−1.42	−0.51 (0.09)	−5.69****
Parietal	−1.14 (0.11)	−10.90****	−1.31 (0.09)	−14.57****
Occipital	−1.46 (0.11)	−13.90****	−1.40 (0.09)	−15.59****
Lt-Temporal	−0.74 (0.10)	−7.06****	−1.08 (0.09)	−11.98****
Rt-Temporal	−0.62 (0.10)	−5.91****	−0.84 (0.09)	−9.30****

Degrees of freedom (1, 669), SE = Standard error
**** With Bonferroni adjustment Sig. <0.0001.

NoGo N2 mean amplitudes were largest at the frontal regions and Go N2 mean amplitudes were largest at the central regions in both groups. The mean NoGo N2 amplitude at frontal regions was the largest ($m = -5.71$) in controls whereas mean Go N2 amplitude at central region was the largest ($m = -4.46$) in alcoholic subjects.

Both groups differed significantly on Go and NoGo N2 amplitudes, where alcoholics had reduced N2 amplitudes compared to normal controls. These differences were observed at all except occipital and left temporal regions for the NoGo N2, whereas for the Go N2, these differences were observed at frontal and central regions (Table 5). The NoGo N2 accounted for the maximum difference between groups and was observed at frontal regions followed by central regions (Table 5). Age did not have significant effects on the outcome. This indicates that the observed main and interaction effects and differences are comparable across age (Table 3).

For the N2 latency, all main effects except Group, as well as all interaction effects except Group × Condition and Group × Condition × Region (three way), were found to be significant (Table 3). The evaluation of least-squares means revealed a shorter latency of Go compared to NoGo N2 at all regions. However, age had a significant effect on the outcome (Table 3). This indicates that observed main and interaction effects and differences are not comparable across age for the N2 latencies and hence were not discussed further.

3.3. Standardized low resolution tomography analysis (sLORETA)

The statistical differences between conditions and between groups for current density at the source are shown in Table 6. The cortical areas that show significant differences at <0.05 level are shown in yellow color in Figs. 5 and 6. As shown in Table 6, the difference between current densities of task conditions was found to be significant in both groups with activation during NoGo task being higher. This difference was maximum at BA 32 of the right frontal cortex (*Log of ratio of averages* = 0.996, $p < 0.01$) in the control group whereas it was maximum at BA 24 of the right limbic lobe (*Log of ratio of averages* = 0.996, $p < 0.01$) in the alcoholic group. However, groups differed significantly only on the NoGo current density with a maximum difference (*Log of ratio of averages* = 1.611, $p < 0.01$) at BA 10 of the left anterior prefrontal cortex (Table 6).

Fig. 5 demonstrates statistical differences between task conditions for the control (a and b) and alcoholic (c and d) groups. As seen in the figure, while both groups show maximum significant differential current densities in ACC regions of the right medial frontal cortex, the differences were much larger and widespread bilaterally in the control subjects. Additionally, control subjects also showed more NoGo current density than Go at the left inferior temporal regions.

Fig. 6 illustrates the statistical differences between groups for the NoGo (a and b) task condition. As seen in the figure, the NoGo N2 of control subjects shows more differential current density bilaterally in anterior prefrontal cortical regions. The Go condition did not yield statistically significant differences between groups and therefore is not illustrated.

4. Discussion

The results of the present study yielded several important findings. Regarding differences between groups: (1) the alcoholics showed reduced Go as well as NoGo N2 amplitudes compared to the normal controls, and this reduction was statistically significant at the frontal and central regions, (2) in the sLORETA analysis, although alcoholics showed lower current density at the source than control subjects on Go as well as NoGo tasks, this difference was statistically significant only for NoGo N2 in the bilateral anterior prefrontal cortices with a maximum difference in the left superior prefrontal region (BA 10).

Regarding differences between task conditions: (1) the NoGo N2 amplitude was significantly larger compared to the Go N2 at frontal regions only in the control group, (2) the NoGo N2 amplitudes at the frontal regions and the Go N2 amplitudes at the central regions were largest in both groups. Further, the NoGo trials in the control and the Go trials in the alcoholic subjects elicited the largest N2 amplitude across regions, (3) in the sLORETA analysis, difference plots revealed maximum significant activation (current density at the source) in both groups during the NoGo task at right cingulate cortical regions in the time-range of N2. However, in the control group, the activation was much higher and bilaterally widespread than in the alcoholic group.

4.1. NoGo N2 "effects"

The equal probability Go/NoGo task design was aimed at controlling the possible 'bias' towards the "Go" response and other possible sources of variability as mentioned in Sections 1 and 2. The NoGo N2 "effect" was observed in both groups with the task used in the present study. Normal subjects showed significantly larger NoGo N2 amplitude compared to Go at frontal regions (Table 4, Fig. 3a and b) that was further evident in the current density findings in the N2 time-range with sLORETA (Table 6, Fig. 5a and b). These findings of the traditional NoGo N2 "effects" conform to previous studies that have used either the "reverse oddball" paradigm (e.g., Falkenstein et al., 1999; Kopp et al., 1996) or the "equal probability" paradigm (e.g., Lavric et al., 2004) or both (e.g., Jodo and Kayama, 1992; Nieuwenhuis et al., 2003). Although the alcoholic group did not show any significantly larger NoGo N2 amplitude than Go N2 at frontal regions (Table 4), when peak N2 amplitude values were taken as dependent measures, the sLORETA difference maps suggest significantly higher current density at the sources for NoGo in the time-range of N2 (Table 6, Fig. 5c and d). However, this differential activation was observed to be much smaller in the alcoholic subjects compared to the control subjects.

As reviewed in Section 1, the published literature on frontocentral NoGo N2 (N2 effect) suggests a few possibilities of its functional

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Table 5
Least-squares mean differences of N2 amplitude by subtracting alcoholic from control subjects.

Regions	Go		NoGo	
	Difference (SE)	Wald's *t* value (Sig.)	Difference (SE)	Wald's *t* value (Sig.)
Frontal	−1.06 (0.18)	−5.78****	−1.60 (0.18)	−8.72****
Central	−0.97 (0.18)	−5.30****	−1.34 (0.18)	−7.28****
Parietal	−0.61 (0.18)	−3.30	−0.77 (0.18)	−4.20**
Occipital	−0.46 (0.18)	−2.53	−0.41 (0.18)	−2.22
Lt-Temporal	−0.35 (0.18)	−1.88	−0.68 (0.18)	−3.73
Rt-Temporal	−0.68 (0.18)	−3.69	−0.89 (0.18)	−4.87***

Degrees of freedom (1, 669), SE = Standard error
**** With Bonferroni adjustment Sig. <0.0001.
*** With Bonferroni adjustment Sig. <0.001.
** With Bonferroni adjustment Sig. <0.01.

significance. The first considers NoGo N2 as reflecting inhibitory processing (e.g., Falkenstein et al., 1999; Jodo and Kayama, 1992; Kopp et al., 1996; Lavric et al., 2004). A second views N2 as an index of response conflict monitoring rather than inhibition (Botvinick et al., 2001, 2004; Donkers and van Boxtel, 2004; Jonkman, 2006; Kopp et al., 2006; Nieuwenhuis et al., 2003, 2004; Ridderinkhof et al., 2004a, 2004b). A third view suggests that N2 reflects neither inhibition nor conflict (e.g., Bruin et al., 2001; Smith et al., 2007).

The findings of the present study tend to support the view of N2 as reflecting inhibitory processing, at least in part, in light of implemented task design, which was aimed at eliminating the inherent "bias" towards the Go stimulus. With no "prepotency" established (equal probability task) and no apparent task demand "bias" (emphases on equal importance given to speed and accuracy as well as feedback on all possible outcomes) for the Go stimulus, according to the conflict monitoring view, the task would predictably show no difference between Go and NoGo N2 amplitudes. In contrast, in the present study, NoGo N2 amplitude was significantly larger in the frontal areas, confirming studies that have interpreted this effect in terms of response inhibition (Eimer, 1993; Falkenstein et al., 1999; Jodo and Kayama, 1992).

It has been argued that NoGo "effects" may be confounded with motor potentials (Kok, 1986; Kopp et al., 1996). Kopp et al. (1996) found significant positive deflections in their lateralized readiness potentials from NoGo trials along with the N2 modulation based on response priming. More recently, Smid et al. (2000) also found N2 modulation in a simple Go/NoGo task and a positive deflection in LRP from the NoGo trials of the simple conditions. The Go/NoGo task in the present study was not designed to control for the confounds that may be presented by the motor potentials. However, based on the findings of no LRP activity in response to the specific Go priming cues in the cue-target interval, Bruin et al. (2001) concluded that "*there is no differential preparation of the primary motor cortex on the basis of the cue information about the potential response hand*" (p. 1668). In the same study, the N2 component in NoGo trials was not modulated as a function of response priming. The authors have speculated that a modulation of the N2 inhibition component in NoGo trials is dependent on the occurrence of LRP activity. Nevertheless, on the basis of their findings that there was a difference in the N2 amplitudes between Go and NoGo trials, the authors have suggested that the presence of LRP activity in NoGo trials is not a requisite to replicate the traditional Go/NoGo effect. Therefore, their results suggest that a modulation in the N2 is due to activation in response to Go stimuli, rather than a modulation due to inhibition in response to NoGo stimuli.

Observations and findings in the present study can also be explained with the conflict monitoring hypothesis as well. More anteriorization was observed for the NoGo N2 with the largest mean amplitude in the frontal regions, which is consistent with previous studies. However, the present study also found the largest mean amplitude of Go N2 in the central regions (second largest was observed in the frontal regions for controls), rather than the traditionally reported parietal (posterior) regions (Figs. 3a and 4). Together, these observations suggest increased activity in anterior and central regions during both task conditions, which may be reflecting the detection of conflict between two competing response tendencies. Therefore, the findings of the present study, i.e., both NoGo and Go N2s having largest amplitudes in anterior and central regions, respectively, suggest involvement of an anterior executive conflict monitoring system when a single motor response was to be executed or withheld. Support for the conflict monitoring view gets further strengthened by the sLORETA finding of significantly larger NoGo differential current density in the N2 time-range at the ACC regions in both groups, which have strongly been suggested to be involved in conflict monitoring and effortful processing (Bekker et al., 2005; Botvinick et al., 2004; Ridderinkhof et al., 2004a, 2004b) rather than inhibition, which have more often been associated with the activation of dorsolateral prefrontal cortex (DLPFC), inferior prefrontal cortex (IFC), or orbitofrontal cortex (OFC; Simmonds et al., 2008, see for a review Aron et al., 2004).

4.2. The N2 in alcoholics

In the group comparison of N2 peak amplitudes, control subjects were found to have larger N2 peak amplitudes than alcoholics for both task conditions. For the Go N2, this difference was statistically significant at the frontal and central regions, whereas for the NoGo N2, it was significant at the frontal, central, parietal, and right-temporal regions (Table 5). However, in the sLORETA findings it was observed that although controls showed larger current

Table 6
Comparison of Go and NoGo tasks as well as control and alcoholic subjects in sLORETA.

Difference	Log of ratio of averages (Sig.)	MNI coordinates (*x*, *y*, *z*)	Brodmann area	Lobe
Control (NoGo–Go)	0.996**	(10, 10, 40)	32	CG in frontal lobe
Alcoholic (NoGo–Go)	0.638*	(10, 15, 30)	24	CG in limbic lobe
NoGo (Ctl-Alc)	1.611**	(−15, 60, 25)	10	SFG in frontal lobe
Go (Ctl-Alc)	1.419	(5, 55, 30)	9	SFG in frontal lobe

MNI = Montreal Neurological Institute, CG = Cingulate gyrus, SFG = Superior frontal gyrus.
* Sig. <0.05.
** Sig. <0.01.

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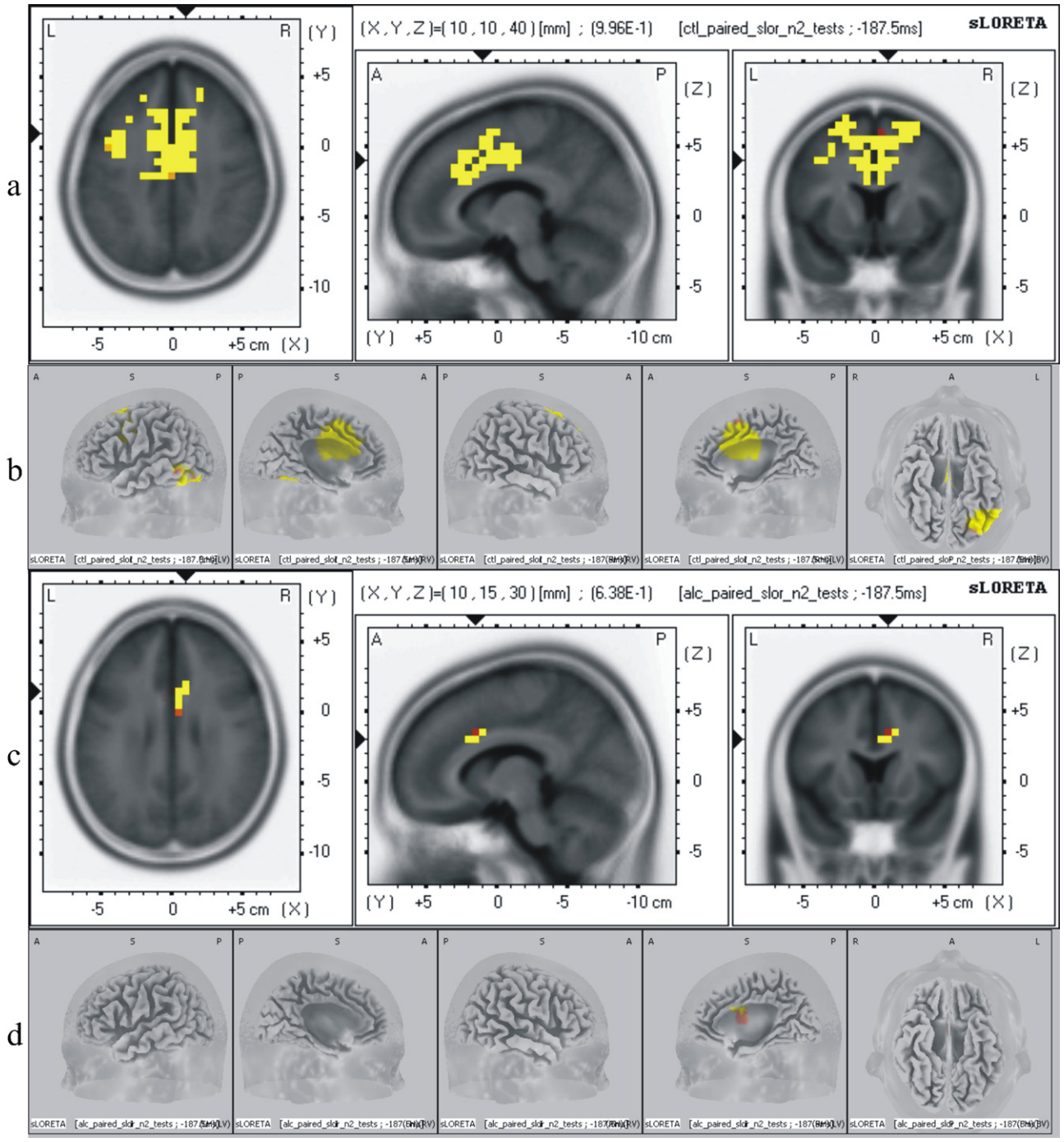

Fig. 5. The sLORETA images showing statistical differences (Log of ratio of averages) between Go and NoGo task conditions for control (a and b) and alcoholic (c and d) subjects in the N2 time-range.

densities at the source compared to alcoholics on both Go and NoGo trials in the N2 time-range, this difference was statistically significant only for the NoGo trials in the bilateral anterior prefrontal regions, with a maximum difference at the Brodmann area 10 of the left hemisphere (Table 6, Fig. 6a and b). Therefore, these findings suggest that in general, alcoholics show reduced N2 amplitudes and current density at the source compared to control subjects, and this reduction is more pronounced for NoGo N2 amplitudes and current density in the anterior prefrontal cortical regions that are suggested to be involved in "cognitive branching" (see for a review Koechlin and Hyafil, 2007) or act as a "supervisory attentional gateways" (SAG; Burgess et al., 2007b; see for a review Burgess et al., 2007a).

Chronic alcoholism has been linked to a wide range of structural and functional abnormalities in frontal lobes (for review, see Moselhy et al., 2001). Several studies have reported neuropsychological and frontal executive function deficits in alcohol dependent individuals (Acker, 1985; Beatty et al., 1996; Jones and Parsons, 1972; Jones, 1971; Nixon and Bowlby, 1996; Ratti et al., 2002; Sullivan et al., 1993, 2002; Tarter, 1973; Wilkinson and Poulos, 1987). Neuroimaging studies have reported that the executive function deficits of alcohol dependent individuals may be associated with decreased frontal glucose metabolism (Adams et al., 1993; Gansler et al., 2000; Wang et al., 1993) and regional cerebral blood flow in frontal lobes of alcoholics (Gansler et al., 2000; Nicolas

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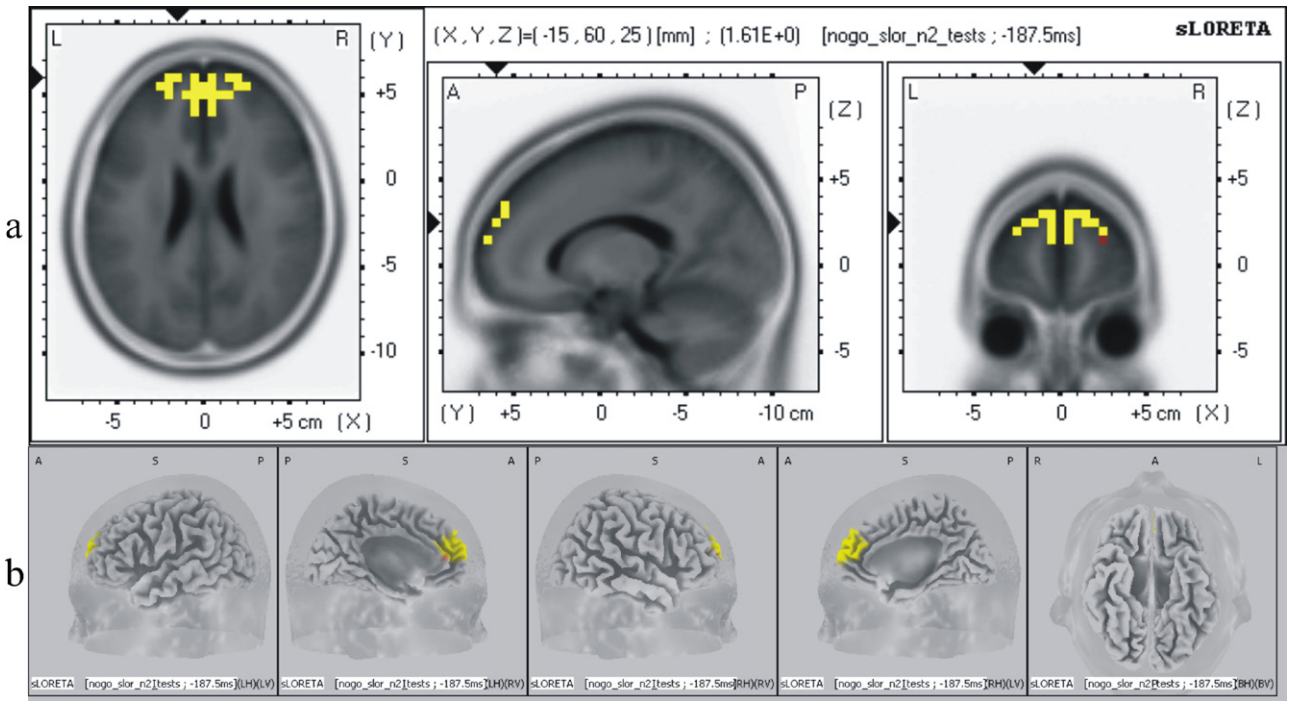

Fig. 6. The sLORETA images showing statistical differences (Log of ratio of averages) between groups for NoGo trials in the N2 time-range.

et al., 1993; O'Carroll et al., 1991). Furthermore, postmortem and neuroradiological studies have revealed cortical atrophy and reduction in grey matter and white matter in the frontal lobes of alcoholics (Harper et al., 1985; Pfefferbaum et al., 1997).

Evidence from electrophysiological studies has shown frontal lobe abnormalities in alcoholics (Begleiter et al., 1980; Hada et al., 2000; Kamarajan et al., 2004, 2005a; Michael et al., 1993; Padmanabhapillai et al., 2006; Porjesz and Begleiter, 1987; Rodriguez Holguin et al., 1999). Curtin and Fairchild (2003) have reported an intact parietal P3 and stimulus evaluation during alcohol intoxication but reduction in frontal components of ERP that index evaluative and regulative cognitive control processes. In a simulation study, Yeung and Cohen (2006) have interpreted reduced N2 after alcohol consumption as showing deficient processing of irrelevant stimulus information and indicated possible frontal lobe involvement. The findings of the present study are consistent with the notion of frontal lobe dysfunction observed in alcoholics. The differences between groups were statistically significant at N2 peak amplitude for Go as well as NoGo tasks at frontal and central regions, with NoGo N2 differences being larger than Go N2 differences. Therefore, the findings indicate that chronic alcoholism may be related to dysfunctional frontal activation, and this deficiency is pronounced when effortful suppression of a motor response is required. These findings are evident in the head plots of surface potentials (frontocentral focus of N2 with weaker strength in alcoholics; Fig. 3b) and the sLORETA statistical difference brain maps of current density (less differential activation in the brain areas of alcoholics, Fig. 5c and d). Furthermore, sLORETA findings suggest that the difference in current density between groups is significant only for the NoGo condition in the N2 time range. This finding, along with the observation of Go as well as NoGo N2 being anterior-central and significantly reduced amplitude in alcoholics compared to normal controls, suggests dysfunctional frontal activation in alcoholics.

As discussed earlier, the explanation of N2 as reflecting conflict monitoring processes and effortful processing is supported by the findings of the present study. The findings of higher NoGo N2 amplitude at frontal regions and current density in the ACC in the absence of a bias towards Go response may also reflect inhibition, at least in part. These observations are consistent with the views expressed in a recent editorial review (Falkenstein, 2006). Furthermore, findings of group difference on sLORETA (Fig. 6a and b) in the present study suggest that the reduction of current density at the source in the time range of NoGo N2 in alcoholics may reflect deficits in "cognitive branching" (Koechlin and Hyafil, 2007) or in SAG (Burgess et al., 2007a). However, this interpretation is speculative at best since the task was not designed to assess anterior prefrontal cortical functions. Studies are needed with tasks that specifically assess functions related to the anterior prefrontal cortex involving alcoholic samples to test this hypothesis.

Most importantly, although strong efforts were made to evaluate the effect of age differences between groups statistically, the major limitation of the present study is the significant age difference between groups. In order to counter this limitation, an identical statistical analysis (using mixed-linear model) was performed on a smaller age-matched sample (15 subjects in each group). The results of the present study were replicated. More studies are required with larger age-matched samples to further evaluate these findings. Nevertheless, the findings of the present study shed light on functional aspects of NoGo N2 and indicates possible deficits in alcoholics. The present study was conducted on male samples that may pose a limitation to the generalization of the findings. Gender differences in the characteristics of ERP waveforms have often warranted separate studies in the alcoholism literature. A proper sampling based on gender was not possible due to lower availability of female subjects who meet the inclusion criteria of the present study. More studies are required with representation of both genders and larger samples to evaluate these findings and extend generalizability.

In conclusion, on the basis of the findings of the present study in a clinical population of male alcoholics following detoxification, it is suggested that the N2 in an equal probability Go/NoGo task may reflect conflict monitoring and effortful processing, and/or inhibition, at least in part. The results further indicate that alcoholics manifest deficient cognitive processing mechanisms, as evidenced by reduced N2 amplitude in general, and this reduction is more

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pronounced during effortful suppression of a motor response, in particular. The weaker NoGo N2 in surface potentials coupled with less activation of medial frontal cortex, mainly in the ACC and left superior frontal cortex (BA 10) as suggested by sLORETA findings in alcoholics, is suggestive of reduced functioning of these areas that participate in cognitive control. The deficits in these functions may lead to the resultant deficits in inhibition that may be reflected in impulsive behaviors.

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