Electrophysiological Evidence of Memory Impairment in Alcoholic Patients

Xiao Lei Zhang, Henri Begleiter, Bernice Porjesz, and Ann Litke

In a series of event-related potential (ERP) studies, we have consistently demonstrated an ERP component correlate of visual short-term memory. There have been frequent reports on the deficits of information encoding, retention, and retrieval in chronic alcoholics. In the present study, we investigated that the ERP mnemonic effects could be influenced by long-term alcohol abuse. ERP data were recorded from 48 controls and 77 alcoholics while the subjects performed a modified delayed matching to sample paradigm using a series of object pictures as stimuli. The alcoholics completed the task with more errors and longer response times than the controls. The major differences in the evoked potentials between the two groups are found at the temporo-occipital and frontal regions in the sample and nonmatching trials, and mostly prominent in the right hemisphere. The current study indicates that the ERP technique can be a useful tool to index short-term memory. The ERP mnemonic effect difference between the two groups may be a reflection of a working memory deficit caused by long-term alcohol abuse. Our data also suggest right hemisphere dysfunction in alcoholics, with deficits in information encoding. © *1997 Society of Biological Psychiatry*

Key Words: Event-related potential, visual working memory potential, alcoholism, memory

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Introduction

The deleterious effects of alcohol on memory are widely recognized (for review, see Oscar-Berman 1990; Riege 1987). In fact, the effects of alcohol on memory range from temporary short-term memory loss seen in social drinkers, to blackouts observed in some alcoholics, to a permanent inability to form memories apparent after years of chronic alcohol abuse (Wilkinson and Poulos 1987). The studies on the memory loss of alcoholics are mainly based on neuropsychological tests; for example, a common diagnostic criterion for identification of the amnesic Wernicke–Korsakoff patients is a 20–30 disparity between IQ and the memory quotient (MQ) on the Wechsler Memory Scale (Aggleton et al 1988; Squire et al 1988); however, there is evidence that the Wernicke-Korsakoff neuropathology occurs with a much higher incidence in the alcohol-dependent population than is suggested by the clinical diagnosis (Harper 1979; Torvik et al 1982). Some patients with Wernicke-Korsakoff syndrome show little or no apparent impairment, others show mild to moderate global deficits, and some may show considerable recovery after severe episodes (Bowden 1990). For the above reasons, the assessment of amnesic Wernicke-Korsakoff patients with the use of neuropsychological tests is not

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totally satisfactory to detect the presence of Wernicke-Korsakoff neuropathology.

Several paradigms designed to model human amnesia in monkeys have been successfully applied to the studies of human amnesia, particularly in alcoholic patients and in the Wernicke-Korsakoff patients (Aggleton et al 1988; Kessler et al 1986; Bowden et al 1992). One test that has received particular attention is delayed nonmatching (or matching) to sample, a test of recognition memory (Mishkin 1982; Zola-Morgan and Squire 1985). Generally, this test consists of different trials, each trial involving two stimuli. First, a novel (sample) stimulus A (picture A) is shown briefly on a screen; after some delay, the test stimulus that contains picture A and B is presented to the subject. The subject is asked to make his choice of whether the picture matches (or does not match) the sample picture. To mimic the animal version, the subjects are never told the matching rule, but undergo reward training to learn the rule. The acquisition of the matching rule would also be taken into account when the test is applied in the amnesic population. This test is performed poorly by human amnesic subjects both in the nonmatching version (Oscar-Berman and Bonner 1989; Squire et al 1988) and in the matching version; however, Aggleton et al (1988) suggested that the matching version was better suited to human subjects' natural preference for the familiar object. These results bear clear similarities to those obtained from experimental amnesic syndromes in monkeys. Experimental studies suggest that only monkeys with specific lesions perform poorly on this test. Bilateral lesions of the medial thalamic structures, including the mediodorsal thalamic nucleus, or bilateral lesions of the temporal region, including the hippocampal formation, entorhinal cortex, parahippocampal gyrus, and amygdala, produce deficits on delayed matching to sample test (Mishkin 1982; Zola-Morgan and Squire 1985). Since Wernicke-Korsakoff patients are known to suffer damage to diencephalic, medial temporal structures, and cortical atrophy, it is reasonable to assume that these patients perform poorly on this type of test.

Event-related potential (ERP) techniques permit the observation of electrophysiological manifestations of cognitive activity and thereby offer a unique approach for assessing brain function. Recently, we have modified the delayed matching to sample test and incorporated it with ERP techniques to identify an ERP component correlate of visual memory (Begleiter et al 1993). We observed that the component of the ERP to matching stimuli, occurring between 170 and 240 msec, was significantly smaller than the component of the ERP to nonmatching stimuli. This component is generally located in the occipitotemporal region. Both the spatial and temporal characteristics of this component are in keeping with single cell studies in monkeys (Mikami and Kubota 1980; Miller et al 1991). We named this component the visual memory potential (VMP) because it indexes properties related to visual memory. With the modified matching to sample paradigm, several experiments on working memory have been carried out using nonsense lines (Begleiter et al 1993), faces and face scrambles (Hertz et al 1994), familiar faces and unfamiliar faces (Begleiter et al 1995), and concrete object pictures (Zhang et al 1995) as stimuli. Though these experiments placed different emphasis on working memory in the visual system, all of them generated the VMP with almost the same peak latencies and consistently over the occipitotemporal region, where the neural mechanisms of the medial and inferior temporal (TE) cortices play an important role in the linkage between vision and memory. This linkage role of TE cortices gets strong support from animal experiments. A number of investigators have explored the role of TE neurons by studying monkeys trained to perform delayed matching to sample tasks. Generally, the studies of temporal neurons during performance of working memory tasks have found modulation of responses when a current stimulus matched an item in memory. The memory of the sample stimulus affected not only the responses to matching stimuli but also those to nonmatching stimuli, i.e., the more similar a nonmatching stimulus to the sample, the more the response was suppressed (Baylis and Rolls 1987; Miller et al 1991; Riches et al 1991). Moreover, the waveforms of most neurons were significantly modulated by both the pattern and the context of the stimulus presentation (Eskandar et al 1992; Vogels and Orban 1994). These results suggest that the role of temporal neurons in visual memory tasks is to compare the internal representations of current visual images with the internal representations of recalled images. So the human VMP in the occipitotemporal region, in fact, reflects the functional integrity of visual memory systems in the brain; specifically, it represents overlapping activity emanating from neural generators to higher cortical integrative centers in the brain (Porjesz and Begleiter 1993).

Given the specificity of the delayed matching to sample test and characteristic of ERP techniques, it is of interest to examine the VMP in nonamnesic alcoholic patients. Much of the memory literature focuses on Wernicke-Korsakoff patients, often to the exclusion of seemingly nonamnesic alcoholic patients. Thus, the deficits in ERP components and/or poor performance on the animal memory tests by subjects who are not clinically amnesic and who show no neurological signs of Wernicke-Korsakoff syndrome may nevertheless provide some objective evidence of changes in brain function that is at least responsible for visual memory.

Because human memorization can frequently employ

verbal cues, many measures of human recognition memory have used highly verbal stimuli. The significance of this feature is suggested by the reports that some amnesics may perform differently on recognition tasks using abstract rather than representational or verbal stimuli (Starr and Phillips 1970). In the current experiment, we selected a set of object pictures with definite verbal labels as stimuli with the following considerations. Picture naming, reading, and categorizing have been widely used in cognitive psychology to explore human cognitive functions, since their chronometric analysis elucidates cognitive structures and processes (Glaser 1992). The technique of double stimulation such as the paradigm of priming with pictures, which is frequently used to tap working memory in cognitive psychology, has also been extensively employed to elicit cognitive ERPs (Barrett and Rugg 1990; Holcomb and McPherson 1994; Nigam et al 1992; Posner 1993; Pratarelli 1994). Moreover, in the reading and naming tasks, pictures are more effective as primes and are more primable as targets (Glaser 1992).

The aims of our study were to further investigate cognitive impairments in nonamnesic alcoholic patients. We wanted to test whether the VMP could be elicited from these patients, and if yes, whether there was any difference between alcoholic patients and controls in VMP. There have been frequent reports on the deficits of information encoding, retention, and retrieval in alcoholic patients. In the current study, we also analyzed and compared the ERP to sample stimuli in the two groups, since the ERP in sample trials mainly reflects the processes of information encoding and retention compared to the ERP in test trials. While comparing the amplitude of VMP between the two groups, we used 61 electrodes and scalp current density to assess the VMP topographic distribution in the two groups.

Methods

Subjects

The control group in the current experiment consisted of 48 male subjects recruited from among hospital employees. The screening procedure for control subjects required that each potential subject fill out a questionnaire regarding alcohol and drug use, as well as medical and psychiatric histories of himself as well as family members. All the control subjects were right-handed and had no personal and no family history of alcohol and/or drug abuse, or any history of neurological or psychiatric disease. All subjects had normal vision or corrected normal vision. The mean age of the control group was 25.81 years old (SD = 3.38) ranging from 19.4 to 38.6 years of age. The alcoholic group consisted of 77 male alcoholics (mean age: 35.83 ± 5.33 years; range: 22.3–49.8 years). All individuals were assessed by clinical psychiatrists. The initial diagnosis of alcohol abuse or dependence was made by the intake psychiatrist of the Addictive Disease Hospital in Brooklyn according to DSM-III criteria, and the confirming diagnosis was made in our laboratory by one of the authors (HB or BP) using instruments developed by the COGA (Collaborative Studies on the Genetics of Alcoholism) group, which includes the SSAGA (Semi-Structured Assessment for the Genetics of Alcoholism) and the standard Folstein MMSE (Mini Mental Status Examination). All alcoholic patients were hospitalized for a minimum period of 30 days on a closed ward before participating in our ERP studies. Thus, all alcoholic patients were fully detoxified and had no alcohol available for that period of hospitalization. Most alcoholics had been drinking heavily for a minimum of 15 years, and started drinking at approximately 20 years of age. Alcoholic individuals were excluded from the study if they had a history of overt liver (e.g., cirrhosis), metabolic (e.g., diabetes), vascular (e.g., coronary artery disease), or neurological (e.g., head injury, encephalitis, epilepsy) disorders. Patients with a history of drug dependence or of major psychiatric illness (e.g., schizophrenia, bipolar affective disorder) predating the onset of alcoholism were also screened from the study. The MMSE results indicated that no individual manifested serious memory deficits. The alcoholics were significantly older than the controls [$t(118.9) = 12.64$, $p < .0001$].

Experimental Design

STIMULI AND STIMULUS PRESENTATION. The stimuli were composed of 90 pictures of objects that were chosen from the 1980 Snodgrass and Vanderwart picture set (Snodgrass and Vanderwart 1980). All the pictures we selected represented different concrete objects and were easily named. These stimuli were presented on a white background at the center of a computer monitor and were approximately 5–10 cm in height and 5–10 cm in width, thus subtending a visual angle of 0.05–0.1°. To elicit the ERP, a modified delayed matching to sample task was used in which two picture stimuli appeared in succession with a 1.6-sec fixed interstimulus interval. The duration of the first (S1) and second (S2) picture stimulus in each test trial was 300 msec. The interval between each trial was fixed at 3.2 sec. All pictures were paired into two conditions, i.e., matching and nonmatching. In the matching condition, the S1 was repeated as S2. In the nonmatching condition, the S1 was followed by a picture that was completely different from S1, even in terms of its semantic category. The presentation of matching and nonmatching trials was randomized. On half of the trials, the test stimuli (S2) were identical to S1; on the other half of the trials, the

S2 was different from S1. No S1 was repeated as S1; it was suggested that the so-called "trial-unique" version of delayed matching to sample test is most sensitive to amnesia (Aggleton et al 1988; Mishkin 1982).

SUBJECTS' TASK. The subjects' task was to decide whether the second picture (S2) was the same as the first stimulus (S1). They were asked to press a mouse key in one hand if the S2 matched S1 and to press a mouse key in the other hand if the S2 differed from S1, after the presentation of S2 on each trial. The designation of the hand indicating match or nonmatch was alternated across subjects. Response accuracy and speed were equally stressed.

ELECTROPHYSIOLOGICAL RECORDING. The subject was seated in a reclining chair located in a sound-attenuated RF shielded room and fixated a point in the center of a computer display located 1 m away from his or her eyes. Each subject was fitted with a 61-lead electrode cap (ECI, Electrocap International). We used the entire International 10/20 montage along with additional 41 sites as follows: Fpz, Afz, Af1, Af2, Af7, Af8, F1, F2, F5, F6, Fcz, Fc1, Fc2, Fc3, Fc4, Fc5, Fc6, Fc7, Fc8, C1, C2, C5, C6, Cpz, Cp1, Cp2, Cp3, Cp4, Cp5, Cp6, Tp7, Tp8, P1, P2, P5, P6, Poz, Po1, Po2, Po7, and Po8 (Standard Electrode Position Nomenclature, American Electroencephalographic Association 1990). All scalp electrodes were referred to Cz. The selection of this reference electrode is based on best results obtained during pilot studies, and our interest in studying topographic distribution using the Laplacian operator. Moreover, Rudell and Fox (1991) suggested that the vector of electrode position as well as the absolute position may be critical in observing certain physiological data. By using the Cz reference instead of the nose reference, we could more clearly document the ERP changes occurring at the temporal and occipital regions where the neurons play an important role in visual processing. Subjects were grounded with a nose electrode and the electrode impedance was always below 5 kΩ. Two additional bipolar derivations were used to record the vertical and horizontal electro-oculogram (EOG). The signals were amplified with a gain of 10,000 by an EPA-2 amplifier (Sensorium, Inc) with a bandpass between 0.02 and 50 Hz, and recorded on a Concurrent 55/50 computer. The amplified signals were sampled at a rate of 256 Hz during an epoch of 190 msec of prestimulus baseline and 1440 msec following each stimulus presentation. Trials with excessive eye or body movements (> 73.3 μV) were rejected on-line.

DATA ANALYSIS. ERPs were averaged only on artifact-free electroencephalogram (EEG) segments sampled during three stimulus conditions: sample S1, match S2, and nonmatch S2. To compare the two types of ERPs, we restricted our selection of EEG segments to those trials in which the subject made correct behavioral responses on either the match or nonmatch trials. This experiment yielded an ERP waveform, both in control and alcoholic patients, consisting of four components that were most clearly discernible at the more posterior electrodes (Figures 1 and 2): component 1 (c110) ranging between 100 and 125 msec, component 2 (c180) ranging between 170 and 190 msec, component 3 (c240) ranging between 220 and 260 msec, and component 4 (c320) ranging between 290 and 340 msec. As Figures 1 and 2 illustrate, the c320 to test stimuli could be more easily identified; however, the ERPs to sample stimuli have a different pattern than those to test stimuli after c240. Unlike the c320 to test stimuli, which develop a large trough within 250–400 msec poststimulus, the ERPs to sample stimuli seem to have a peak within the same time window. To more logically explain our statistical results, we also named a c320 on ERPs to sample stimuli and measured the amplitudes of c240 and c320 to sample stimuli according to the latencies of corresponding components for nonmatching stimuli. There was no absolute polarity in this experiment; the upgoing wave represented relative positivity at the recording electrode compared to the reference at Cz and vice versa. Amplitude and latency for the four components were initially measured at P8, the electrode site with maximal amplitudes and the most consistent morphology. Amplitudes were measured from baseline to each peak, and latencies were recorded from the onset of stimuli to the peaks of each component. Measurements at other electrodes were based on the latency of each component obtained at P8. Because of space limitation, only the amplitude of c240 on several electrodes is shown in Table 1 to provide the amplitudes for the three different kinds of stimuli at a glance.

For the purpose of statistics, the measurements of amplitudes of each component at each electrode were organized into groups by region. The frontal region consisted of Fp1, Fp2, Fpz, Af7, Af8, Af1, Af2, Afz, F7, F8, F5, F6, F3, F4, F1, F2, and Fz. The central region consisted of Fc1, Fc2, Fc3, Fc4, Fc5, Fc6, Fcz, C1, C2, C3, C4, C5, and C6. The parietal region consisted of Cp1, Cp2, Cpz, Cp3, Cp4, Pz, P1, P2, P3, and P4. The occipital region consisted of Po1, Po2, Poz, Po7, Po8, O1, O2, and Oz. The temporal region consisted of T7, T8, Tp7, Tp8, Cp5, Cp6, P7, P8, P5, and P7. A number of multivariate analyses of variance (MANOVAs) were carried out separately for each component, using amplitudes at each regional electrode array as a dependent vector for comparisons among different stimulus conditions.

Because the scalp potentials may reflect the average

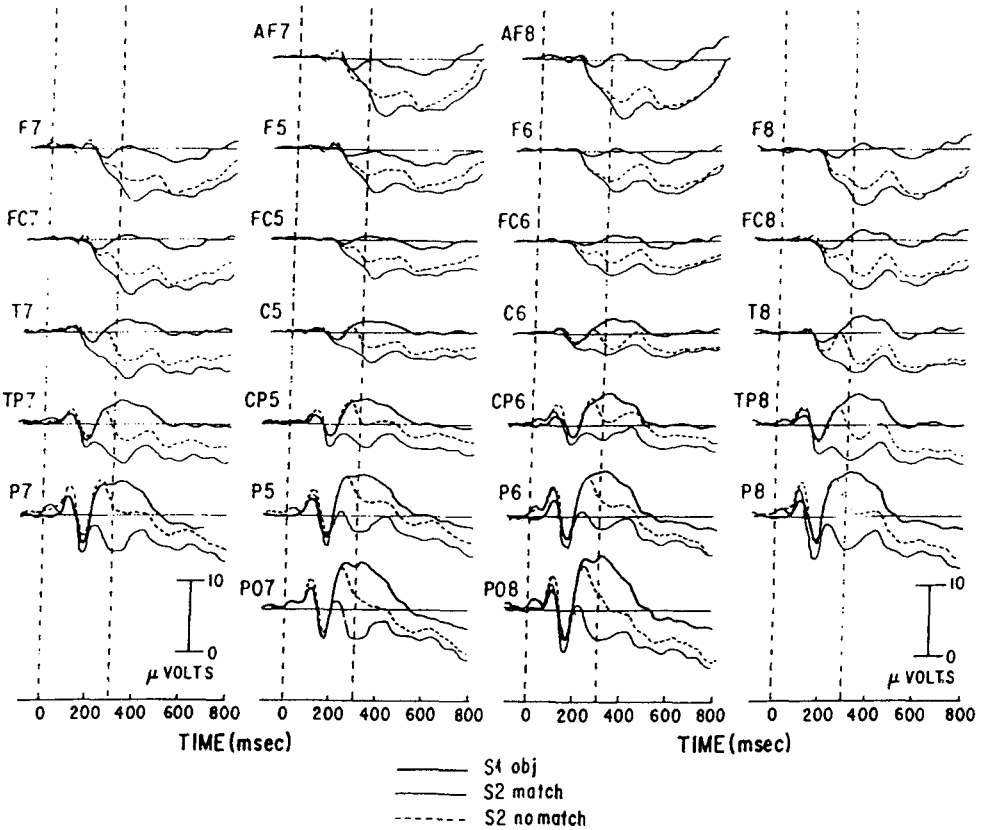

Figure 1. Grand mean of ERPs obtained in 48 control subjects. A downward deflection indicates greater negativity with respect to the vertex electrode and vice versa. Because of space limitation, only 24 electrodes are presented.

activity of multiple neural sources recorded at a distance, they are neither reference free, nor independent of the volume conductor effects of the brain, skull, and scalp. These limitations mean that ERP components will be altered if the placement of the reference is changed or if it is not a "quiet" reference (Nunez et al 1991), and there may be spatial smearing of the potential record as a consequence of volume conductor effects. For further analysis of our data, we made topographic maps of local SCD (current source density), a newly designed method of measurement of neural activity that is both reference free and independent of any physical conductive head models (Le et al 1994). The SCD represents both scalp sources and sinks of current, but mainly reflects cortical generators; a scalp region having a positive current density corresponds to a source region where local radial current is flowing through the skull into the scalp.

Results

As the t test showed that the control subjects were significantly younger than the alcoholic subjects in this study [$t(118.9) = 12.64$, $p < .0001$], all the following statistical analyses concerning the comparisons between the two groups employed analyses of covariance controlling for age.

Behavioral Data Analysis

Both groups had a low response error rate in the operation of the task as shown in Table 2. There were no significant differences in response errors between matching and nonmatching trials in either of the two groups; however, alcoholic patients made significantly more errors than control subjects in nonmatching trials [$F(2,1) = 9.86$, $p < .003$]. The results of a two-way analysis of variance (ANOVA) indicated that stimulus condition had a significant effect on response time [$F(1,241) = 30.28$, $p < .0001$]; further analysis indicated that the response time to matching stimuli was significantly shorter than to nonmatching stimuli in both groups, as shown in Table 3. The group effect also reached significance [$F(1,241) = 6.97$, $p < .0088$], suggesting that the alcoholic group tended to have a longer response time than controls; however, there was no significant interaction between group and stimulus condition factors. Further analyses indicated that no sig-

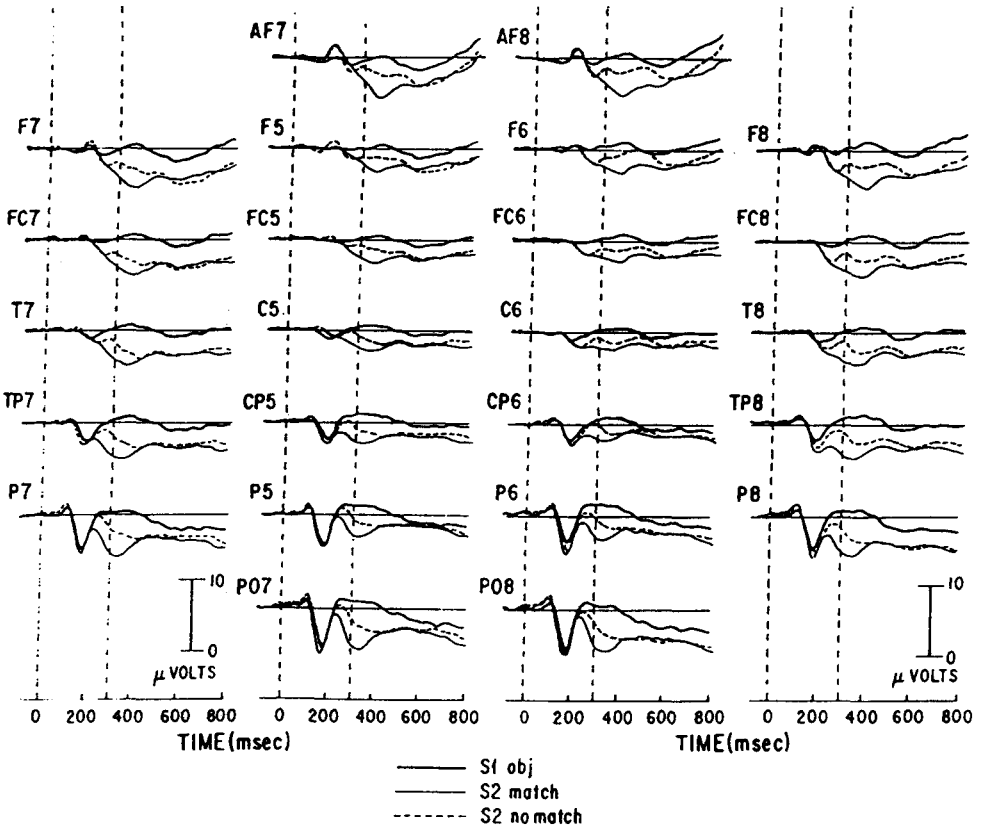

Figure 2. Grand mean of ERPs obtained in 77 alcoholic subjects. A downward deflection indicates greater negativity with respect to the vertex electrode and vice versa. Because of space limitation, only 24 electrodes are presented.

nificant group difference could be found in each corresponding stimulus condition.

Statistics among Control Subjects

Several MANOVAs were carried out separately among control subjects to compare each ERP component evoked by different stimulus conditions, using the amplitude at each of the scalp electrodes as a dependent vector. Namely, each ERP component to nonmatching stimuli was compared to the same ERP component to matching stimuli over various brain areas. For the temporal areas, although no significant stimulus effects on c110 and c180 were found for both left and right temporal regions, there were significant differences between c240 to matching and to nonmatching stimuli at left temporal [$F(5,90) = 5.91, p < .0001$] and right temporal [$F(5,90) = 9.31, p < .0001$]. The amplitude of c320 to nonmatching stimuli was also higher than to matching stimuli on the left [$F(5,90) = 4.66, p < .0008$] and on the right [$F(5,90) = 4.23, p < .0016$] side of the temporal regions. In the occipital region, the stimulus condition began to exert a significant effect on c180 [$F(6,89) = 3.29, p < .0057$]. The amplitude of c240 to nonmatching stimuli was also significantly higher than to matching stimuli [$F(6,89) = 8.88, p <$

Table 1. Mean Amplitudes for C240

	Fz	C3	C4	Pz	P7	P8
CS	−1.79 ± 2.3	1.08 ± 1.3	1.03 ± 1.2	4.12 ± 2.9	6.24 ± 4.9	6.62 ± 4.5
CM	−0.77 ± 2.5	−1.10 ± 1.4	−1.38 ± 1.6	1.84 ± 3.1	1.07 ± 4.6	1.16 ± 4.7
CN	−3.31 ± 3.0	1.09 ± 1.9	1.59 ± 2.0	4.64 ± 3.5	5.96 ± 5.4	7.90 ± 5.2
AS	−0.62 ± 2.0	0.71 ± 1.4	0.66 ± 1.4	1.62 ± 2.4	1.76 ± 3.0	1.93 ± 3.1
AM	0.03 ± 2.0	−0.29 ± 1.4	−0.77 ± 1.5	0.10 ± 2.5	−1.32 ± 3.3	−1.66 ± 3.8
AN	−1.28 ± 2.7	0.43 ± 1.8	0.24 ± 1.4	1.30 ± 2.8	−0.68 ± 3.9	0.31 ± 3.8

C represents the control group; S represents the sample stimuli; M represents the matching stimuli in the test trials; N represents the nonmatching stimuli in the test trials; A represents the alcoholic group.

Table 2. Response Errors during the Performance of the Tasks

	Controls (mean ± SD)	Alcoholics (mean ± SD)
Errors in match trial	0.29 ± 0.59	0.62 ± 1.11
Errors in nonmatch trial	0.12 ± 0.31	0.39 ± 0.78[a]

[a] $t(116.8) = 2.43$, $p < .05$.

.0001] in the occipital area. This significant effect of stimulus condition could also be found for c320 [$F(6,89) = 9.64$, $p < .0001$]. For the parietal area, the stimulus effect reached significance for the amplitude of c240 [$F(10,84) = 4.29$, $p < .0001$], where the c240 in the nonmatching condition had a higher amplitude than in the matching condition. This significant effect lingered for the amplitude of c320 [$F(10,84) = 2.31$, $p < .0186$], which showed higher amplitudes in the nonmatching condition. In the central area, there was a significant difference between the amplitudes of c240 to nonmatching and to matching stimuli [$F(13,82) = 4.69$, $p < .0001$]. No significant difference between the amplitudes of c320 to nonmatching and matching stimuli could be revealed on the central region. For the frontal region, the significant stimulus condition effect for c240 could be demonstrated at the left frontal [$F(7,88) = 5.61$, $p < .0001$] and right frontal [$F(7,88) = 8.05$, $p < .0001$] areas. This effect for c320 reached significance only at the right frontal area [$F(7,88) = 2.24$, $p = .038$]. These overall results for the control group are presented in Figure 3.

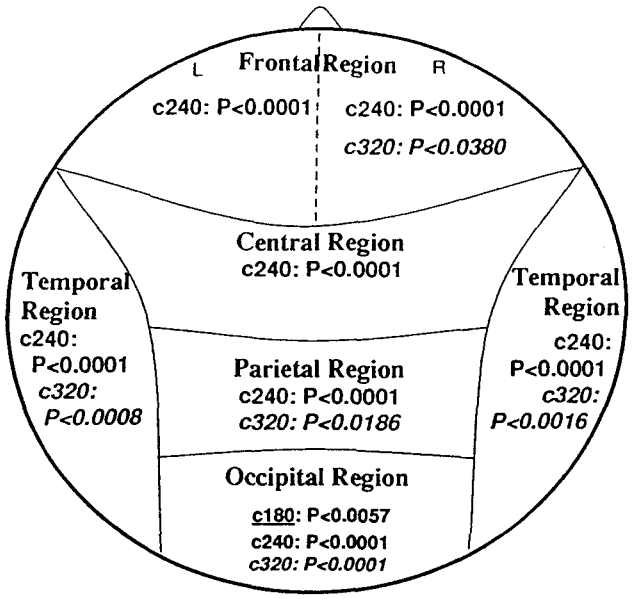

Figure 3. Topographic presentation of p values from MANOVAs on amplitudes of c180, c240, and c320 for comparisons between ERP components to matching and nonmatching stimuli in the control group ($n = 48$).

Statistics among Alcoholic Patients

The same MANOVA analyses as above were carried out among the alcoholic group. The results of statistical analysis on alcoholic patients are illustrated in Figure 4. As found in controls, the amplitude of c240 to nonmatching stimuli was also higher than to matching stimuli over the left temporal [$F(5,140) = 4.05$, $p < .0018$] and right temporal [$F(5,140) = 7.35$, $p < .0001$]. The same effects for c320 could be demonstrated on the left [$F(5,140) = 3.69$, $p = .0036$] and right [$F(5,140) = 2.76$, $p < .0206$] temporal areas. The stimulus condition had a significant effect only on c320 [$F(6,138) = 2.58$, $p < .0211$] over occipital areas in alcoholics. For the parietal area, the c240 to nonmatching stimuli had a significantly higher amplitude than the c240 to matching stimuli [$F(10,134) = 3.84$, $p < .0001$], but the stimulus conditions did not have significant effects on any other components. In the central area, the amplitude of c240 to nonmatching stimuli was also significantly higher than to matching stimuli

Table 3. Response Times in Each Condition

	n	Matching trials (mean ± SD)	Nonmatching trials (mean ± SD)
Controls	44	575.7 ± 109.8	644.1 ± 107.1
Alcoholics	77	608.6 ± 90.32	678.6 ± 90.10

Control group (match vs. nonmatch): $F = 9.71$, $p = .0025$; alcoholic group (match vs. nonmatch): $F = 19.58$, $p = .0001$.

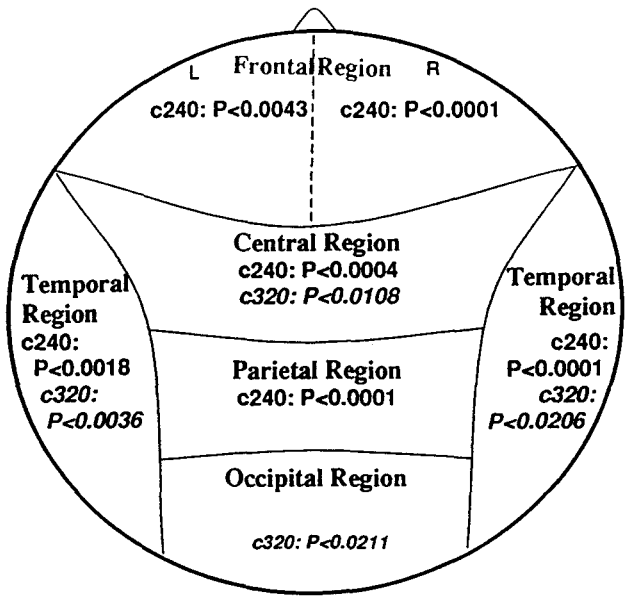

Figure 4. Topographic presentation of p values from MANOVAs on amplitudes of c180, c240, and c320 for comparisons between ERP components to matching and nonmatching stimuli in the alcoholic group ($n = 77$).

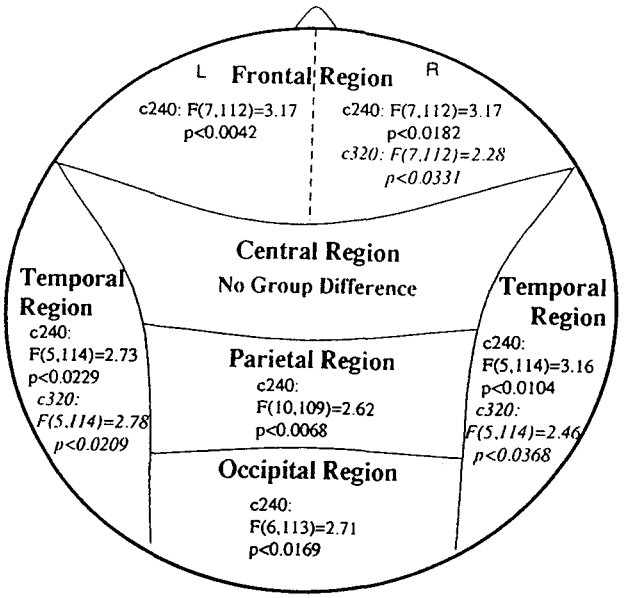

Figure 5. Topographic presentation of F and p values from MANCOVAs on amplitudes of c180, c240, and c320 for comparisons between the two groups in ERP components to sample stimuli (controls, n = 48; alcoholics, n = 77).

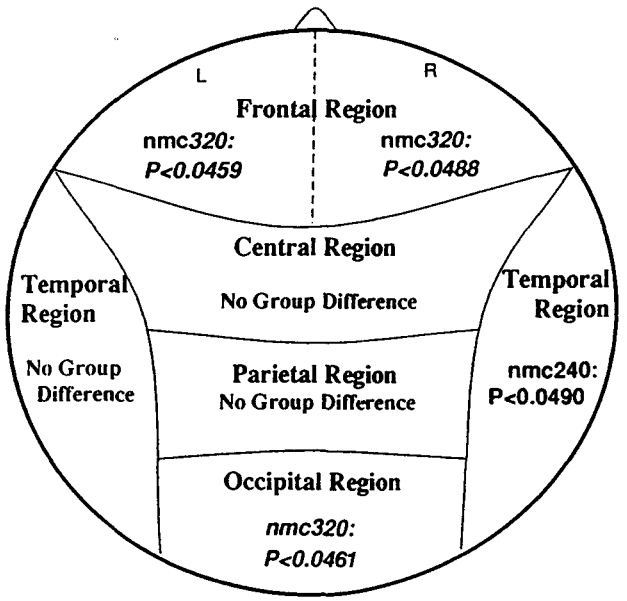

Figure 6. Topographic presentation of p values from MANCOVAs for comparisons between the two groups in ERP components to nonmatching stimuli (controls, n = 48; alcoholics, n = 77).

[$F(13,132) = 3.13, p < .0004$], but unlike the controls, the stimulus condition had a significant effect on c320 over the central area in alcoholics [$F(13,132) = 2.25, p < .0108$]; however, like the control group, the stimulus condition had significant effects for c240 on both left [$F(7,138) = 3.12, p < .0043$] and right [$F(7,138) = 5.32, p < .0001$] frontal areas.

Comparisons between Control Subjects and Alcoholic Patients for Amplitudes of Different Components

A number of the multivariate analyses of covariance (MANCOVAs) using age as covariate were carried out to test whether there were baseline differences between the

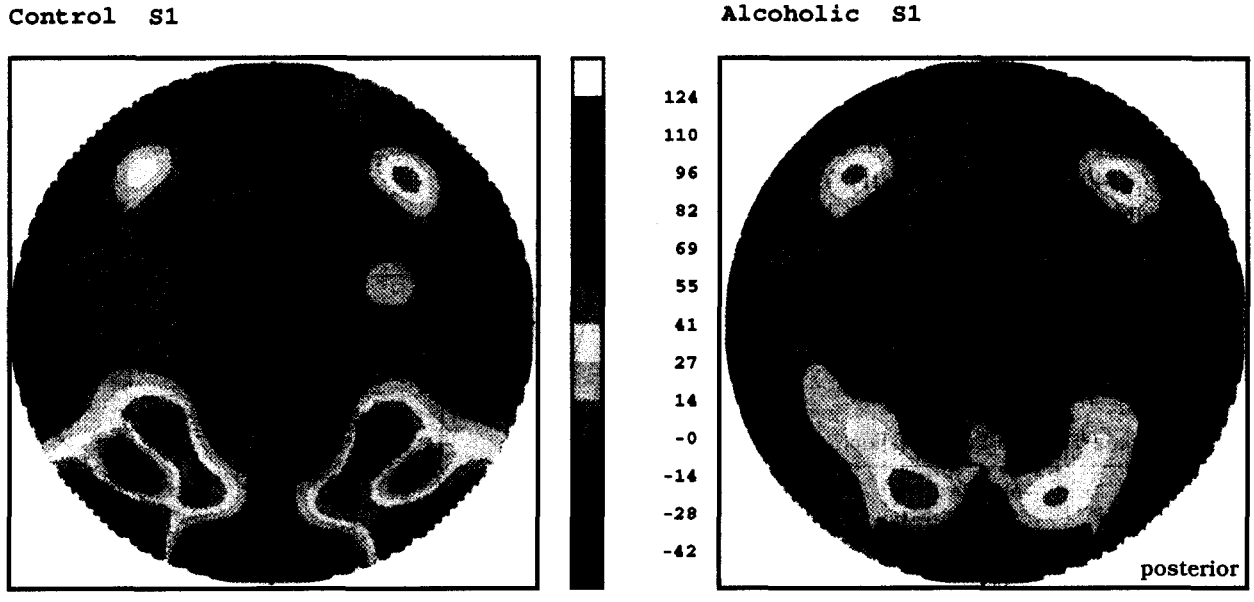

Figure 7. Grand mean SCD maps of c240 to sample stimuli. The left one, representing controls, has stronger activities over both sides of occipitotemporal regions than the right one, representing alcoholics.

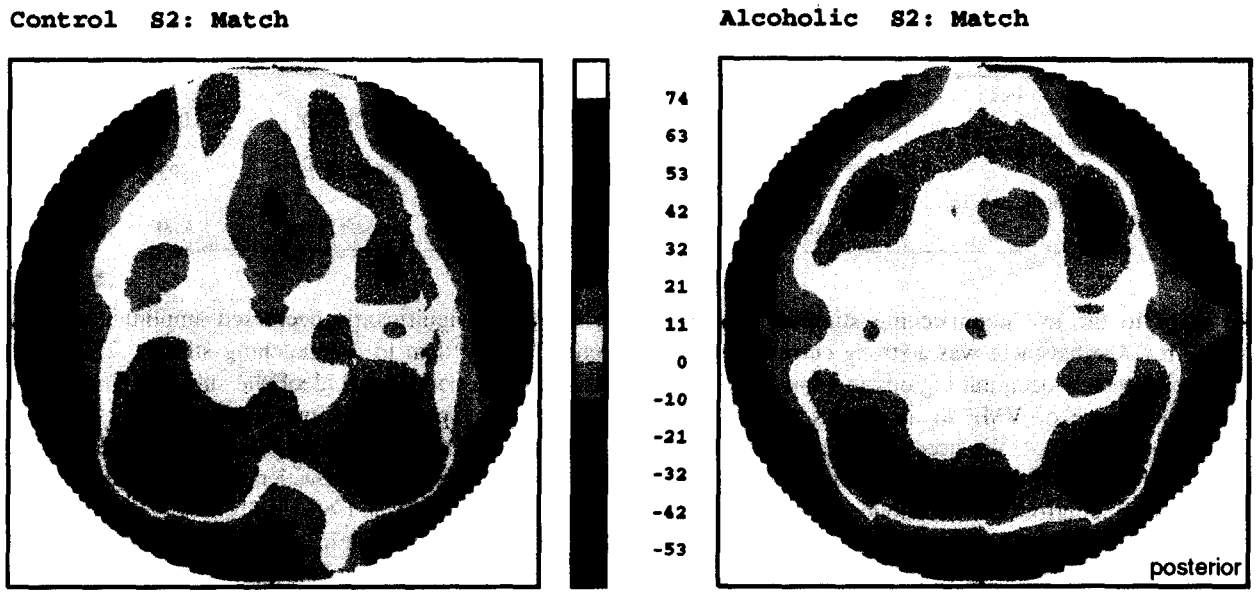

Figure 8. Grand mean SCD maps of c240 to match stimuli. The patterns in control and alcoholic groups are almost the same.

two groups, i.e., the differences between the two groups in the ERP responses to sample stimuli. The results are illustrated in Figure 5. There were group differences for c240 to sample stimuli at all brain regions except the central region. The group differences for c320 reached significance at the right frontal as well as the left and right temporal regions. Then, each ERP component in controls was compared separately with that of alcoholic patients in the corresponding stimulus condition by MANCOVAs, using the age or both the age and the analogous ERP component to sample stimuli as covariates, which depended on whether the two groups differed significantly from each other in the amplitudes of the corresponding component to sample stimuli.

The amplitudes of the c240 to nonmatching trials in controls were significantly higher than in alcoholic patients at the right temporal region [$F(5,105) = 2.31, p < .0490$] as revealed by MANCOVA. The stimulus condition had a significant effect on c320 to nonmatch trials [$F(6,113) = 2.22, p < .0461$] over the occipital region. No group difference on c180, c240, and c320 could be shown over parietal and central regions; however, the c320 to nonmatch stimuli at the left [$F(7,112) = 2.11, p < .0459$] and the right [$F(7,105) = 2.15, p < .0448$] frontal areas in the control group differed significantly from those in the alcoholic group. No significant difference between control and alcoholic subjects for any ERP components in matching trials could be found. These results are illustrated in Figure 6.

Statistical Analysis of Latencies for Each ERP Component

Analyses of covariance (ANCOVAs) were performed to test the within- and between-group differences in latencies of each peak for the different stimulus conditions. No significant result could be found for the latency of c180. The results of a two-way ANCOVA indicated that the only significant effect on the latency of c240 came from stimulus condition [$F(1,240) = 37.09, p < .0001$], though the alcoholic group tended to have a longer latency of c240 [$F(1,241) = 3.81, p = .0521$]. Further statistical analyses suggested that c240 to matching stimuli had a shorter latency than to nonmatching stimuli both in control [$F(1,95) = 17.10, p < .0001$] and in alcoholic [$F(1,145) = 23.00, p < .0001$] groups. The latency of c320 to matching stimuli was also significantly shorter than the latency of c320 to nonmatching stimuli in both the control [$F(1,95) = 5.45, p = .0217$] and alcoholic [$F(1,145) = 14.60, p = .0002$] groups. There was no group difference between the c320 latency for corresponding stimulus conditions.

SCD Topographic Results

The topographic maps of SCD from controls and alcoholics for different stimulus conditions are presented in Figures 7–9. The topographic SCD maps in the test matching stimulus condition were almost the same between the control and alcoholic groups; however, there were strong differences between the two groups in the

Table 4. *t* Test on the Z Estimator

Stimulus condition	Group	Mean ± SD	*t* value	*p*
Sample stimuli	Control	0.218 ± 0.298		
	Alcoholic	0.395 ± 0.252	−3.23(115)	.0016
Test matching	Control	0.176 ± 0.192		
	Alcoholic	0.202 ± 0.270	−0.54(64.7)	.5930
Test nonmatching	Control	0.174 ± 0.243		
	Alcoholic	0.379 ± 0.204	−4.645(115)	.0000

SCD maps to the test nonmatching stimulus condition. Figure 7 reveals that there was a strong current source of VMP over temporo-occipital regions in controls, whereas the current source of VMP in alcoholics seemed to be dispersed and scattered. We used the "Z estimator" (Desmedt and Chalklin 1989) to assess the dissimilarity of the maps between control and alcoholic subjects in corresponding stimulus conditions. The Z estimator is a measure of shape, not amplitude difference. The dissimilarity was then assessed with a *t* test. As indicated in Table 4, the *t* test showed that the SCD maps of the control group in nonmatching trials differed from those of alcoholics for the analogous stimulus conditions.

Discussion

The electrophysiological manifestations of neuronal processing to repeated (match) pictures of common objects were significantly different than to unrepeated (nonmatch) pictures. Specifically, an ERP component, named c240 by its peak at 240 msec after stimuli presentation, to matching stimuli had significantly decreased amplitude and shortened latency than to nonmatching stimuli. This was the case in both control and alcoholic subjects. The results of the present experiment, especially c240 in this case, were in agreement with the former studies on visual short-term memory in which we identified an ERP potential named VMP (Begleiter et al 1993, 1995; Hertz et al 1994), not only because they were in accordance with the characteristics of the topographic distribution, but also because the latency of c240 was in keeping with that of the VMP. We labeled the c240 in this study as the VMP and suggest that it reflects the information processed in visual working memory. It was reasonable that the VMP could be elicited in alcoholic populations, considering that the VMP was derived by averaging artifact-free EEG segments with correct behavioral responses. In the present study, the target stimuli in the matching trials were the repetitions of the priming stimuli; the repetitions of the same primers should produce efficient priming effects (Carr et al 1982; Posner 1978; Sperber et al 1979). In contrast, the target stimuli in nonmatching trials were different from the

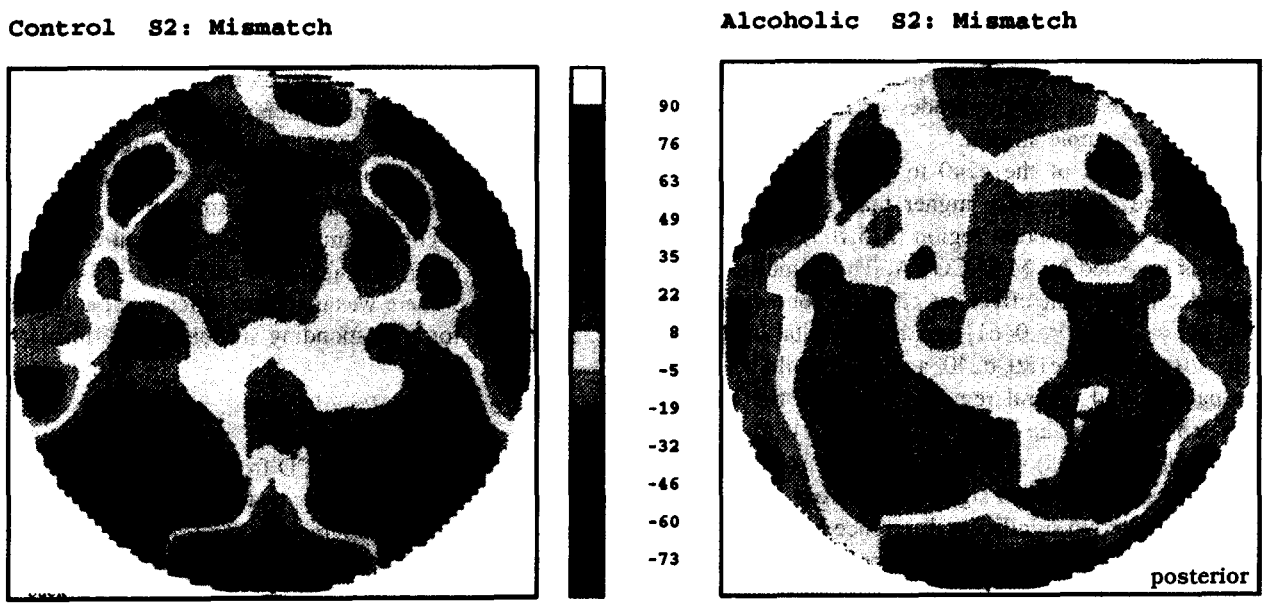

Figure 9. Grand mean SCD maps of c240 to nonmatch stimuli. Stronger activities in control than in alcoholic occipitotemporal regions can be found.

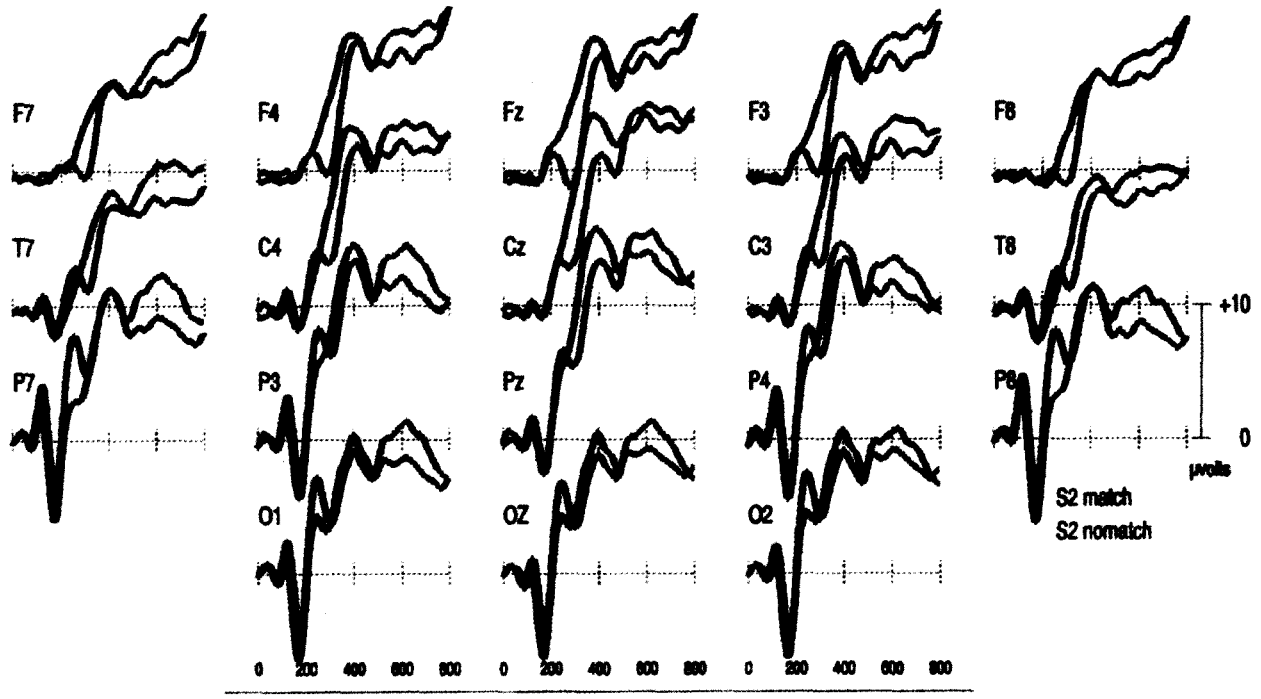

Figure 10. The same ERP data as shown in Figure 1 but re-referenced to the nose electrode.

prime stimuli physically and semantically; the recognition of the targets in nonmatching trials had not been facilitated by the preceding stimuli at all. The subjects had to encode the information from the sample stimulus, hold it in memory during the delay interval, and subsequently retrieve and compare the sample and test stimuli. Both the neuropsychological and neurophysiological processes should be different at some stage between matching and nonmatching trials.

The maximal amplitude and most consistent ERP morphology to both matching and nonmatching stimuli occur at the P8 electrode, which is located in the occipitotemporal region. The decreased amplitude and shortened latency of c240 on matching trials compared with those on nonmatching trials suggest that the recognition of the object pictures could be facilitated by the preceded registration of the same picture in memory. These phenomena are in fact the electrophysiological reflections of the priming effect during picture recognition. These results are in agreement with the studies in animals in which the responses to matching stimuli were normally suppressed (Mikami and Kubota 1980; Riches et al 1991; Miller et al 1991; Fahy et al 1993). Moreover, in the experiments in monkeys with delayed matching-to-sample paradigms, Miller et al (1991, 1993) reported that for most affected neuronal cells, the responses to matching stimuli were significantly attenuated compared to the nonmatching stimuli, though for a few cells the opposite effect was seen. The memory of the sample stimulus affected not only the responses to matching stimuli, but also those to nonmatching stimuli, i.e., the more similar a nonmatching stimulus to the sample, the more the response was suppressed.

Similar ERP studies using pictures as stimuli have shown that ERPs are sensitive to item repetition (Barrett and Rugg 1990; Friedman 1990; Friedman et al 1990). The ERPs to repeated items are generally more positive-going than those to the first presentations. The difference between the two kinds of ERPs, which is called an ERP repetition effect, usually begins around 250 msec poststimulus and persists for a further 300–400 msec, with its maximum location over the frontocentral region. Thus, there are some discrepancies between our current results and the previous studies; however, we believe that the difference in the selection of the reference electrode is mainly responsible for such disparities. The selection of reference electrode does effect ERP waveforms. As shown in Figure 10, the ERP pattern is dramatically changed if the reference electrode at Cz is replaced by the electrode on the nose. By re-referencing our data to the nose electrode, we also find the same ERP results as previous studies (Barrett and Rugg 1990; Friedman 1990; Friedman et al 1990); however, the nose referenced ERP data do not allow us to observe the electrophysiological phenomena as

clearly as the Cz referenced data over occipitotemporal regions during visual working memory processes where these areas play a key role.

The robust differences in c240 between matching and nonmatching stimuli could be demonstrated in almost all of the brain regions in both control and alcoholic subjects. This phenomenon might indicate the overlapping activity of the ERP component caused by cortical integrating effects; however, the ERP components over different brain regions have their own characteristics. The positive difference in c180 between matching and nonmatching stimuli could only be found over the occipital area in the control group, suggesting that the occipital cortex initially processes the visual information electrophysiologically. The matching factor on c320 reached significance in the right frontal region, where cognitive and executive functions are mediated (Goldman-Rakic 1987, 1988). Moreover, the different patterns between c320 to sample stimuli and to test stimuli might reflect different neuronal processing patterns to the two kinds of stimuli. We could observe the same sequential features of the ERP component distributions over the brain in the alcoholic group.

The suppression in ERP voltage to stimuli that match short-term memory traces is also consistent with some neural network architectures for memory storage (McClelland and Rumelhart 1986; Carpenter and Grossberg 1987; Kohonen 1988), as well as with the results of a recent positron emission tomography study of cortical activation in humans. In the latter study, subjects performing a visual word-stem completion task showed less activation of temporal cortex when they had recently seen the same word than when the words had not been seen (Squire et al 1992).

Both control and alcoholic subjects had significantly shortened response times to matching stimuli than to nonmatching stimuli as shown in Table 2; however, there was no difference between control and alcoholic subjects on homologous trials. The shorter response times on repeated trials suggested that the initial registration of the picture produced physical or lexical traces that could facilitate the recognition and judgment of the forthcoming stimulus. These results are in agreement with the findings of the earlier behavioral studies. Kroll and Potter (1984) showed that judgments involving related line drawings had faster response times. In picture naming studies, Sperber et al (1979) and Carr et al (1982) reported that the response time of naming primed pictures was shortened by 175 msec compared to the unprimed picture naming. Young et al (1986) revealed that there was a priming effect to semantic decisions (occupation) of familiar but not unfamiliar faces, regardless of prior familiar or semantic decisions about the same face.

The subjects in both groups performed the task with few errors as illustrated in Table 2; the alcoholics differed significantly from then controls in the performance of nonmatching trials. The poorer performance of alcoholic subjects on nonmatching trials on our modified delayed matching to sample tasks is in accordance with the study results by Bowden et al (1992) suggesting that behavioral impairment may occur in alcohol-dependent subjects who are not clinically amnesic. We noticed that the control as well as alcoholic subjects made almost twice as many response errors in matching trials than in nonmatching trials; however, significant group differences in behavioral performance in matching trials could not be found. Bowden et al (1992) suggested that a matching rule seems to fit the subjects' preferences or expectation, and matching is a more appropriate analogue for the nonmatching task used with monkeys (Aggleton et al 1988). We believe that the experimental method has a strong influence on the study results. The modified delayed matching to sample paradigm in our current experiment is different than the former neuropsychological tests in which either a matching or nonmatching rule was employed (Aggleton et al 1988; Bowden et al 1992; Oscar-Berman and Bonner 1985, 1989). Our stimulus paradigm required subjects to respond to both matching and nonmatching stimuli. The matching and nonmatching rule used in this experiment might account for the slight discrepancy of our behavioral data and other behavioral studies with delayed matching (or nonmatching) to sample tests in alcoholics.

Nevertheless, although the VMP could be elicited in abstinent chronic alcoholics, the current investigation further demonstrated that there were widespread, significant differences in the VMP correlates of working visual memory between control and alcoholic subjects. The group difference on c240 to sample stimuli could be demonstrated at almost all brain regions. The robust difference of c320 to sample stimuli between the two groups existed on the right frontal region and both sides of the temporal regions. In the right temporal region, the amplitude of c240 to nonmatching stimuli in control subjects was significantly higher than in alcoholic subjects. The amplitude of c320 to nonmatching stimuli in controls differed significantly from those in alcoholic subjects at both the right and left frontal regions as well as the occipital region. The results from the SCD topographic mappings of the two groups were consistent with the statistical results on amplitudes, i.e., the significant group differences were found in the nonmatching stimulus condition; the temporo-occipital areas were strongly involved in generating VMP in both control and alcoholic subjects. A model of memory and its relationship with underlying processes have been proposed (Cermak 1982; Oscar-Berman 1991) that consider memory to involve a number of interacting processes. One process consists of dynamic

interactions related to the encoding, storing, and retrieval of information. In addition to the neuronal processes of visual processing, encoding, and retention during the sample stimuli, the neuronal processes of retrieval of the latest encoded information in the sample trial, and comparisons between that latest encoded and newly encoded information in the test trial, are also included in the test stimuli. The different patterns between c320 to sample stimuli and to test stimuli might partly account for these processing differences, i.e., the c320 to sample stimuli as compared to that to test stimuli is more related to information encoding and retention. Neuropsychological experiments in alcoholics have shown that only when the demand or effort in information processing was high, have memory tasks shown deficits in recognition of patterns or objects (Cutting 1978; Riege et al 1981; Riege 1977), in delayed recall of story or design (Miglioli et al 1979), and in immediate and delayed recognition of auditory patterns (Riege et al 1981, 1984). Our ERP data in the current experiment also suggest that there are deficits in the modified matching to sample task that demanded effortful coding and retrieving of information. The decreased amplitudes of ERP components to nonmatch stimuli in the alcoholic group, compared to those in the control group, would suggest that alcoholic subjects assess the nonmatch stimuli as being more of a "match" to the sample than controls do. This could be due to inadequate encoding of the information from test stimulus or/and inefficient retrieval of the memory trace that had been encoded from sample stimuli. The widespread differences on c240 to sample stimuli between the two groups further suggest that there may be deficits in the processes of information encoding in alcoholics. Thus our studies provide some support for the hypothesis that alcoholic memory deficits occur in encoding and retrieval processes (for review, see Butters et al 1995).

Physiological recordings in the principal sulcus and arcuate regions of monkeys trained to perform delayed-response tasks have demonstrated that neurons in these areas hold representations of spatial stimuli "on line" for brief periods when such stimuli are no longer present and must be recalled (Funahashi et al 1989). This activity is considered a neuronal correlate of working memory, a process for updating information on a trial-by-trial basis. Wilson's results (Wilson et al 1993) further suggested that the inferior convexity may be involved in mnemonic processing of objects and faces. Clinical studies have revealed that patients with damage to the inferior frontal cortex are impaired in recognizing recently seen faces and words and in the classification of visual patterns (Rocchetta and Antonio 1986). The anatomic, physiological, and ablation studies in monkeys suggest that the region where the neuronal mechanisms that link vision and memory occur is in the inferior temporal (IT) cortex (Miller et al 1991; Baylis and Rolls 1987; Riches et al 1991; Vogels and Orban 1994; Eskandar et al 1992). In the current experiment, we found there were significant group differences on c240 and c320 over the temporal and frontal areas, suggesting functional differences in these two areas in alcoholics. These two anatomical regions are now known to play important roles in human memory functions.

Another prominent phenomenon in the current study was that the group difference in VMP only occurred over the right temporal region. There has been some evidence indicating that the right hemisphere is more vulnerable than the left hemisphere to the adverse effects of acute doses of alcohol (for review, see Tarter and Edwards 1985). The right hemisphere functions are depressed more by acute alcohol ingestion, as suggested by the performance of visual–spatial tasks, which is dominated mainly by the right hemisphere (Porjesz and Begleiter 1985). Neuropsychological findings indicate that chronic alcoholics tends to perform most poorly on tasks sensitive to right-hemisphere dysfunction or pathology (Bolter and Hannon 1986). Electrophysiological evidence also supports the view that in chronic alcoholism the hemispheric interaction is disturbed due to predominant deficiency of the visual–spatial function in the right hemisphere (Tsagareli 1995). The results from the current study showed that the strongest differences between the two groups were located in the right hemisphere, which is in accordance with the findings of right-hemisphere dysfunction in alcoholics.

In conclusion, the present study indicates that the VMP can be evoked in both control and alcoholic subjects; however, the alcoholic subjects differ from the controls in several aspects. The alcoholics complete the task with more errors and longer response time than controls do. The major differences in the evoked potential between the two groups are found over the temporo-occipital and frontal areas in the sample and nonmatching trials. Because of the involvement of these cortical areas in human memory functions and the characteristics of the delayed matching to sample task, the current data may reflect electrophysiological evidence of memory deficits in alcoholics.

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