Event-Related Potential Index of Semantic Mnemonic Dysfunction in Abstinent Alcoholics

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Background: *The objective of the study was to expand the investigation of the match/mismatch mnemonic impairment in the semantic domain in sober alcoholics.*

Methods: *Event-related potentials (ERPs) were recorded from 28 healthy adults and 36 sober alcoholics in a category (either animals or fruits/vegetables) match/nonmatch S1–S2 paradigm.*

Results: *There was a significant interaction of ERP amplitude (c3) between groups (controls vs. alcoholics) and stimulus conditions (category match vs. nonmatch) at the posterior brain regions; the c3 component was smaller for the category match than for nonmatch trials in controls, with the absence of such c3 differences in alcoholics. There were no significant ERP differences between the two groups in processing the sample stimuli. The ERPs (c2) elicited by the animal category were larger than those for the vegetable category in both groups. The alcoholics showed prominent suppressed activation of left temporo-occipital brain regions under both matching and nonmatching conditions, as demonstrated by the current source density maps. The alcoholics were also slower and less accurate than the controls in judging both category matching and nonmatching stimuli, while neither of the two groups demonstrated shorter response times to the matching stimuli.*

Conclusions: *These data suggest that alcoholics are less efficient in the semantic mnemonic match/nonmatch process, and are less likely to be deteriorated in the stage of forming the template for such match/nonmatch comparisons.* Biol Psychiatry 1999;45:494–507 © *1999 Society of Biological Psychiatry*

Key Words: Abstinent alcoholics, event-related potential category, visual short-term memory potential

Introduction

Alcohol dependence and abuse affects approximately 13% of the adult American population (American Psychiatric Association 1987). Compared to the deleterious effect of alcohol on the various organ systems (liver, peripheral nervous system, etc.), where the pathological processes are relatively clear, the underlying mechanisms of the psychoactive effects of alcohol are poorly understood; however, the neuropsychological literature does reveal a wide range of cognitive deficits associated with alcohol dependence, including impairment in perceptual–motor skills, visual–spatial functions, learning, memory, and abstraction and problem solving (Parsons and Nixon 1993; Glenn et al 1994; Porjesz and Begleiter 1996; Braun and Richer 1993). Among these deficits, the alcohol-related memory problems have received special attention (Oscar-Berman 1990). This is not only due to the existence of Wernicke–Korsakoff's syndrome, whose distinguishing symptoms are memory problems (Glass and Butters 1985; Jacobson et al 1990; Pollux et al 1995), but also because mnemonic difficulties might be especially sensitive indicators of alcoholism-related cognitive impairment (Ryan and Butters 1986). In sober alcoholics who failed to meet criteria of organic mental syndromes, the cognitive impairments have been more diverse, generalized, and subtle, and up to half of sober alcoholics often failed to manifest any apparent impairments with the usual neuropsychological measures (Parsons 1986; Parsons and Nixon 1993).

The assessment and evaluation of subtle memory dysfunction in sober alcoholics requires appropriate methods. The typical tests to assess mnemonic aspects in nonhuman primates have been forced-choice tests of recognition, either the delayed nonmatching-to-sample (DNMS) or the delayed matching-to-sample (DMS) (Oscar-Berman 1990; Zola-Morgan and Squire 1985; Zhou and Fuster 1996; Webster et al 1995). The basic steps of DNMS/DMS are: a sample stimulus (S1) is presented to an animal; after some delay, the animal is exposed to the test stimulus (S2, which is either identical to S1 or is novel) and gets rewarded upon its correct choice of the nonmatching or matching stimulus. It is reported that human subjects have a strong bias to match in comparison to monkeys' spontaneous preference for novelty in these forced-choice recognition tests (Aggleton et al 1988). The DMS has thus been widely accepted to test anterograde amnesia, visual short-term memory, and other mnemonic processing in

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human subjects (Holdstock et al 1995; Lange et al 1995; Swearer and Kane 1996).

Event-related potentials (ERPs) are neuroelectric indices shown to be sensitive to various aspects of alcohol use, such as alcohol intoxication, tolerance, and withdrawal (Porjesz and Begleiter 1987). A cluster of ERP components (P3, N400, N2, N1) have been found to be aberrant in sober alcoholics (Realmuto et al 1993; Frank et al 1994; Porjesz and Begleiter 1995; Cohen et al 1995). These aberrations are associated with certain information processing deficits that are involved in the various operations of ERP paradigms, such as oddball tasks for the P300, semantic processing paradigm for the N400, and discrimination tasks for the N2. It is interesting that, despite the different cognitive emphasis involved in each ERP paradigm, rudimentary template match–mismatch memory processes are somehow shared by these ERP paradigms (Porjesz and Begleiter 1996). To distinguish deviant stimuli from repetitive background stimuli, or to discriminate stimuli on the basis of semantic congruity/incongruity, a template needs to be formed for comparison. The ERP aberrations of the alcoholics (reduced P3 amplitude, prolonged N2 latency) indicate that they have less efficient match/mismatch processes than controls; it has been speculated that either the template is not formed or retained or that the match/mismatch processes themselves are impaired (Porjesz and Begleiter 1996).

In a modified DMS task using visual line fragment stimuli that were difficult to name, Begleiter et al (1993) detected an ERP component peaking around 247 msec that differentiates recognized from unrecognized stimuli; it is termed the visual memory potential (VMP). In previous studies in our laboratory, similar VMPs were elicited in DMS tasks by nonsense lines (Begleiter et al 1993), faces and face scrambles (Hertz et al 1994), familiar and unfamiliar faces (Begleiter et al 1995), and concrete object pictures (Zhang et al 1995). In these tasks, the VMP occurs at almost the same peak latency; higher voltages are obtained to the nonmatching S2 compared to the matching S2, and the strongest sources are over occipitotemporal regions in healthy adults. This temporal and spatial pattern of the VMP in combination with its cognitive features resembles the functional role of inferior temporal (IT) neurons of monkeys, which has been hypothesized to compare the representations of current visual stimuli with the internal representations of remembered stimuli (Eskandar et al 1992). In particular, the VMP proved to be sensitive to a subset of processes that contribute to the visual mnemonic comparison between the trace held in short-term memory and the current input stimuli. Not surprisingly, the VMP was significantly increased to novel, unfamiliar stimuli compared to previously observed, familiar stimuli in controls but not in alcoholics, suggesting visual memory aberrance in alcoholics (Porjesz and Begleiter 1996). Unlike the oddball tasks, where neither ERP waveforms elicited to novel stimuli nor frequent stimuli could index the neural representation of the template for comparison, the VMP was found to be involved in the encoding processes of the sample (Ji et al in press), which actually serves as the template in matching-to-sample processes. Therefore, the VMP could be an appropriate tool to test the aforementioned speculation proposed by BP and HB on the impaired match/mismatch processes in alcoholics, i.e., whether the alcoholics have problems in forming the template and/or they are simply impaired in match/mismatch processes per se. This study attempts to further investigate the match/mismatch mnemonic impairment in sober alcoholics by additional examination of the ERP elicited by the template sample in DMS tasks.

Evidence from a series of studies conducted in our laboratory also demonstrated that the VMP could reflect differences between the processing of object pictures with and without verbal labels (Hertz et al 1994; Begleiter et al 1995; Zhang et al 1995). To elaborate the semantic sensitive feature possessed by the VMP, this study employed a paradigm similar to those delayed matching-to-sample tasks where the VMP was elicited in healthy subjects, with one modification. Rather than judging whether the S1 and S2 are matched on physical identity, subjects judged whether sequentially presented pairs of stimuli were in the same superordinate category. This modification requires subjects to use information other than that available in the surface features of the pictures; that is, they must respond with the superordinate labels. For example, when pictures of cow and cat are presented sequentially, instead of responding to the visual features (recognizing the picture as “cow” and “cat”), responding at the superordinate label (categorizing the two pictures as “animals”) is required. We hypothesized that the semantic information was extracted explicitly to make correct judgments for this experiment. By investigating the effect of semantic information on the VMP, we are able to examine mnemonic processes that were semantically mediated, which has been found to be impaired in abstinent alcoholics (Porjesz and Begleiter 1996).

Methods and Materials

Subjects

There were 64 adults in this study. The experimental subjects (male:female = 27:9, $n = 36$, mean age = 36.8 years, SD $\pm$ 6.7 years) were recruited from the Addictive Disease Hospital of Kings County Hospital Center and were diagnosed as alcohol dependent without concomitant diagnosis of alcohol-induced organic mental disorders (DSM-III-R). Over the past 6 months, 7

alcoholics claimed to be abstinent from alcohol; the remaining 29 subjects had 17.4 ± 13.7 (4–60) drinks per day (a drink is a 12-oz. can of beer, a 4-oz. glass of wine, a single shot, or a single mixed drink) and drank 24.1 ± 9.0 (4–30) days per month. All experimental subjects were undergoing a 30-day treatment program that included vitamin and nutritional therapy, and were abstinent from any drug and/or alcohol for at least 30 days before participating in this study. Control subjects (male:female = 17:11, n = 28, mean age = 25.1 years, SD ± 4.1 years) were recruited either through newspaper ads or notices posted in the Health Science Center. The screening procedure required each individual to fill out a questionnaire detailing alcohol and drug use, and the medical (including psychiatric) histories for both himself/herself and his/her relatives. Inclusion in the control group depended on both the responses to the questionnaire and the requirement that none of the candidate's first- or second-degree relatives be diagnosed with any kind of alcohol-related disorder. Exclusionary criteria for both groups included major medical problems, a current requirement for medication with effects on the central nervous system, or a history of psychiatric (including psychoactive substance use) problems, and non–right-handedness. Information for exclusion were based on the interview assessments (by HB or BP) using instruments (which are semistructured, using both DSM-III-R and Feighner criteria for the determination of alcoholism) developed by the COGA (Collaborative Studies on the Genetics of Alcoholism) group. A breathalyzer test was administered to all subjects on the day of testing, and those with values greater than zero were not used in the study.

Experimental Design

The stimuli consisted of 92 picture pairs. A match/mismatch S1–S2 paradigm was employed in which framed pairs of animal drawings (half of the trials) or fruit/vegetable drawings (half of the trials) were presented with a 1.6-sec interstimulus interval, and the stimulus duration was 15 msec. The interval between each trial was fixed to 3.2 sec. Each picture was presented on a computer screen subtending a visual angle of 6–8°. On half of the trials, both the first stimulus (S1) and the second stimulus (S2) were of the same category, but S2 was never the same animal or fruit/vegetable as the first; it was another kind of animal or another kind of fruit/vegetable. On the other half of the trials, the S1 and S2 were not of the same category.

The 61-lead electrode cap (ECI Electrocap International), where all sites are included in the Standard Electrode Position Nomenclature (American Electroencephalographic Society 1991), was fitted to each individual. The reference electrode was Cz, and the impedances were kept below 5 kΩ. We used Cz as the reference electrode to best visualize some components, such as the VMP, and because of our interest in studying topographic distribution using the Laplacian operator (see Begleiter et al 1993). Subjects were grounded with a forehead electrode. The vertical and horizontal electro-oculogram were recorded. Trials with artifacts (>73.3 μV) were rejected on-line. The signals were amplified with a gain of 10,000 by a set of amplifiers (Sensorium 2000) with a band-pass of 0.02–50 Hz, and recorded on a Concurrent 5550 computer. The sampling rate was 256 Hz. The total length of the ERP epoch was 1600 msec, including a prestimulus period of 187 msec. The data were averaged and digitally filtered with a 32-Hz low-pass filter. After digital filter, the prestimulus baseline epoch was 125 msec.

The subject was seated in a reclining chair located in a sound-attenuated radio frequency shielded room (Industrial Acoustics Corporation (IAC)) and fixated a point in the center of a computer display located 1 m away from his eyes. Subjects were told: "You will see a frame on the screen which contains a drawing of something which is either an animal or a fruit/vegetable. The second drawing will never be exactly the same animal or fruit/vegetable as the first; it will be just another kind of animal or another kind of fruit/vegetable." On each trial, after the presentation of S2, the subject was asked to press a mouse key in one hand if both the first and second drawing were of the same category, and to press another mouse key in the other hand if not. The designation of the hand indicating match or nonmatch was alternated across subjects. Response accuracy and speed were equally emphasized.

Data Analysis

ERP components were measured via an semiautomatic peak detection program for each subject. The semiautomatic peak detection program finds the desired extremum in a window determined by the extremum of a given electrode, in this case the P8, which was used to identify the components at the other electrode sites due to its morphological consistency. The validity of the peaks chosen by the program was assessed by visual inspection. The peak latency varied across electrodes within the time window around the peak latency at P8. The amplitudes were measured at the peak with respect to a 125-msec prestimulus baseline. Latencies were measured from the time of the stimulus onset to the peak of each component. Grand average waveforms for the two groups are shown in Figures 1 and 2, respectively. At the most posterior electrodes the ERPs take the form of three discernible deflections, which are labeled as c1, c2, and c3 (which is called the VMP in our previous experiments), respectively; at the anterior electrodes the three ERP components are much less discernible, and will not be included in the following analytical procedure.

Statistical analyses of ERP data were only conducted on artifact-free trials with correct behavioral responses. Five regional groupings of the 61 electrodes were created to evaluate ERP characteristics by region: frontal—FP1/2, AF7/8, AF1/2, F7/8, F5/6, F3/4, F1/2, FPZ, AFZ, FZ; central—FC5/6, FC3/4, FC1/2, FCZ, C5/6, C3/4, C1/2; parietal—CP3/4, CP1/2, CPZ, P3/4, P1/2, PZ; occipital—PO7/8, PO1/2, POZ, O1/2, OZ; and temporal—FT7/8, T7/8, TP7/8, CP5/6, P7/8, P5/6.

Overall multivariate analysis of variance (MANOVA) (SAS v6.09, PROC GLM) was carried out in each of the aforementioned regions except the frontal, using group (controls vs. alcoholics) and gender as between-subject effects, stimulus condition (S2 category match vs. S2 category nonmatch) and electrodes as within-subject effects, and age as a covariate effect. Table 2 summarizes the overall MANOVA results. The main effect of electrode site and its interaction with other main effects were not reported because the electrodes employed in each

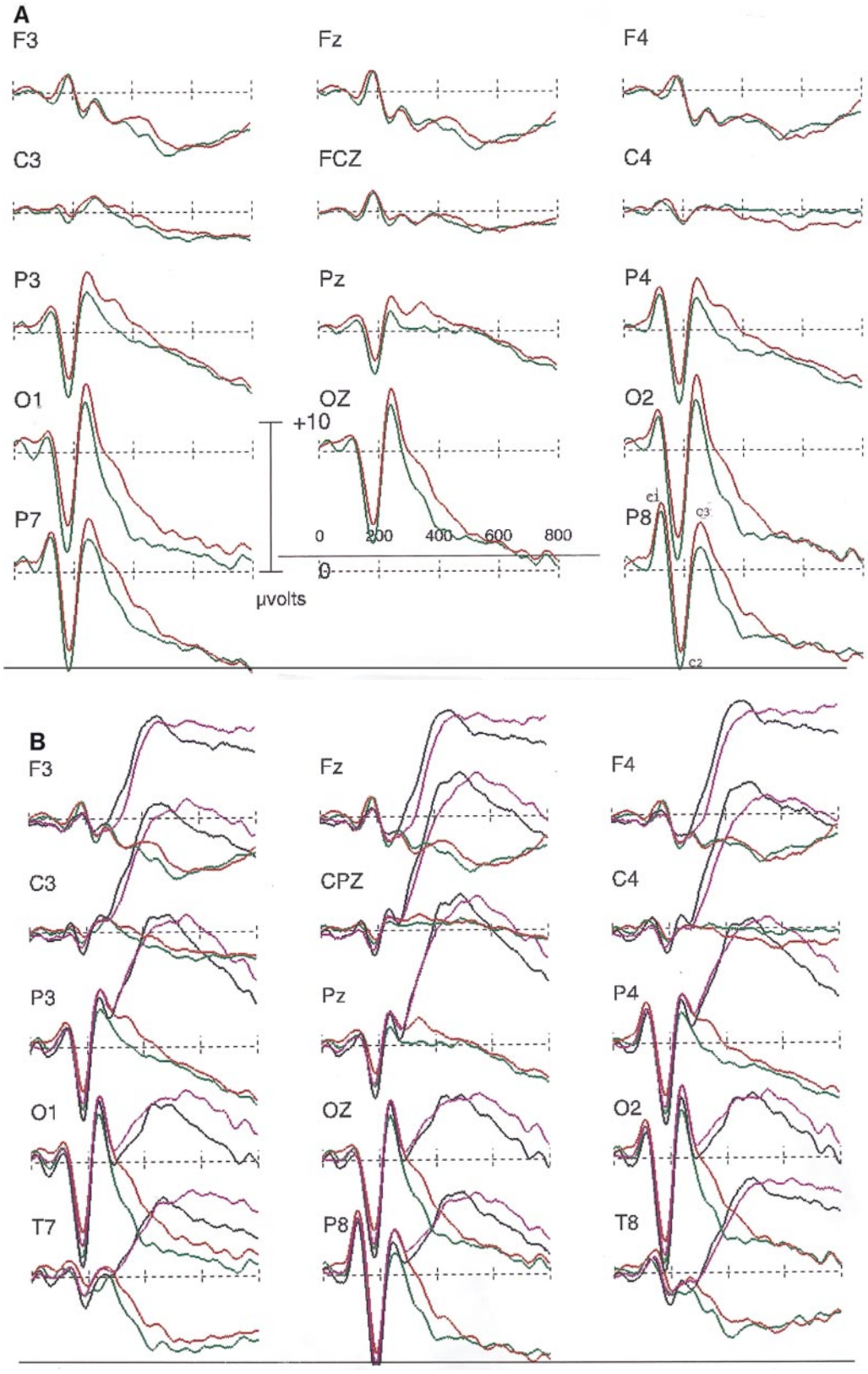

Figure 1. Purple-category different/nose reference; black: category same/nose reference; red: category different/Cz reference; green: category same/Cz reference. Grand mean ERPs elicited by S2 for control subjects; green = category match; red = category nonmatch; Cz reference.

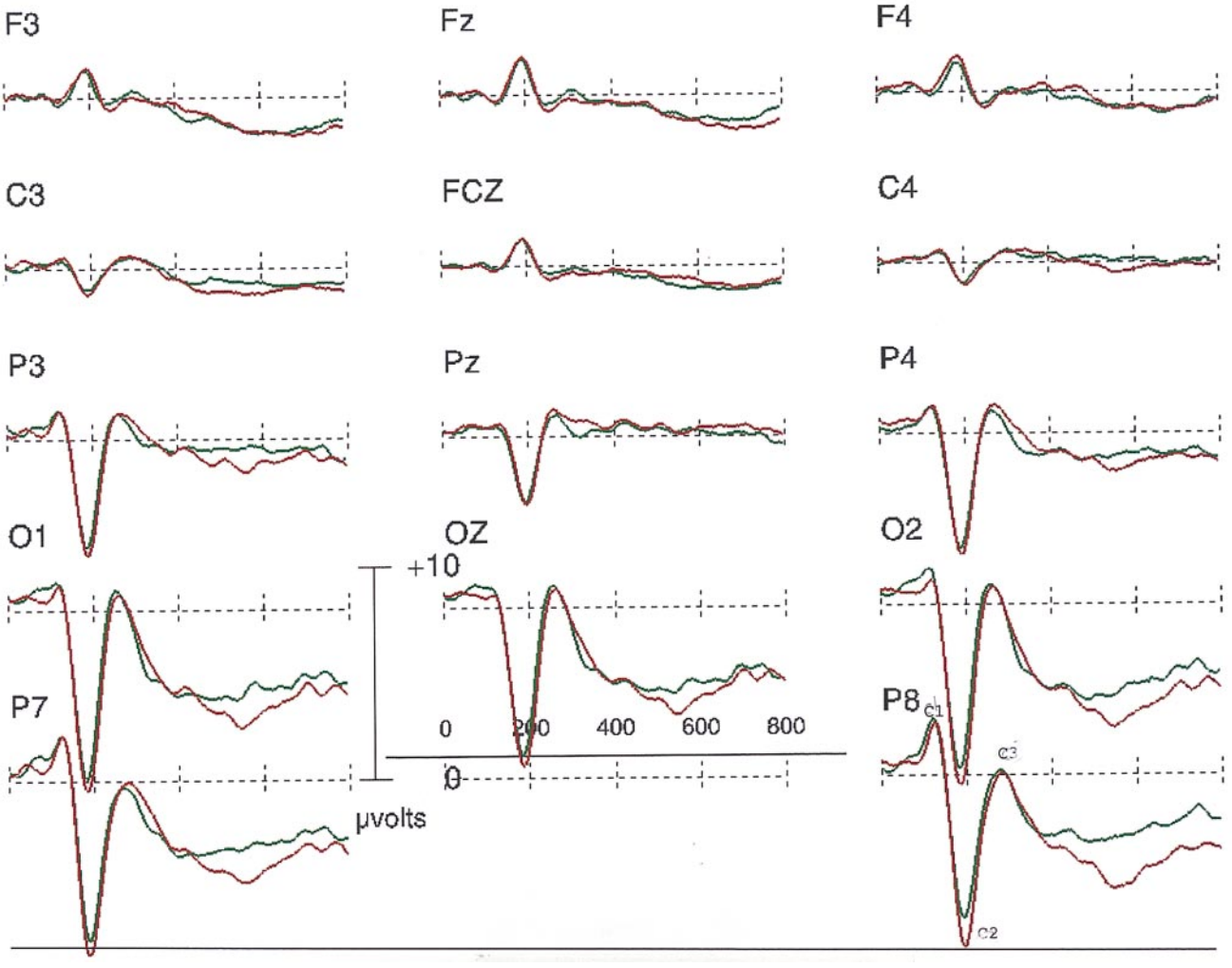

Figure 2. Grand mean ERPs elicited by S2 for alcoholic subjects; green = category match; red = category nonmatch; Cz reference.

regional analysis are within each brain region; thus these effects have no practical significance (i.e., they carry no information on regional differences but only on loci differences within each brain region). When the interaction between group and stimulus condition is significant, we did not interpret the main effects for group or stimulus condition; we tested instead for the simple effects (see Hatcher and Stepanski 1994, pp 361–374) for each group (alcoholics or controls).

Thus, the second step MANOVA was carried out separately 1) for each group (Table 3) to assess whether the match/mismatch effect (stimulus condition) is significant; or 2) for each stimulus condition (Table 4) to assess whether the group effect is significant.

In addition, the grand mean waveforms of S1 are illustrated in Figures 3 and 4. To assess whether there are any category-specific differences (animal vs. vegetable), and whether there are any group-specific category differences, similar analyses were conducted by redefining the stimulus condition as animal S1 vs. vegetable S1.

The topographic distribution of the c3 (Figures 5 and 6) was obtained by using the Spline Laplacian methods (Nunez and Pilgreen 1991), where simultaneously recorded values from all the scalp electrodes are used to provide a derived value for the current source density (CSD).

Results

The alcoholic group consisted of 27 men (36.5 ± 6.9 years old) and 9 women (37.3 ± 6.2 years old); there was no significant difference [$F(1,34) = 0.09$, $p = .77$] between the group mean age of male and female subjects. The control group consisted of 17 men (25.8 ± 4.4 years old) and 11 women (24.2 ± 3.5 years old); there also was no significant difference [$F(1,26) = 1.00$, $p = .33$] between the group mean age of male and female subjects; however, there was a significant age difference [$F(1,60) = 63.68$, $p < .0001$] between the alcoholic group (36.7 ± 6.7 years old) and the control group (25.1 ± 4.1 years old); neither

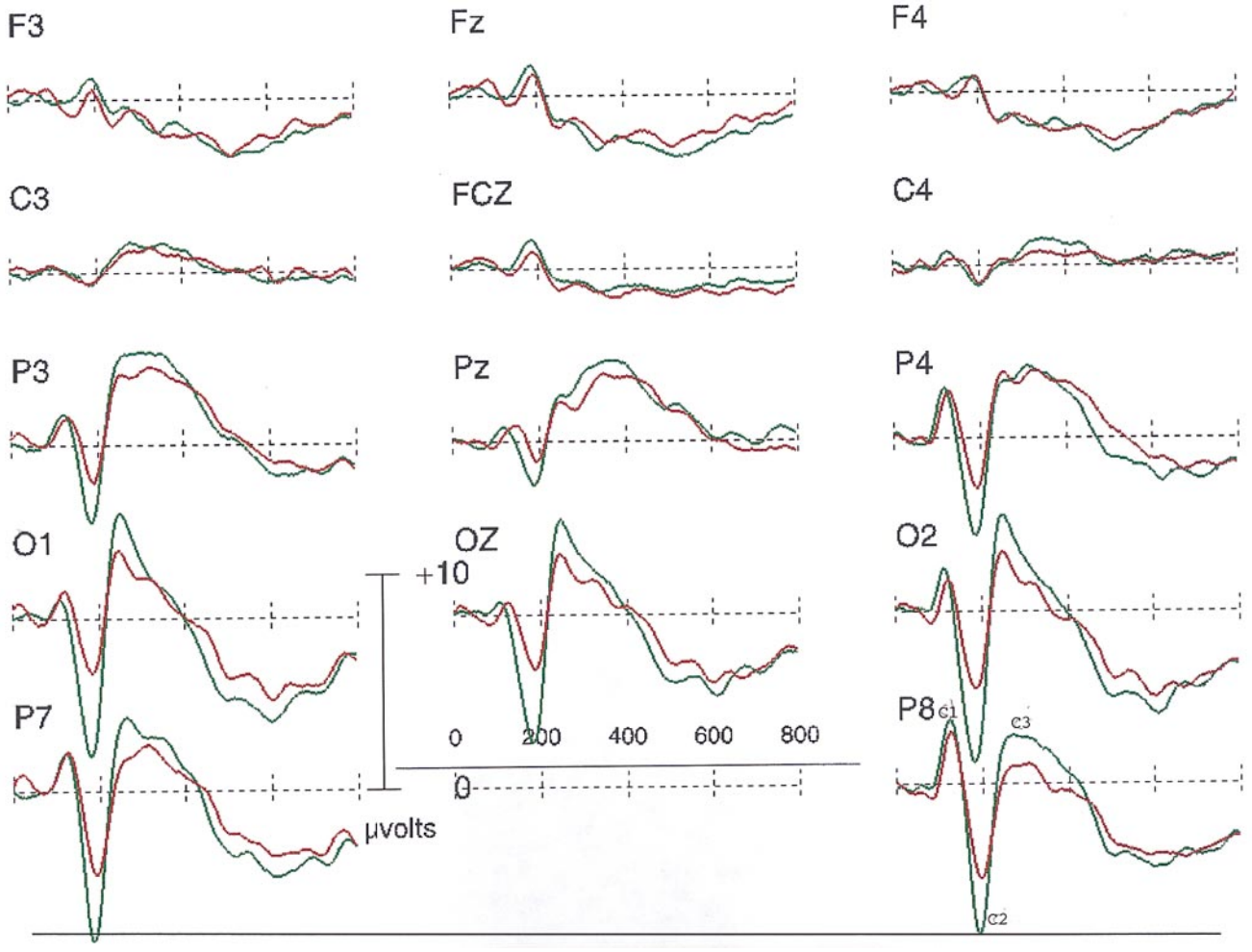

Figure 3. Grand mean ERPs elicited by S1 for control subjects; red = vegetable; green = animal; Cz reference.

gender effect nor the interaction between gender and group was significant. Considering that there is no age difference between men and women within each group, while the alcoholics are older than the controls, we employed age as a covariate only if group effect was involved in the analyses.

Behavioral Data

Table 1 shows the response time and accuracy data. ANOVA of response time (group, stimulus condition, and gender as independent variables, and age as covariate) revealed only one significant effect: group [$F(1,120) = 18.28$, $p < .0001$]. The result of no interaction between group and stimulus condition indicates that under both category matching and category nonmatching conditions, the alcoholics took longer to make their decisions (see Figure 7). While both groups took longer in judging category nonmatching stimuli (see Figure 7), the stimulus condition failed to reach significance [$F(1,120) = 3.28$, $p = .07$]. Figure 7 is the box plot of response time by stimulus condition and group.

The comparison of accuracy of the category matching trials revealed significant group [$F(1,59) = 9.25$, $p < .05$] and gender [$F(1,59) = 6.69$, $p < .05$] effects, but no significant interaction [$F(1,59) = 0.82$, $p = .37$]. Table 1 revealed that the alcoholics were less accurate than the controls in judging category match trials, and women were less accurate than men. Whereas in judging category nonmatching trials, there were neither gender differences [$F(1,59) = 1.26$, $p = .27$], nor interaction [$F(1,59) = 0.54$, $p = .47$] between gender and group, the group effect was significant [$F(1,59) = 11.86$, $p < .05$], revealing that the alcoholics were less accurate than the controls (see Table 1).

ERP Data Matching/Nonmatching Effect

Tables 2–4 summarize the overall and separate MANOVA results performed on the c3 amplitude or latency array for each brain region. For the latencies of c3,

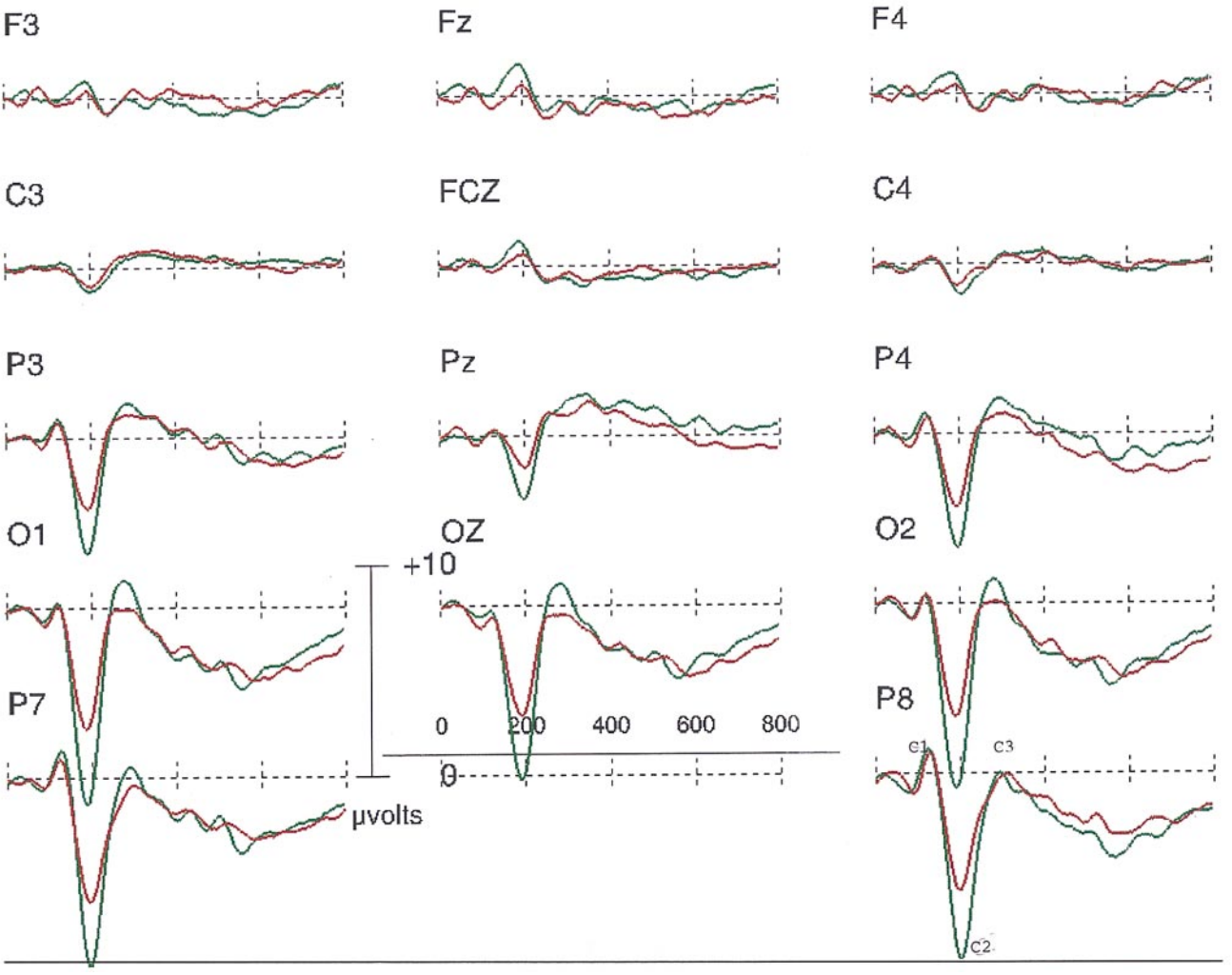

Figure 4. Grand mean ERPs elicited by S1 for alcoholic subjects; red = vegetable; green = animal; Cz reference.

the two groups responded similarly to category matching and nonmatching conditions (no significant interaction effects between group and stimulus condition, nor significant effects of either group or stimulus condition, Table 2); thus the nonsignificant results from the separate MANOVA on the latency data will not be discussed further; however, the latencies of c3 at the central and parietal regions under matching/nonmatching conditions are different between the male and female subjects (significant interaction effect between gender and stimulus condition, Table 2). The c3 latency at the occipital electrodes is longer for the alcoholics (260.33 ± 24.37 msec) than for the controls (247.07 ± 25.71 msec) under nonmatching condition.

For the amplitude (Table 2), there were significant interaction effects between group (alcoholics vs. controls) and stimulus condition (category match vs. category nonmatch) at the parietal and occipital regions, suggesting that the relationship between the amplitude of c3 and the match/nonmatch condition is different for control subjects and alcoholic subjects. The interaction effect was plotted in Figure 8, illustrating that control subjects showed suppressed ERP responses to matching trials compared to nonmatching trials, while alcoholic subjects' ERP responses did not differentiate the matching trials from nonmatching trials, suggesting no (or weakened) ERP suppression to matching trials in comparison to nonmatching trials.

This interaction was confirmed by the separate MANOVA of the c3 amplitude for each group (illustrated in Table 3). Only for the control subjects were there significant stimulus condition effects (different matching and nonmatching responses) at the parietal, occipital, and temporal regions (Table 3), and the c3 was smaller for the category match than for the category nonmatch trials, as illustrated in Figure 1; for the alcoholic group, the c3 showed no difference between category matching and nonmatching trials at all of the four brain regions (Table 3

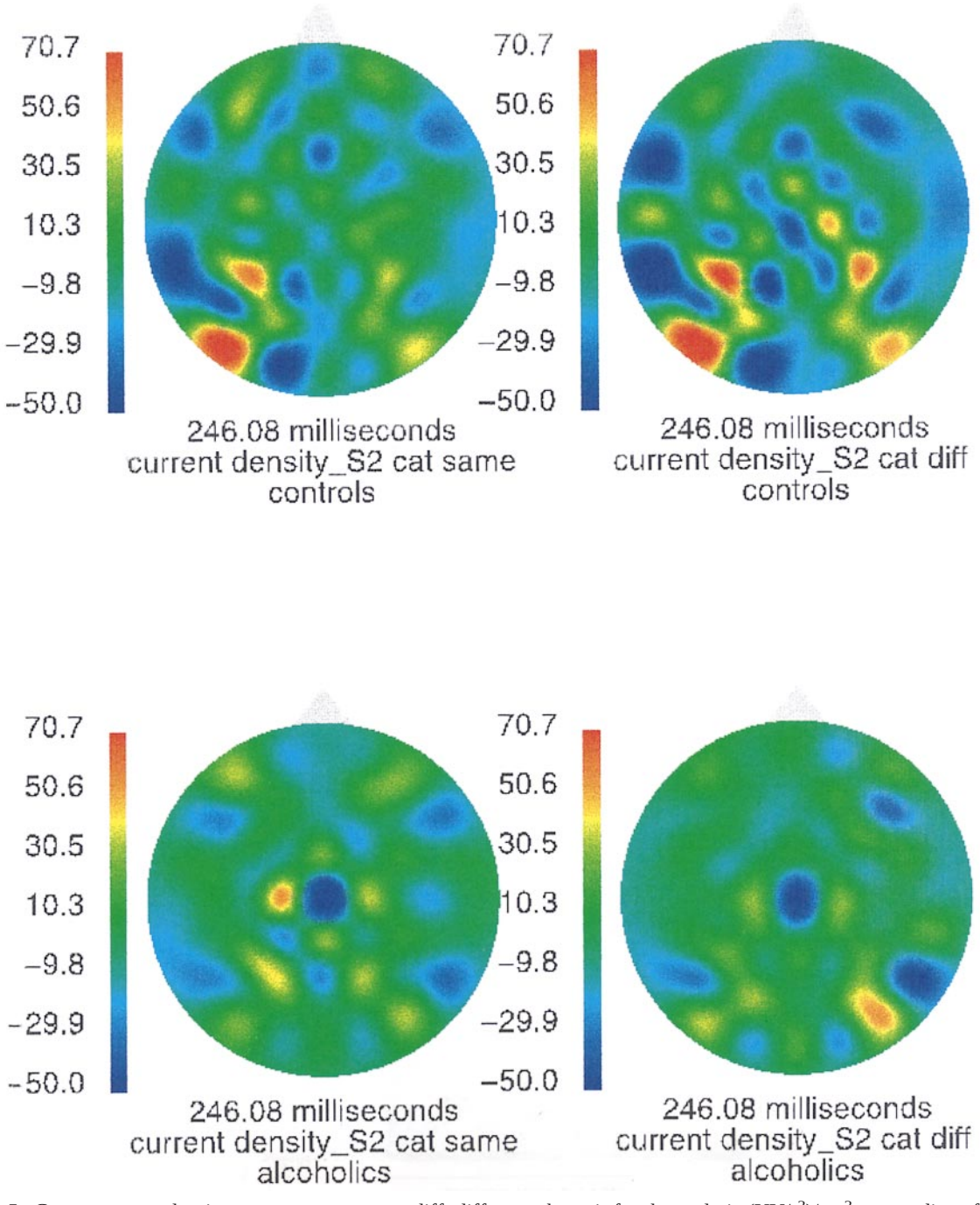

Figure 5. Current source density maps; cat, category; diff, different; the unit for the scale is $(UV/r^2)/cm^2$; r = radius of head.

and Figure 2); however, separate MANOVA of the c3 amplitude for each stimulus condition failed to reveal any significant group effect; neither matching nor nonmatching c3 is different between the alcoholics and the controls (Table 4). Thus no between-group c3 effect was observed when matching trials were considered separately from nonmatching trials, but significantly different ERP response patterns were obtained between groups when considering whether there was a difference between matching and nonmatching stimulus-elicited ERPs.

Visual assessment of CSD (Figures 5 and 6) suggests strikingly stronger sources over the occipitotemporal region in the control group compared with the alcoholic group. For the control group, the activation of the left occipitotemporal region was much higher than the right side in the matching process, and slightly higher in the

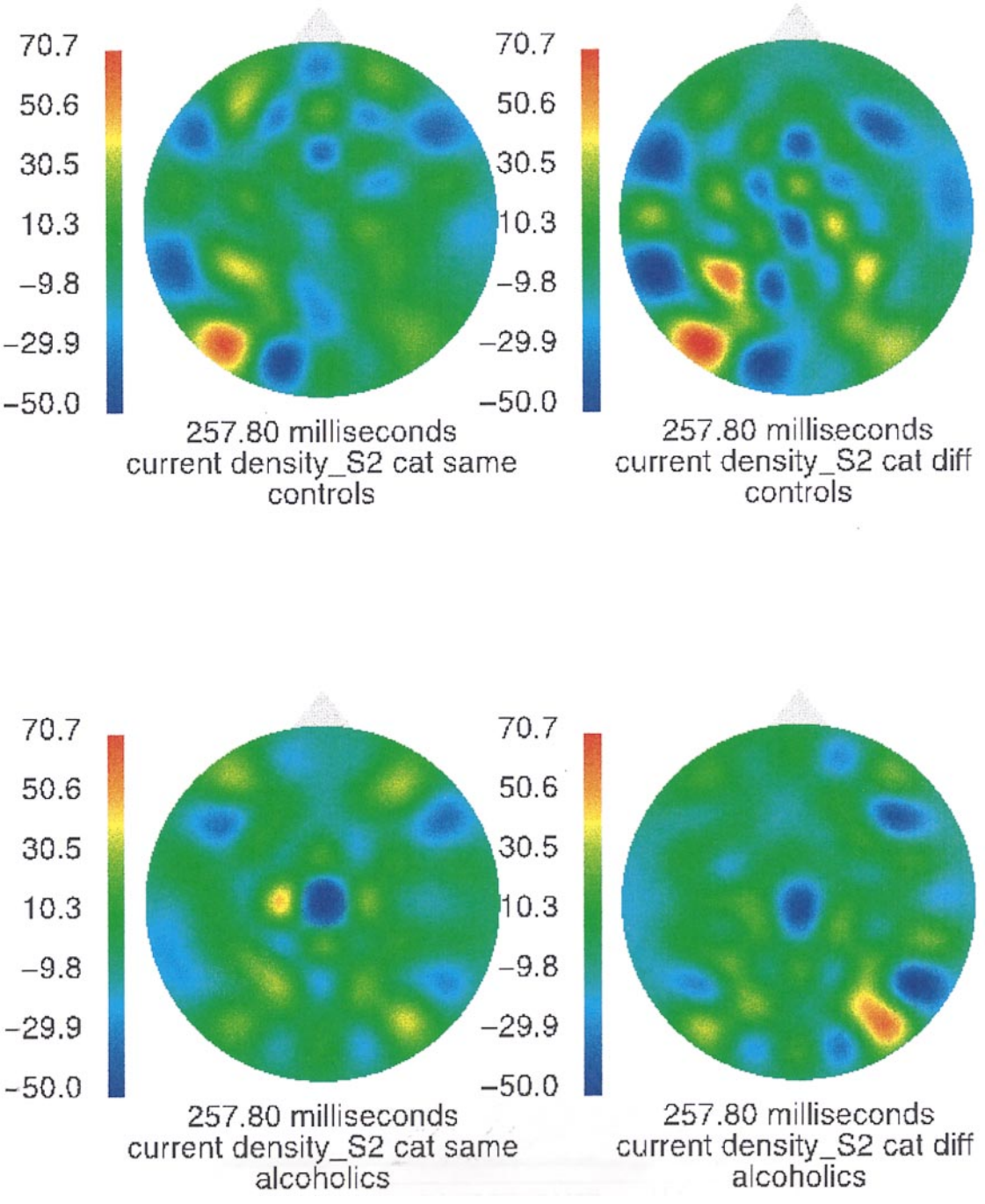

Figure 6. Current source density maps; cat, category; diff, different; the unit for the scale is $(UV/r^2)/cm^2$; r = radius of head.

nonmatching process. In contrast, for the alcoholic group, there was no obvious strong activation of any brain region in the matching process, though the CSD map demonstrated slight activation of frontal and occipitotemporal regions; in the nonmatching process, the CSD map demonstrated brain activation over the right occipitotemporal region. Furthermore, over time, the right occipitotemporal region activation of the alcoholics in the nonmatching process failed to show a similar decay pattern as in the matching process in controls.

ERP Data Animal/Vegetable Effect

There was no significant group effect in S1-elicited ERP data analysis. Animal-elicited ERPs are different from vegetable-elicited ERPs for both the alcoholics and the

Table 1. Reaction Time (RT) and Accuracy

	Male (mean ± SD)	Female (mean ± SD)	Total (mean ± SD)
RT (msec)			
Controls			
Match	729 ± 145 (n = 17)	786 ± 116 (n = 11)	751 ± 135 (n = 28)
Nonmatch	786 ± 175 (n = 17)	841 ± 138 (n = 11)	808 ± 161 (n = 28)
Alcoholics			
Match	869 ± 123 (n = 27)	873 ± 194 (n = 9)	870 ± 141 (n = 36)
Nonmatch	904 ± 139 (n = 27)	918 ± 133 (n = 9)	907 ± 136 (n = 36)
Accuracy (%)			
Controls			
Match	93 ± 8 (n = 17)	88 ± 8 (n = 11)	91 ± 8 (n = 28)
Nonmatch	96 ± 4 (n = 17)	96 ± 4 (n = 11)	96 ± 4 (n = 28)
Alcoholics			
Match	86 ± 9 (n = 27)	77 ± 13 (n = 9)	83 ± 11 (n = 36)
Nonmatch	89 ± 10 (n = 27)	85 ± 15 (n = 9)	88 ± 11 (n = 36)

controls, as demonstrated in Figures 3 and 4 (c2). There was a significant animal vs. vegetable effect (of c2 amplitudes) on the parietal [alcoholics: $F(1,34) = 27.03$, $p < .001$; controls: $F(1,26) = 7.62$, $p < .05$], occipital [alcoholics: $F(1,34) = 40.95$, $p < .001$; controls: $F(1,26) = 28.21$, $p < .001$], and temporal [alcoholics: $F(1,34) = 17.52$, $p = .001$; controls: $F(1,26) = 11.48$, $p = .01$] regions. As shown in Figures 3 and 4, animal stimuli elicited larger c2s than did vegetable stimuli for both alcoholic and control subjects at these posterior sites.

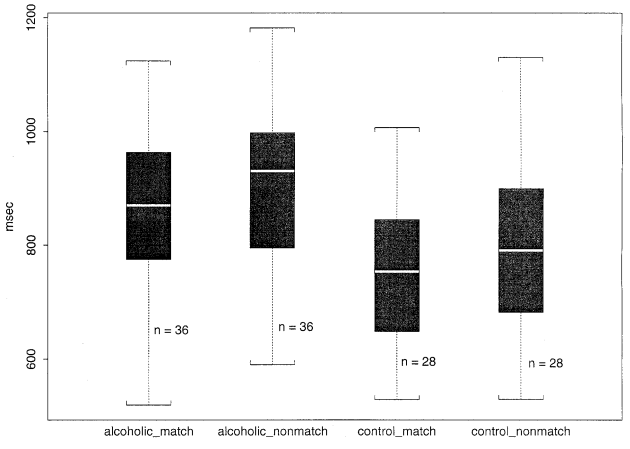

Figure 7. Boxplots of response time by group and task (match/nonmatch).

Discussion

Neither in processing the sample stimuli (S1) as a whole, nor in processing the two different samples (animal S1 and vegetable S1) respectively, do alcoholics manifest any significant differences from controls. Both groups demonstrate larger ERPs (mainly the c2 component) response to the animal sample compared to the vegetable sample to the same extent (no interaction of group × stimulus condition). Since encoding/extracting information from the sample stimulus enables the forming of the template for the subsequent comparison in this category match/nonmatch ERP paradigm, our data help to clarify that the well-documented match/nonmatch process deficits of alcoholics (Porjesz and Begleiter 1996) are less likely deteriorated in the stage of forming the template for comparison.

Sober alcoholics, however, manifest an ERP pattern quite different from controls in the integrated category match/nonmatch task, which is reflected by the significant interactions between group and stimulus conditions. While the ERPs of control subjects revealed a substantially smaller amplitude (c3) for the category matching than nonmatching pictures at the posterior brain regions, the ERPs of alcoholics showed no significant differences between category matching and nonmatching processes.

The suppressed c3 voltage (peaking around 247 msec) to the category match trials (compared to nonmatch trials) in the controls is in agreement with the former studies on visual short-term memory (Begleiter et al 1993; Hertz et al 1994; Zhang et al 1995), where a similar component peaking around 240 msec (VMP) was smaller to identical visual stimuli than physically different visual stimuli. The suppressed VMP amplitude indicates that previously encountered pictures (the sample pictures) have introduced a mnemonic availability for the recognition of the matching pictures (identical to the samples); this mnemonic availability provides an efficient method in cognitive matching processes in the DMS tasks. In the current study, to make a correct matching judgment, the inner representation (semantic label) of the sample category must be extracted and held in memory, serving as the template for comparison; thus the subjects are semantically primed in the matching process. This semantic priming is consistent with the CSD analysis, which demonstrates that the major activated brain area in the matching processes is in the left hemisphere. Our previous study demonstrated the right-lateralized hemispheric activation in processing visual stimuli devoid of or with implicit involvement of semantic information (Begleiter et al 1993). With the explicit extraction of semantic information in the present study, the involvement of the left hemisphere demonstrated a more active role compared to the right hemisphere under both

Table 2. Overall Regional MANOVA Results for c3

		Central 13 electrodes		Parietal 10 electrodes		Occipital 8 electrodes		Temporal 12 electrodes	
	df	Amplitude	Latency	Amplitude	Latency	Amplitude	Latency	Amplitude	Latency
Nonmatch/match (S)	1,60	0.003	0.85	0.59	2.63	0.22	2.66	0.32	0.07
Group (G)	1,60	0.01	0.47	2.24	1.27	1.48	1.49	0.45	1.14
S · G	1,60	1.65	1.56	8.86[a]	3.99	5.86[b]	2.83	2.29	1.58
Gender	1,60	0.04	0.66	0.03	0.43	0.40	0.28	0.00	0.03
S · Gender	1,60	2.05	4.57[b]	0.84	7.08[b]	0.40	0.66	0.10	8.00[a]

F value:
[a] $p < .01$.
[b] $p < .05$.

matching and nonmatching conditions. This is in concordance with the traditional assumption that the left hemisphere engages dominantly in processing semantic information (cf. Hass and Whipple 1985). Thus the c3 amplitude differences between category matching and nonmatching conditions in the current study may stem from semantic priming, and therefore represent cognitive efficiency in the healthy controls.

On the other hand, the current observation of no significant c3 amplitude difference between category matching and nonmatching processes in alcoholics might be taken as evidence that alcoholics lack the ability to take advantage of previous experiences (the processing of sample stimuli) in dealing with current events (the processing of matching stimuli). Since no behavioral data (such as shorter response time in matching than in nonmatching trials), no ERP data (smaller voltage in matching than in nonmatching trials), nor supporting information from CSD maps (the expected brain electric activity in the left occipitotemporal region) was observed in the alcoholic subjects, there was no direct or indirect evidence that could lead us to the belief that (semantic) priming may take place in alcoholics' match/nonmatch performance. On the contrary, alcoholics did take longer and were less accurate in making matching decisions, though in the matching process no ERP voltage difference was found between controls and alcoholics. The alcoholics' failure of c3 match/nonmatch difference might reflect the aberrance of the mnemonic availability that is evidenced in healthy controls, and indicate their less efficient cognitive processing. This result is consistent with the neurobehavioral studies in chronic alcoholics (Nixon and Bowlby 1996; Parsons and Nixon 1993; Nixon and Parsons 1991), where a multiple information store, process-oriented model has been developed to account for the alcohol-related cognitive deficits. This model assumes that there are two information stores, the episodic information store, which is associated with processes related to context-bound information, and the knowledge store, which is associated with processes related to the use of language, logic, and structural relations (Parsons and Nixon 1993). Successful cognitive functioning involves the effective functioning of three processes: *availability*, referring to the retention of information; *access*, referring to the ability to retrieve information; and *efficiency*, referring to the capacity to utilize accurate or relevant information while ignoring or disregarding inaccurate or irrelevant information (Nixon and Bowlby 1996). Consistent with our data, efficiency processes have been found to be particularly susceptible to alcohol-related disruption (Nixon and Bowlby 1996; Glenn and Parsons 1991; Nixon and Parsons 1991), and our data suggest that the ERP may be a sensitive means of assessing cognitive efficiency in the visual memory do-

Table 3. Separate (for Each Group) Regional MANOVAs for c3 Amplitude Match vs. Nonmatch Effect

		Alcoholics ($n = 36$) (df = 1,34)	Controls ($n = 28$) (df = 1,26)
Central 13 electrodes	Nonmatch/match (S)	2.23	0.53
	Gender (Gd)	0.00	0.06
	S · Gd	0.47	1.51
Parietal 10 electrodes	S	0.57	23.12[a]
	Gd	0.18	0.28
	S · Gd	3.18	0.53
Occipital 8 electrodes	S	0.17	29.49[a]
	Gd	0.12	0.29
	S · Gd	0.00	1.15
Temporal 12 electrodes	S	0.27	10.25[b]
	Gd	0.12	0.09
	S · Gd	1.20	0.43

F value:
[a] $p < .001$.
[b] $p < .01$.

Table 4. Separate (Matching Condition) Regional MANOVAs on the Group Effect of the c3 (*F* Values)

Regions	df	Match	Nonmatch
Central	13,48	0.43	0.90
Parietal	10,51	1.01	0.95
Occipital	8,53	0.63	1.34
Temporal	12,49	1.83	1.62

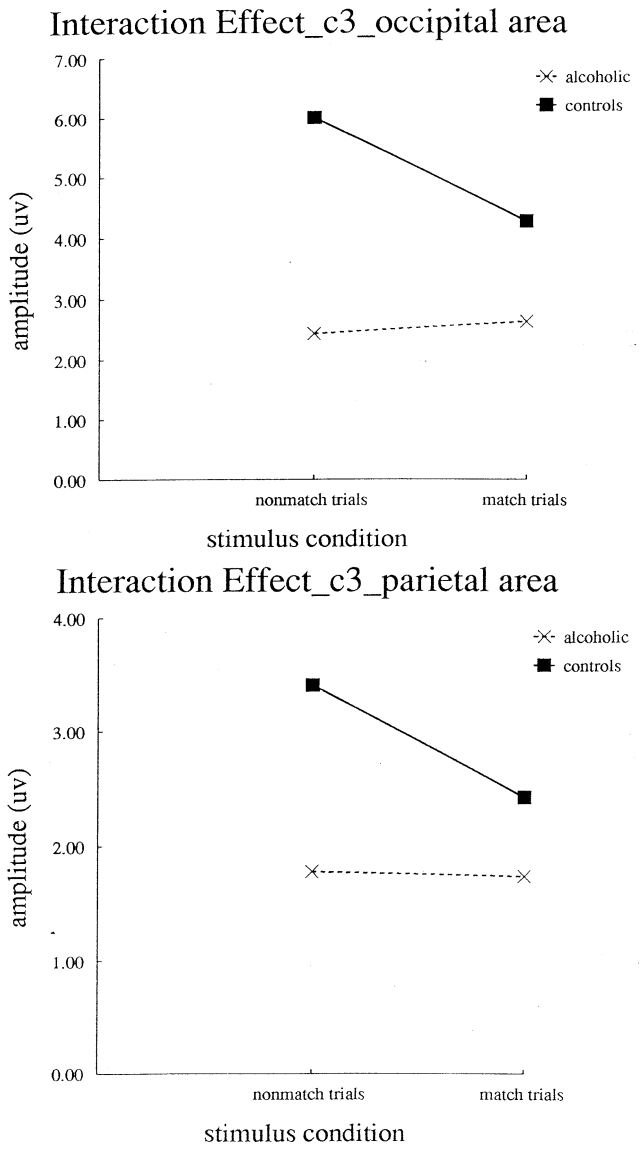

Figure 8. The interaction effects between groups (control/alcoholic) and stimulus conditions (match/nonmatch trials).

main of alcoholics. The lack of ERP differences between matching and nonmatching stimuli might also reflect alcoholics' tendencies toward uniform, rather than dynamic, adaptive responses to changing environmental stimuli. This is supported by the most consistent findings of the presence of smaller P3 amplitudes in abstinent alcoholics, which, in turn, indicated that they have difficulty in discriminating between relevant and irrelevant stimuli (Begleiter et al 1980; Porjesz and Begleiter 1985; Pfefferbaum et al 1987; Patterson et al 1987; Emmerson et al 1987; Cadaveira et al 1991).

In a similar experiment on 77 sober alcoholics and 48 controls conducted in our laboratory (Zhang et al in press), where the subjects were asked to match S1 and S2 on the basis of visual identity, however, both groups demonstrated suppressed voltage to matching stimuli in comparison to nonmatching stimuli; however, data are not available on whether the extent of the suppressed VMP voltage (the difference between matching- and nonmatching-elicited ERP) is similar between alcoholics and controls. Unlike the current study, where the sober alcoholics failed to differentiate category match pictures from category nonmatch pictures in their ERP responses, the alcoholics (Zhang et al in press) did not show the failure of the VMP response in differentiating identical object pictures from different object pictures. In addition, the VMP amplitude (Zhang et al in press) differentiated the two groups in response to nonmatching pictures of concrete objects, with smaller voltages for the alcoholic group than for the control group, but not in response to matching object pictures. As mentioned earlier, in the current study, the semantic information is extracted explicitly during category match/nonmatch processes. Thus the mnemonic availability indexed by the suppressed ERP voltage (to the matching stimuli in comparison to the nonmatching stimuli) has been associated with the semantic memory domain. The alcoholics in our study respond to category matching pictures in a similar fashion as to nonmatching pictures, indicating they have semantic memory deficits. The differences between the current experiment and the previous study (Zhang et al in press), regarding whether alcoholics differentiate matching from nonmatching stimuli in their ERP voltages, might indicate that the alcoholics have different aberrant patterns in mnemonic processes that are explicitly mediated by semantic labels. In fact, semantic memory deficits in alcoholics have been previously demonstrated in a lexical decision task (Porjesz and Begleiter 1996) requiring the subject to indicate as rapidly as possible whether a letter string is or is not a word; the N400 is elicited to unprimed unrelated words but not to primed antonym words in normal subjects, while alcoholics exhibit N400 to primed words in a similar fashion as to unprimed words. Since N400 has been found to vary as a function of semantic priming (Deacon et al 1995; Pratarelli 1995), these impaired priming mechanisms suggest possible semantic memory deficits in alcoholics. Considering the fact that the research methods have been less sensitive to alcohol-related verbal deficits in comparison to alcohol-related visual–spatial deficits (Nixon and Bowlby 1996), the current study may provide an alternative approach to the understanding of alcohol-related subtle deficits in the semantic/verbal domain.

Despite the integrated picture of the functional failure of alcoholics' ERP responses in differentiating the category matching from nonmatching process, neither the separate analysis of ERP amplitude in category matching nor that in the category nonmatching process yielded any signifi-

cant differences between groups. Nevertheless, the CSD maps differentiate the alcoholics from the controls not only in their response pattern to the match/nonmatch process as a whole but also at each step of the process. As Figure 5 illustrates, there was additional brain electric activity in the right occipitotemporal region of controls only in the nonmatching condition. This additional right brain activation in healthy controls suggests the sensitivity of the ERP (c3/VMP) spatial feature to the underlying neural activity in the nonmatching process, i.e., extra neural resources using additional nonsemantic clues appeared to be necessary in updating working memory when semantic priming was not available. The nonmatch-related extra brain effort has also been observed in other ERP paradigms, i.e., the larger P3 to novel stimuli (Wright et al 1995) and the larger N400 to semantic incongruity (Kutas et al 1987). In comparison to the controls, the CSD maps (Figures 5 and 6) of the alcoholics indicate an aberrant persistence of the right occipitotemporal electric activity over time. These data illustrate the failure of alcoholics in taking advantage of semantic priming, and the unnecessary brain activation required to fulfill the corresponding task. This suggests that alcoholics are less efficient in the processing of semantic match/mismatch stimuli in contrast to controls, as they are unable to respond differentially to category matching and nonmatching stimuli.

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