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Is working memory intact in alcoholics? An ERP study

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Abstract

Few investigators have applied the working memory theory to studies on abstinent chronic alcoholics, though it has been reported that the deficits in short-term memory appear to be specific to visuo-spatial and problem-solving tasks. In the present study, we recorded ERPs from 40 male control subjects and 78 alcoholics performing a modified delayed matching to sample task. To minimize the possible confound of retinotopic projections for the matching stimuli, in contrast to the non-matching stimuli, we employed a unique set of stimuli in our delayed matching to sample task. Our results indicate that an ERP component, occurring at approximately 250 ms post-stimulus, may be a reflection of the ERP mnemonic effect for working memory. This component distinguishes the two groups at the right occipitotemporal region, providing evidence of right hemisphere dysfunction in alcoholics. Thus, the current experiment may show electrophysiological evidence of working memory deficits in alcoholics. © 1997 Elsevier Science Ireland Ltd.

Keywords: Event-related potentials; Retinotopic; Delayed matching to sample paradigm

1. Introduction

Empirical studies of groups of alcoholics compared with control subjects indicate that lowered performance levels are obtained across a wide range of cognitive skills, including measures of perceptual-motor skills, visual–spatial performance, abstraction/problem solving and learning/memory processes (Oscar-Berman and Ellis, 1987; Parsons, 1987). Nevertheless, moderate to severe deficits on most other cognitive functions, especially memory, and normal range in IQs are typical symptoms in Korsakoff patients. In addition to the characteristic memory perturbations,

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patients with Wernicke–Korsakoff encephalopathy suffer other cognitive losses similar to those of chronic alcoholics (Wilkinson and Carlen, 1980). Thus, it was hypothesized (Lishman, 1986) that Korsakoff syndrome is a continuum of alcoholic cognitive deterioration commonly observed in sober chronic alcoholics. The defects in cognitive functions that can arise from prolonged alcohol abuse may well include deficits in various forms of memory.

A major source of difficulty in defining the separate memory problems of the alcoholic lies in the multidimensionality of memory. It has been considered that memory involves a number of interacting dimensions. One dimension is composed of dynamic processes related to the encoding, storing and retrieval of information. Another is the 'linear' flow of information from pre-attensive memory to short-term and long-term memory. This multiplicity may explain the inconsistent results of memory deficits in chronic alcoholics (for review, see Riege, 1987). Recently, Baddeley (1992) defined working memory as a system that provides temporary storage and manipulation of the information necessary for a large variety of cognitive tasks. An important feature of working memory is that it involves active information storage processes. An active storage mechanism involves rehearsal, a process by which the system reads information from the store and then feeds it back, thereby continually refreshing or updating the memory trace. Therefore, working memory describes the active aspects of short-term memory, and acts as an interface between memory and cognition (Baddeley, 1994; Logie et al., 1990).

A complete specification of various subsystems of working memory in both 'normal' and chronic alcoholics has been difficult to obtain from behavioral data or neuropsychological tests because these data reflect the combined results of three aspects of working memory, i.e. storage, maintenance and retrieval operations. A possible approach for isolating these three operations is the use of the delayed matching to sample task (DMS), with electrophysiological recording to specify their respective spatial–temporal patterns. The DMS paradigm contains the basic processes of working memory, such as information encoding, maintaining, retrieving and comparing. The electrophysiological recording techniques, among which the event-related potential (ERP) technique is most appropriate for studies in human cognition, provide a method for establishing the timing and general scalp localization of working memory processes. In a series of ERP studies, we have identified a visual memory potential (VMP) which indexes visual working memory (Begleiter et al., 1993, 1995; Hertz et al., 1994; Zhang et al., 1995, 1997, in press). This ERP component is generally located in the occipitotemporal regions, essential for object vision and visual memory (Tanaka, 1996). This ERP component is also in keeping with the temporal and spatial characteristics of the electrical activities recorded in animal experiments on visual working memory (Fuster and Jervey, 1981; Baylis and Rolls, 1987; Miyashita, 1988; Miyashita and Chang, 1988; Miller and Desmone, 1994).

However, the DMS paradigm performed both in human and monkey experiments may be confounded, because of the identical retinotopic projections for the matching stimuli, in contrast to the non-matching stimuli, though studies in monkeys have indicated inferior temporal mechanisms for invariant object recognition (Lueschow et al., 1994; Ito et al., 1995). The adjustment of an object's size and position on the retina for subsequent recognition may occur even at the primary visual cortex (Chino et al., 1992; Gilbert and Wiesel, 1992). Since IT mechanisms for invariant object recognition exist, the identical contents between sample and test stimuli may produce an identical neural representation. Thus, mnemonic effects might be due to an isomorphic 'pixel-by pixel' comparison of the current stimulus to previously seen stimuli. One way to eliminate this possible confound is to make stimuli differ from sample stimuli. Consequently, the judgment on matches or mismatches between test and sample stimuli can only be gained after further deductive reasoning. Moreover, the encoded information can either be held in working memory to prevent forgetting during the process of maintenance (maintenance rehearsal) or be further processed to lead to an increase in the depth at which an

item is encoded (elaborative rehearsal) (Baddeley, 1990). One of the most powerful features of human complex cognitive activities is the ability to reason or recognize objects that have been transformed in some ways from the time of their first appearances. Therefore, a DMS paradigm with such a task requirement should strongly activate both the visuospatial sketchpad and the central executive of working memory, providing a way to describe the mechanism of working memory.

In the present study, we tested whether working memory is influenced by long-term alcohol abuse in a large group of chronic alcoholics without neurological signs of Wernicke–Korsakoff syndrome by incorporating our modified DMS paradigm with ERP techniques. We hypothesized that long-term alcohol abuse would affect visual working memory, because: (1) there is evidence that chronic alcohol abusers perform more poorly on visuo-spatial tests of cognition than they perform on verbal tests (for review, see Cermak, 1990; Oscar-Berman et al., 1992); (2) alcohol abuse decreases the capacity of attention (Josephs and Steele, 1990; Steele and Josephs, 1988) which constitutes an important part of working memory; (3) working memory is considered as an interface between cognition and memory. While trying to describe the processes of working memory and making comparisons between the two groups by ERPs, we also attempted to characterize the general regionalization of subprocesses and subsecond dynamics of the working memory system by using 61 electrodes and scalp current source density to assess their topographic distributions in the two groups.

2. Methods

2.1. Subjects

Forty male control subjects (mean age: 25.5 ± 3.59; range: 19–33 years of age) participated in the experiment. These control subjects were recruited from the students and staff of the SUNY HSCB via advertisements posted on campus. 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 family history of alcohol and drug abuse, or any personal history of neurological or psychiatric disease. The alcoholic group consisted of 78 male alcoholics (mean age 35.47 ± 5.29; range: 26–47 years of age). 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-R criteria, and the confirming diagnosis was made in our laboratory by one of the authors (HB or PB) using instruments developed by the COGA (Collaborative Studies on the Genetics of Alcoholism) group (Begleiter, 1995) which includes the SSAGA (Semi-Structured Assessment for the Genetics of Alcoholism) (Bucholz et al., 1994, 1995) and the standard Folstein MMSE (Mini Mental Status Examination (Braekhus et al., 1992). All the alcoholics in the study were hospitalized for a minimum period of 30 days on a closed ward before participating in our ERP study. Thus, all alcoholics were fully detoxified and had no alcohol available for that period of hospitalization. The average length of drinking for our alcoholics is more than 15 years. Alcoholics 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 alcoholics were significantly older than the control subjects ($T_{107.0} = 12.075$, $P < 0.0001$). All research participants were asked to sign informed consent forms.

2.2. Experimental design

2.2.1. Stimuli and stimulus presentation

The stimuli consisted of 80 different sample stimuli (S1) and 80 different test stimuli (S2). Each individual stimulus was different and hard to verbalize. A matching set of stimuli (S1 and S2) consisted of two complementary shaped stimuli

which fitted together to form a final uniform shape or form. Half of the test stimuli were complementary to the sample stimuli (FIT); the other half of the S2 group were not complementary (NONFIT) (see Fig. 1). All trials (total pairs of stimuli) were intermingled and presented consecutively in a pseudorandom order. The interstimulus interval (S1–S2) was fixed to 1.6 s and the duration of presentation for each stimulus was 300 ms. All the stimuli were presented in white within a 10 × 10-cm dim frame square on the center of a computer monitor, subtending a visual angle of 5–6°. The dim frame was sustained in the center of the CRT for an entire trial. The inter-trial interval (S1 + S2) was fixed to 3.2 s.

2.2.2. Subject's task

The subject's task was to judge whether the S2 was complementary to the S1 within a trial to a regular shape (e.g. a square or a circle). After seeing each S2, the subjects had to press a mouse key in one hand if the S2 was complementary to S1, or press the other mouse key in the other hand if the S2 did not fit into S1. The designation of the hand indicating 'fit' or 'Nonfit' was alternated across subjects. The response accuracy and speed were equally stressed.

2.2.3. Electrophysiological recording

The subject was seated in a reclining chair located in a sound-attenuated RF shielded room

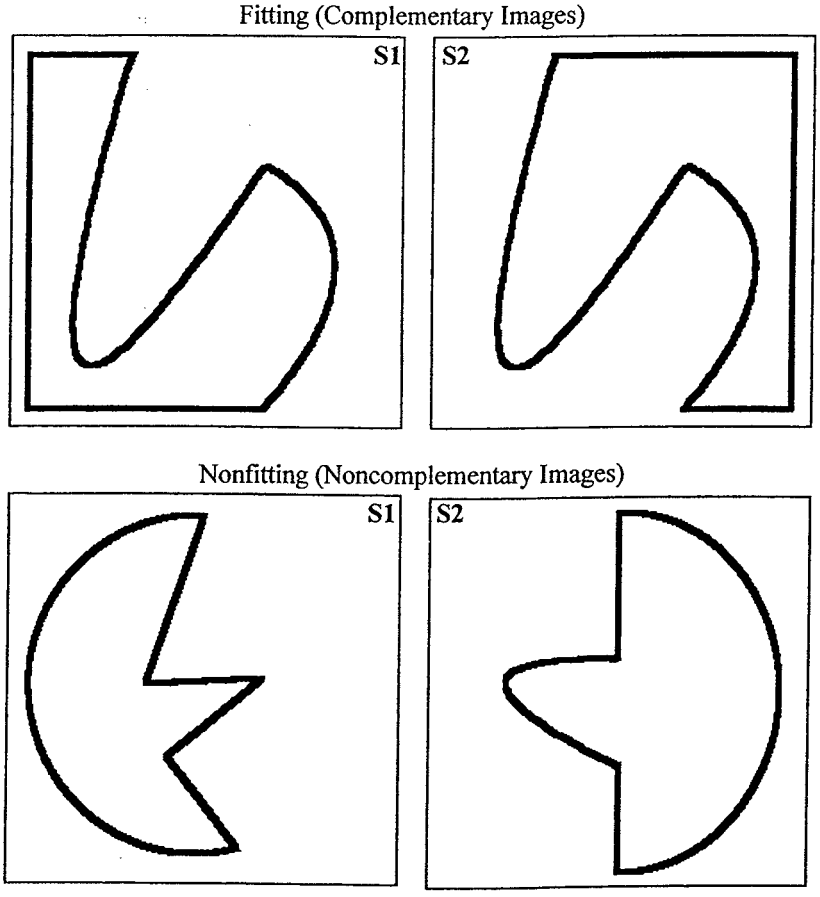

Fig. 1. Two sample pairs of stimuli in Fit and Nonfit trials, respectively, are shown. S1 represents the sample stimulus, and S2 represents the test stimulus in a delayed matching to sample trial.

and fixated a point in the center of a computer display located 1 m away from his eyes. Each subject was fitted with a 61-lead electrode cap (ECI, Electrocap International). We used the entire 10/20 International montage along with an 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, Tp7, Tp8, P1, P2, P5, P6, Poz, Po1, Po2, Po7, and Po8 (Standard Electrode Position Nomenclature, American Electroencephalographic Association, 1990). The nose electrode served as reference and the forehead electrode as ground. The electrode impedance was always below 5 kΩ. Two additional bipolar derivations were used to record the vertical and horizontal EOG. The signals were amplified with a gain of 10 000 by an Ep-A2 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 ms of pre-stimulus baseline and 800 ms following each stimulus presentation. Trials with excessive eye and body movements (> 73.3 μV) were rejected on-line. At least 25 artifact-free ERPs were needed to generate an average ERP for each condition.

2.3. Data analysis

Only ERPs with artifact-free trials and correct responses were averaged, yielding three ERP categories according to different stimulus conditions. Fig. 2 shows the grand mean ERPs to S1, S2-Fit, and S2-Nonfit stimuli in the control and alcoholic groups, respectively. As illustrated in Fig. 2a,b, the ERP patterns both in the control subjects and the alcoholics consist of four components which are most discernible in the posterior electrodes. Component 1 (c1) peaks around 110 ms post-stimulus; component 2 (c2), whose polarity is opposite to that of c1, has a latency of approx. 170 ms post-stimulus; component 3 (c3) peaks around 250 ms post-stimulus; component 4 (c4), which has the same direction as c2, has the maximal absolute amplitude measurements at approx. 340 ms post-stimulus. However, each component latency varies across electrodes, especially from the posterior electrodes to the frontal electrodes. It is also questionable to attribute two waveforms which are located at different electrodes and have different peak latencies to the same generator. Thus, we made the fixed time windows (TWs) by every 100 ms within which the areas between the ERP segments and the baseline were calculated. Therefore, each calculation represented a mean ERP amplitude within a corresponding time window, i.e. TW0–1 represented the mean ERP amplitude between 0 and 100 ms post-stimulus, TW1–2 denoted mean amplitude between 100 and 200 ms post-stimulus, etc.

The mean ERP amplitudes within each kind of TW across electrodes were organized into groups by brain region for further statistical analyses. The frontal region consisted of Fp1, Fp2, Fpz, Af7, Af8, Af1, Af2, Afz, F7, F8, F5, F6, F3, F4, F1, F2, Fz; the central region consisted of Fc1, Fc2, Fc3, Fc4, Fc5, Fc6, Fcz, C1, C2, C3, C4, C5, C6; the parietal region consisted of Cp1, Cp2, Cpz, Cp3, Cp4, Pz, P1, P2, P3, P4; the occipital region consisted of Po1, Po2, Poz, O1, O2, Oz. The left temporal region consisted of T7, Tp7, Cp5, P5, P7, Po7; and the right temporal region consisted of T8, Tp8, Cp6, P6, P8, Po8. Then, a number of MANOVAs were carried out separately for each kind of TW area measurement at each regional electrode array as a dependent vector for comparisons among different stimulus conditions within each group. However, for the ERP comparisons between groups, we further divided the arbitrary brain regions into the left and right sides, because long-term alcohol abuse may affect the right and left hemisphere differently. Because of the significant age difference between our alcoholic and control groups, we initially performed regression analyses between ERP data and the subjects' ages in each group, and found that slopes between ERP data and age did not differ between control subjects and alcoholics. Therefore, age was used as a covariate where it was appropriate to control linear effect from different groups in comparisons between control and alcoholic data.

Since the scalp potentials may reflect the average activity of multiple neural sources recorded at a distance, they are neither reference-free, nor

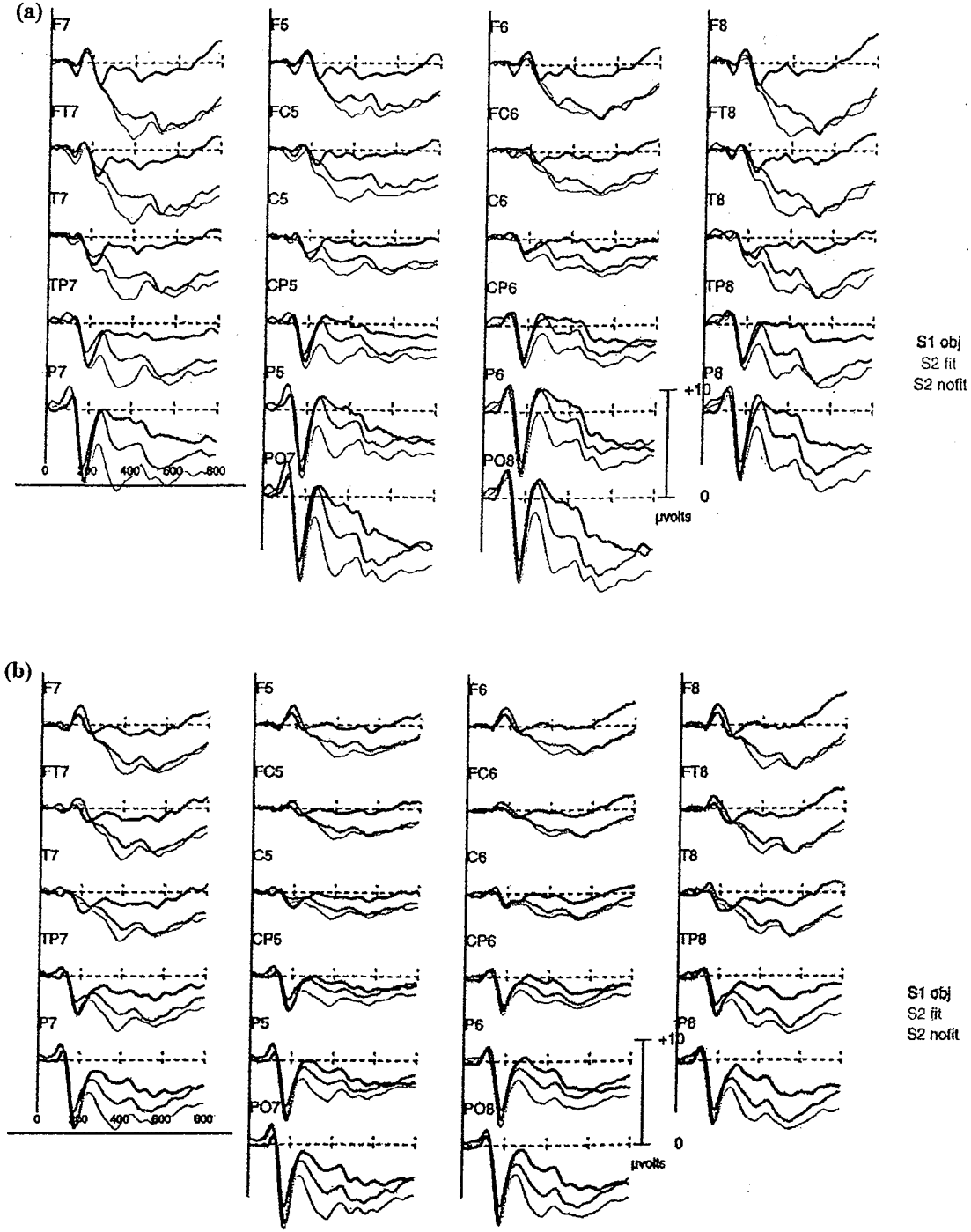

Fig. 2. (a) Grand mean ERPs in the control subjects. An upgoing wave form represents the relative positivity at the recording electrode compared to the reference electrode at Cz, but there was no determination of absolute polarity. S1 represents ERPs to sample stimuli; S2 fit represents ERPs to test Fit stimuli; and S2 nofit represent ERPs to test Nonfit stimuli. Due to the limitation of space, only data from 22 electrodes referenced to Cz are presented. (b) Grand mean ERPs in the alcoholic subjects. An upgoing wave form represents the relative positivity at the recording electrode compared to the reference electrode at Cz, but there was no determination of absolute polarity. S1 represents ERPs to sample stimuli; S2 fit represents ERPs to test Fit stimuli; and S2 nofit represents ERPs to test Nonfit stimuli. Due to the limitation of space, only data from 22 electrodes referenced to Cz are presented.

independent of volume conductor effects. 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 visual analysis of our electrophysiological data, we constructed topographic maps of SCD (Source Current Density). The scalp region having a positive current density corresponds to a source region where a local radial current is flowing through the skull into the scalp.

3. Results

3.1. Behavioral data analyses

Both the control subjects and alcoholics performed with a high percentage of correct response, namely, more than 98% for the control subjects and 97% for the alcoholics. The subject response times for each stimulus condition are listed in Table 1. A two-way ANOVA was run according to the general 0 linear model (GLM, SAS v6.11) using age as the covariate, indicating a significant group effect ($F_{1,239} = 8.7$, $P < 0.01$). The stimulus effect tended to be significant ($F_{1,239} = 3.22$, $P = 0.07$). No significant interaction effect between the group and stimulus condition could be revealed ($F_{1,239} = 0.91$, $P = 0.34$). Further analysis indicated that the source of the significant group effect is the significant longer response times to Nonfit stimuli in the alcoholics than in the control subjects ($F_{1,117} = 8.23$, $P < 0.01$).

Table 1
Response times in each group

	Fit	Nonfit
Control subjects	910.62 ± 197.07	842.27 ± 157.56
Alcoholics	945.39 ± 175.74	921.45 ± 155.55*

*$P < 0.01$.

3.2. ERP data analyses

3.2.1. The control subjects

A number of MANOVAs (GLM, SAS v6.11) were performed to make comparison between the ERPs to Fit and to Nonfit stimuli. No significant stimulus effects could be demonstrated on TW0–1 and TW1–2. However, the significant differences between Fit and Nonfit trials on TW2–3 were found widespread over the scalp brain regions: the left temporal region (Wilk's Lambda = 0.78, $F_{7,72} = 2.9$, $P < 0.01$); the right temporal region (Wilk's Lambda = 0.80, $F_{7,72} = 2.5$, $P < 0.02$); the parietal region (Wilk's Lambda = 0.78, $F_{9,70} = 2.2$, $P < 0.04$); the central region (Wilk's lambda = 0.68, $F_{13,66} = 2.4$, $P < 0.02$; and right frontal region (Wilk's Lambda = 0.80, $F_{7,72} = 2.6$, $P < 0.02$). These significant stimulus effects were also found on TW 3–4 at the brain regions, such as the left temporal (Wilk's Lambda = 0.82, $F_{7,72} = 2.20$, $P < 0.05$), the right temporal region (Wilk's Lambda = 0.77, $F_{7,72} = 3.15$, $P < 0.01$), and the right frontal region (Wilk's Lambda = 0.76, $F_{7,72} = 3.25$, $P < 0.01$). As shown in Fig. 2a, the ERPs to sample stimuli diverge from the ERPs to test stimuli from approx. 300 ms post-stimulus. The MANOVAs verified the significant differences between TW2–3, TW3–4 and TW4–5 in the sample stimulus trials and the Fit stimulus trials at every brain region. However, TW3–4 and TW4–5 in the sample stimulus trials differed significantly from their counterparts in the Nonfit stimulus trials at almost all brain regions except for the parietal region. These significant differences between the ERPs to sample stimuli and to test stimuli lasted to the end of the electrical recording epoch in the frontal regions.

3.2.2. The alcoholics

Like the statistical results in the control subjects, TW0–1 and TW1–2 were not significantly influenced by stimulus conditions. However, TW2–3 in the Nonfit trials significantly differed from those in the Fit trials only at the temporal region (Wilk's Lambda = 0.09, $F_{7,148} = 2.44$, $P < 0.03$). In the alcoholics, TW2–3 in the sample trials significantly differed from those in the Fit trials at all of the brain regions except for the central region: the left temporal region (Wilk's Lambda = 0.86, $F_{7,148} = 3.47$, $P < 0.01$); the right region (Wilk's Lambda = 0.86, $F_{7,148} = 3.46$, $P <$

0.01); the occipital region (Wilk's Lambda = 0.88, $F_{6,149} = 3.51$, $P < 0.01$); the parietal region (Wilk's Lambda = 0.84, $F_{9,146} = 3.20$, $P < 0.01$); the left frontal region (Wilk's Lambda = 0.77, $F_{7,148} = 6.18$, $P < 0.01$); and the right frontal region (Wilk's Lambda = 0.86, $F_{7,148} = 4.03$, $P < 0.01$). However, there was no significant difference in TW2–3 between the sample trials and Nonfit trials. Like the control subjects, the significant differences between TW3–4 in the sample trials and in the Fit trials as well as between TW4–5 in the sample trials and in the Fit trials were ubiquitously demonstrated by the MANOVAs across the brain regions in the alcoholics. Statistical analyses on TW4–5 yielded a similar result pattern except for the parietal region where, unlike the statistical results of TW3–4, no significant differences between the sample test stimulus conditions were demonstrated. Again, the significant differences between the ERPs to sample stimuli and to test stimuli lasted to the end of the electrical recording epoch in the frontal regions in the alcoholics.

3.2.3. Comparisons between the two groups in ERPs

For the group comparisons, MANCOVAs (GLM, SAS v6.11) were performed using age as a covariate. Significant group differences at the right temporal region were demonstrated by MANCOVAs on TW2–3s in the sample trials (Wilk's Lambda = 0.86, $F_{7,109} = 2.50$, $P < 0.03$, in the fit trials (Wilk's Lambda = 0.82, $F_{7,109} = 3.39$, $P < 0.01$, and in the Nonfit trials (Wilk's Lambda = 0.88, $F_{7,109} = 2.10$.$P < 0.03$). Further group differences at the right temporal region were revealed on TW3–4 (Wilk's Lambda = 0.85, $F_{7,109} = 2.81$, $P < 0.01$) and TW4–5 (Wilk's Lambda = 0.87, $F_{7,109} = 2.20$, $P < 0.04$) to fit stimuli. Fig. 3a illustrated ERPs to Fit stimuli in the temporal region in the two groups. In the right parietal region, significant group differences were shown on TW4–5 to sample stimuli (Wilk's lambda = 0.91, $F_{4,112} = 2.71$, $P < 0.04$). In the control subjects TW5–6 to sample stimuli significantly differed from that in the alcoholics at both the right (Wilk's Lambda 0.87, $F_{7,109} = 2.39$, $P < 0.03$) and the left (Wilk's Lambda = 0.85, $F_{7,109} = 2.66$, $P < 0.02$) frontal regions. Fig. 3b shows the frontal ERPs to sample stimuli in the control and alcoholic groups.

3.3. SCD topographic distributions in the two groups

Because the c3 was consistent and stable waveform over the posterior electrodes and maximally reflected the mnemonic ERP effects, the SCD topographic maps were made according to the latencies of the c3s in different stimulus conditions. Fig. 4a shows the SCD topographies of c3 in the control subjects. Fig. 4a shows the SCD topographies of c3 in the control subjects. As illustrated in Fig. 4a, both Fit and Nonfit stimuli activated strong current sources at the occipitotemporal regions. These current sources at the occipitotemporal regions were basically symmetrical. The difference between SCDs in the two stimulus conditions was that the frontal regions were more involved in the processing of Fit stimuli than the Nonfit stimuli. As Fig. 3a shows, there were active current sources and sinks at the frontal regions in the Fit trials, however, the current activities were hardly found at the frontal regions in the Nonfit stimulus trials. Fig. 4b shows the SCD topographies of c3 in the alcoholics. Compared with Fig. 4a, Fig. 4b shows different current source distribution patterns from those in the control subjects. In the alcoholics, the sources evoked by the Fit stimuli were mainly located over the left hemisphere. This phenomenon was mostly obvious at the occipitotemporal regions. Moveover, more dynamic current sources and sinks were also found at the left than at the right frontal region. Unlike the SCD distributions in the control subjects, the Nonfit stimuli could elicit the current sources at the frontal regions in the alcoholics. Generally, the current sources and sinks elicited by both the Fit stimuli and Nonfit stimuli in the alcoholics had lower density smaller fields than those in the control subjects, particularly in the occipitotemporal regions.

4. Discussion

The present results not only describe the operations of working memory, but also imply that

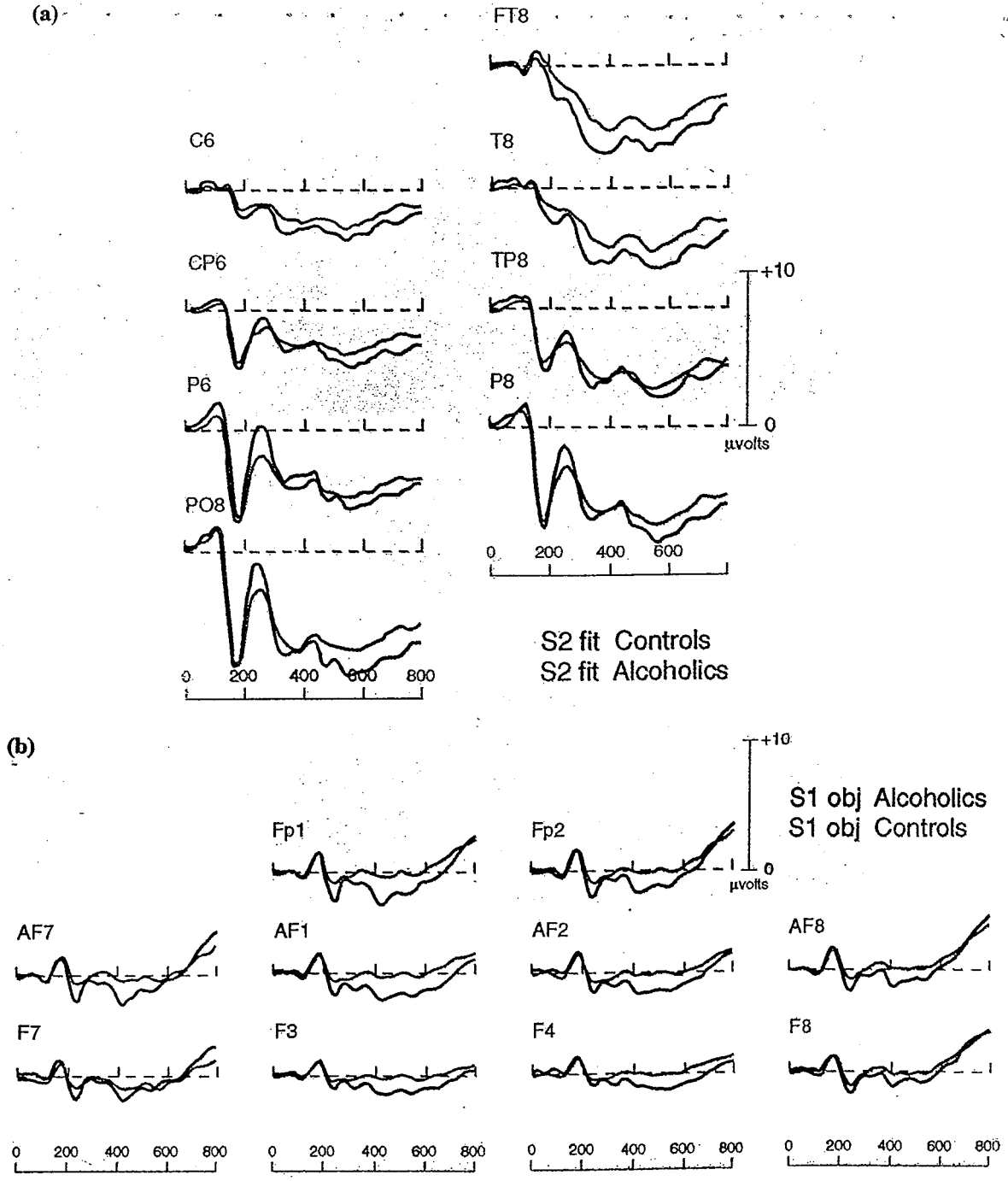

Fig. 3. (a) Grand mean ERPs to Fit stimuli comparisons between the control subjects and the alcoholics in the right temporal region. Cz was used as reference. (b) Grand mean ERPs to Sample stimuli comparisons between the control subjects and the alcoholics in the frontal region. Cz was used as reference.

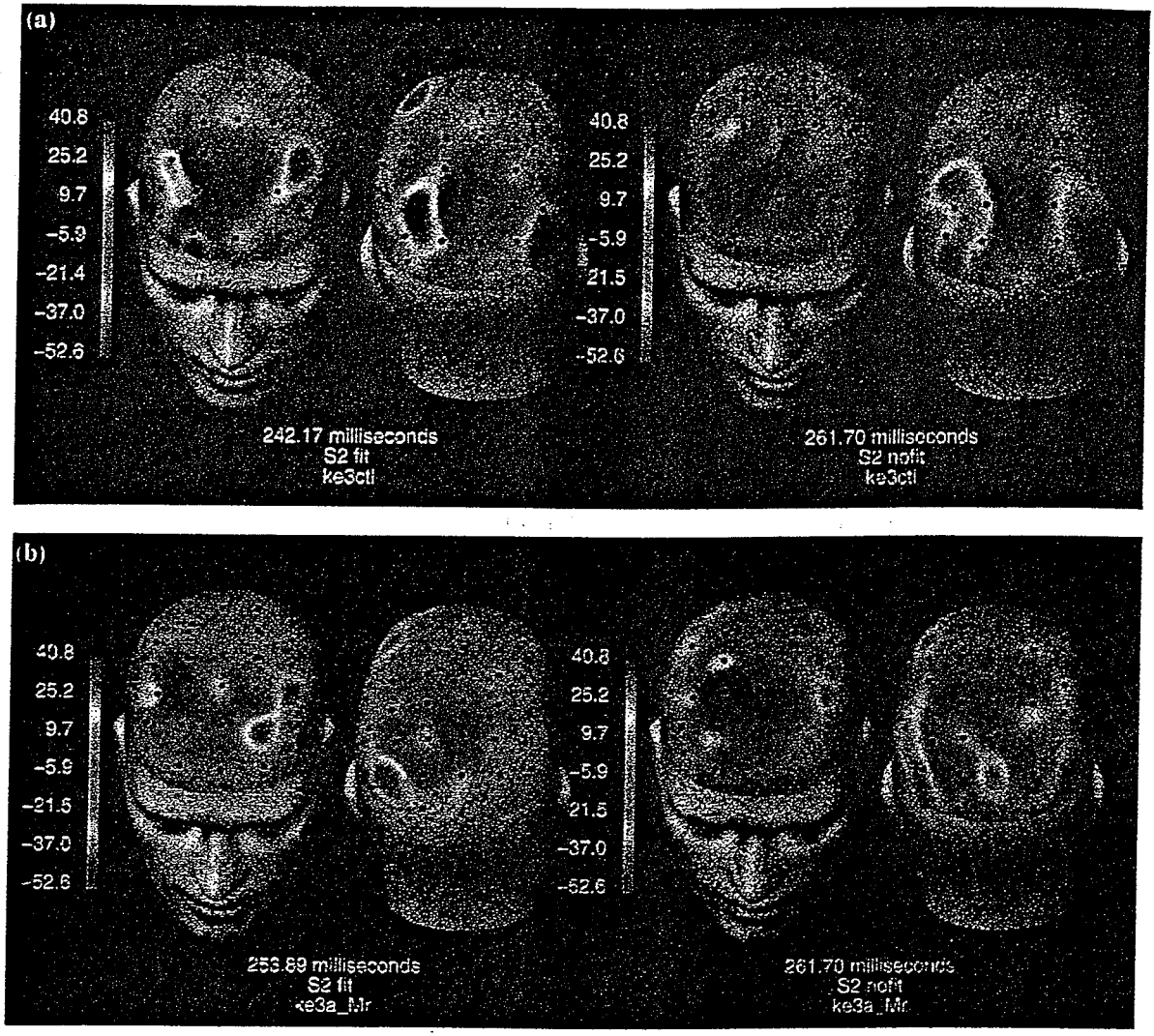

Fig. 4. (a) SCD topographic maps in the control group. The numbers below each pair of heads are latencies when c3 to each test stimulus condition reaches its peak. (b) SCD topographic maps in the alcoholic group. The numbers below each pair of heads are latencies when c3 to each test stimulus condition reaches its peak.

several scalp regions, where several cortical regions have been known to be involved in working memory, are strongly activated with our paradigm. Meanwhile, the present experiment yields significant differences in the ERP mnemonic effects between the control subjects and the alcoholics.

In our experiment, the response times to the Fit stimuli were longer than those to the Nonfit stimuli in both groups. This pattern in the control subjects and the alcoholics is contrary to most studies on RTs in which the RTs to repeated or matching stimuli are generally shorter than those to unrepeated or non-matching stimuli (Kroll and Potter, 1984; Bentin and Moscovitch, 1988; Schacter et al., 1991; Cave and Squire, 1992; Begleiter et al., 1993, 1995; Hertz et al., 1994; Zhang et al., 1995). However, the reversed RT pattern in the present experiment, in turn, indi-

cates the unique mode of our stimuli. By avoiding the identity of the sample and test stimuli in the matching trials (Fit trials) in the modified DMS paradigm, we confidently removed the physical repetition priming effect to which implicit memory contributes a lot. In this experiment, we increased memory loading on the 'match' and 'non-match' trials in a more parallel way than other previous studies to ensure the activation of subjects' working memory. However, the longer RTs in the Fit trials than in the Nonfit trials, though not significant, suggest that the processing of the Fit stimuli may take more execution time than that of Nonfit stimuli.

In the present study, however, we also noticed that the RTs to both kinds of stimuli in the alcoholics were generally longer than those in the control subjects, especially the RTs to the Nonfit stimuli were significantly longer in the alcoholics than in the control subjects. In the present stimulus paradigm, the Fit stimuli triggered processes, such as information encoding, problem-solving and reasoning. However, processing the Nonfit stimuli placed particular emphasis on perceptual-motor skills. Because our alcoholics did not manifest the signs for peripheral neuropathy, the significant delayed response time to the Nonfit stimuli in the alcoholics may indicate the alcoholics' poorer perceptuomotor function which has been demonstrated repeatedly (Glenn and Parsons, 1992; Maylor and Rabbit, 1993; Beatty et al., 1995; Zlotnick et al., 1995).

The ERP patterns in both the control and alcoholic groups are quite similar. That is, at 300 ms post-stimulus, the ERPs to sample stimuli significantly differ from those to test stimuli. This difference is widespread across scalp and most remarkable at the frontal regions. The potential neural process for the sample trials is information encoding. However, sustained activation during the delay has been observed in prefrontal neurons during the performance of behavioral tasks which require monkeys to actively retain information (Fuster et al., 1982; Kojima and Goldman-Rakic, 1982; Watanabe, 1986). Some neurons in other cortices like temporal regions have the property to discharge during the delay period of the DMS task to maintain information encoded from sample stimuli (Fuster and Jervey, 1981; Miyashita, 1988; Miyashita and Chang, 1988). Moreover, in human ERP studies using variations on the delayed matching to sample paradigm, it has been demonstrated that the ERP slow wave amplitudes and topographies have varied as a function of the type of material and information load (Rugg, 1984a,b; Barret and Rugg, 1990; Lang et al., 1992; Ruchkin et al., 1995). Thus, the activation throughout the entire delay period in the sample trials could be a neural correlate of an active storage mechanism for working memory that is required to perform the task correctly (Funahashi and Kubota, 1994). Our current results further suggest that different brain regions are functionally overlapping to maintain information 'on-line' for later use.

Within a time window between 200 and 400 ms post-stimulus approximately, the amplitudes of the ERPs to fitting stimuli are significantly decreased compared to those to Nonfit stimuli. This phenomenon could be typically demonstrated at the right temporal, left temporal, and right frontal regions in the control subjects, and at the left temporal region in the alcoholics. It may well be the similarity between the inner representation from the present stimulus and the memory trace for that stimulus which results in a significant reduction of the ERP. However, the degree of reduction cannot be taken to solely reflect the process of retrieval, but instead, involves a number of different processes including encoding of the original stimulus, active maintenance of the memory trace, and retrieval and comparison stimuli. The current results agree with previous ERP studies in humans (Begleiter et al., 1993, 1995; Hertz et al., 1994; Zhang et al., 1995, 1997), PET studies in humans (Tulving et al., 1996; Cabeza et al., 1997) and experimental investigations in monkeys performing DMS tasks (Baylis and Rolls, 1987; Riches et al., 1991; Lueschow et al., 1994; Miller and Desmone, 1994; Tanaka, 1996). However, the current experiment has some novel implications. Although it has been shown that neuronal responses in monkey inferotemporal cortex do not vary with the size and position of stimulus images on the retinas (Lueschow et al., 1994), the memory of a sample

stimulus did not prime the incoming test stimulus by its initial content in the present experiment. In order to make a judgment as accurately and quickly as possible, the subject may actively process the encoded information from sample stimulus and/or reason out a possible fitting representation (elaborative rehearsal) while maintaining the information in memory. Thus, the memorization of a stimulus within the working memory system could derive from, but not necessarily duplicate the original form of the stimulus in details. The ERP component between 200 and 400 ms post-stimulus in the present study, which was indicated as a memory potential (VMP) by a series of our previous studies (Begleiter et al., 1993, 1995; Hertz et al., 1994; Zhang et al., 1995, 1997), is again shown to be a reflection of ERP mnemonic effects in human beings.

Although the ERP patterns in the alcoholics were similar to those in the control subjects, the current experiment yielded significant group differences. These were found at the right temporal, the right parietal, and both the right and left frontal regions. The inferotemporal cortex is not only assumed to code visual images of objects, but also to store the coded images for a short period. A common deficit detected in alcoholics is the demand for effort in encoding and retrieving of to-be-remembered information (Riege, 1987). Therefore, the group differences at the right temporal region in the current experiment may suggest deficits in encoding and retrieving information in chronic alcoholics. Meanwhile, the longer duration of significant group differences in ERPs to Fit stimuli (from 200 to 500 ms post-stimulus) may well be because the Fit stimuli are more effort-demanding. Moreover, the late onset of the group differences between ERPs to sample stimuli (400–600 ms post-stimulus) at the frontal and the right parietal regions may further imply deficits in short-term retention of information in alcoholics. Information-processing streams (parietal and temporal) in human visual cortex have been proposed (Tootell et al., 1996). It has also been suggested that enhancement and delay activity may depend on feedback to temporal cortex from prefrontal cortex, and are thought to be important for working memory (Desimone, 1996). Furthermore, deficiency in information retention may result in insufficient priming to test stimulus. Therefore, our experiment strongly suggests that long-term alcohol abuse influences working memory.

The SCD topographic maps in the present study again indicate the involvement of the occipitotemporal regions in processing the visual stimuli. However, the SCD topographic maps in the Fit and Nonfit stimulus conditions also show the differences in terms of the current source distribution pattern. The main locations of current sources over occipitotemporal regions in Nonfit stimulus conditions may suggest that the occipitotemporal regions are strongly involved in setting up and manipulating the new imagery in working memory. However, the comparatively confined current sources over the occipitotemporal regions and active current sources and sinks over the frontal regions in the Fit stimulus condition may suggest that an inner representation from preceding stimuli is activated by 'comparing and matching' with the new representation being encoded from the test stimulus. Our SCD topographic patterns activated by the test stimuli are in agreement with working memory studies with PET and fMRI in humans (Andreasen et al., 1995; Tulving et al., 1996; Cabeza et al., 1997). Thus, the SCD map for the FIT and Nonfit stimulus conditions may reflect different neural processes within working memory. Compared with the control subjects, the most conspicuous phenomena in SCD topographic maps in the alcoholics are the lack of current sources over the right hemisphere in the Fit trials and smaller and confined current sources at the occipitotemporal regions in the Nonfit trials. This phenomenon in the alcoholics may suggest that although visual information is encoded and processed in the occipitotemporal regions, further manipulation and retrieval of the encoded visual information are deficient in the right hemisphere. Thus, the distinction in SCD topographies between the two groups may suggest that the subjects in the two groups employ different ways to process the encoded information within working memory. The alcoholics may be more dependent on the left hemisphere; but the control subjects use both

hemispheres efficiently. It has been pointed out that the left hemisphere has more efficient access to 'structural descriptions' of objects (which specify components common to all members of a visual category) because it combines an analytical feature–comparison process with top-down processing; whereas, the right hemisphere, in contrast, may rely more on holistic pattern matching (Vitkovitch and Underwood, 1992). A large number of studies indicated that the right hemisphere is more vulnerable than the left hemisphere to the adverse effects of acute doses of alcohol (Porjesz and Begleiter, 1985; Tarter and Edwards, 1985) and long-term alcohol abuse (Bolter and Hannon, 1986; Lister et al., 1985; Tsagareli, 1995). Thus the present study also lends support to the right-hemisphere hypothesis of chronic alcoholism.

In conclusion, the present study indicated that an ERP component, occurring at approximately 250 ms post-stimulus, was evoked with a modified delayed matching to sample paradigm (DMS). Our results rule out the retinotopic confound as a potential mediator variable in DMS paradigms, and are in agreement with other neurophysiological studies on memory. Thus, we assume this ERP component to be a reflection of a mnemonic effect in working memory. Applying this ERP component to alcoholics, we found it distinguished the two groups. The significant differences between the two groups mainly occurred at the right occipitotemporal region, which is in accordance with the findings of right-hemisphere dysfunction in alcoholics. Therefore, the current data may reflect electrophysiological evidence of a working memory deficits in alcoholics.

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