Suppression of Mismatch Negativity by Backward Masking Predicts Impaired Working-Memory Performance in Alcoholics

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Background: Pronounced disruption of memory traces by subsequent distractors may result in impaired behavioral memory performance in alcoholics.

Methods: This hypothesis was investigated with an electrophysiological index of auditory sensory-memory traces, mismatch negativity, a preattentive event-related potential component elicited by a “deviant” tone within a train of “standard” tones.

Results: Inserting a masking stimulus after these tones abolished mismatch negativity in alcoholics (DSM-IV) but not in social-drinker controls. This effect predicted working-memory impairment in alcoholics, and correlated significantly with self-reported alcohol consumption of the subjects. Furthermore, the backward-masking mismatch negativity paradigm detected sensory-memory impairment in 9 of 20 alcoholics (sensitivity 45%), whereas all 20 social drinkers were unimpaired (specificity 100%).

Conclusions: Vulnerability to memory trace disruption by shortly following sounds may be one of the factors contributing to behavioral memory dysfunction in alcoholics. The present result may provide an objective neurophysiological tool for investigation of alcohol-induced and other degenerative brain disorders.

Key Words: Alcoholism, Auditory Sensory Memory, Event-Related Potentials, Mismatch Negativity, Neuropsychological Tests.

BY ANY MEASURE, alcohol abuse constitutes a worldwide social and health problem. It has been estimated that in the United States alone, there are approximately 13 million individuals who need treatment for alcohol use disorders (Institute of Medicine, 1990). The presence of alcohol-induced structural brain lesions and neurocognitive disorders is well established (Bergman et al., 1980; Brewer and Perrett, 1971; Ishii, 1983; Jernigan et al., 1991; Knight and Longmore, 1994). Despite the high clinical need and profusion of intensive research, satisfactory clinical applications for early detection and monitoring of alcohol-related disturbances of brain function have not yet been developed.

According to brain imaging and pathological studies, chronic alcoholism has been associated with brain atrophy (Bergman et al., 1980; Brewer and Perrett, 1971; Ishii, 1983; Jernigan et al., 1991) and loss or shrinkage of cortical neurons (Harper et al., 1987; Kril and Harper, 1989). Profound alcohol-related changes in cerebral blood flow and metabolism have also been observed (Gilman et al., 1990; Nicolás et al., 1993; Sachs et al., 1987). The studies on auditory event-related potentials (ERPs), electroencephalographic (EEG) changes time-locked to the presentation of auditory stimuli, have shown marked neurocognitive abnormalities in alcoholics (Nixon and Phillips, 1999; Porjesz and Begleiter, 1985). The most consistent result associated with alcoholism is the amplitude reduction of P3b (Patterson et al., 1987; Pfefferbaum et al., 1991; Porjesz et al., 1988; Realmuto et al., 1993), a positive ERP component elicited by attended, infrequently occurring task-relevant stimuli, with a 300- to 500-msec peak latency. Delayed auditory P3b peak latencies have also been frequently reported in chronic alcoholics (Cadaveira et al., 1991; Pfefferbaum et al., 1979, 1991; Steinhauser et al., 1987). Previous ERP studies have also demonstrated the postwithdrawal enhancement of auditory evoked electric or magnetic responses (J. Ahveninen et al., 1999; Pekkonen et
alcohol withdrawal (Buck and Harris, 1991; Tsai et al., 1995). Recently benzodiazepine binding results suggest that these synaptic changes can be detected 3 months after detoxification (Lingford-Hughes et al., 1998).

The most profound neuropsychological deficits, such as retro- and anterograde amnesia, are usually observed only in alcoholics suffering from Korsakoff's syndrome (Butters and Cermak, 1980), caused by thiamine deficiency and subsequent Wernicke's disease (Victor et al., 1989). Conversely, many of the initial studies failed to show any significant cognitive decline in neurologically "intact" alcohol abusers (Butters et al., 1977; Parson and Prigatano, 1977). More recently, subtle but significant verbal short- and long-term memory deficits have also been observed in alcoholics without a history of Wernicke's disease (Acker et al., 1987; Brandt et al., 1983; Knight and Longmore, 1994; Ryan et al., 1980). Although the short-term memory span is rarely impaired in alcoholics (even in those with Korsakoff's syndrome) (Knight and Longmore, 1994), their performance clearly deteriorates when active rehearsal of the information is blocked with a distractor task (Brandt et al., 1983; Knight and Longmore, 1994; Ryan et al., 1980). This vulnerability to interference correlates with alcohol consumption even in social drinkers, which suggests that this type of deficit is one of the first ones to develop with alcohol abuse (MacVane et al., 1982). There is some evidence that alcoholic memory impairment correlates with widening of cerebral sulci and ventricles (Acker et al., 1987; Carlen et al., 1981), and with overall reduction of brain glucose use in alcoholics (Wang et al., 1993). Despite these findings, the exact neurophysiological factors underlying alcohol-related memory dysfunction have remained ambiguous.

One factor possibly underlying the above-mentioned alcohol-related auditory working-memory deficits, namely, the accelerated forgetting during distraction, may be pronounced vulnerability of earlier neural memory representations to interference by later ones (Cowan, 1995). An analog of this hypothesis was used to study alcohol-related abnormalities in transient auditory sensory memory that precedes further processing in the auditory working memory and long-term storage of information (Baddeley, 1986). The rationale of studying auditory sensory-memory traces is that they can be easily and objectively indexed by mismatch negativity (MMN), a preattentive brain electric response evoked when a predictable series of homogenous standard stimuli is interrupted by a deviant stimulus (Nääätänen, 1992, 1995; Nääätänen et al., 1978, 1997; Ritter et al., 1995; Tönttinen et al., 1994). A memory trace is made of the repeated standards, and attention-independent recognition of difference between physical features of the deviant and the memory trace of the standard leads to evocation of MMN (Nääätänen, 1992, 1995; Nääätänen et al., 1978). This memory-trace formation can be interfered with backward-masking stimuli that shortly follow each stimulus of the MMN paradigm (Cowan, 1984; Winkler and Nääätänen, 1995; Winkler et al., 1993). It was hypothesized that the neural abnormalities possibly affecting auditory sensory representations may accumulate at the higher levels of memory processing. Namely, the memory deficits have been shown to correlate with global, rather than focal, functional changes in the alcoholic brain (Wang et al., 1993; George et al., 1999). Furthermore, alcohol consumption may have a cortically widespread impact on buildup of neural representations. The alcohol-sensitive (Tsai et al., 1995) NMDA receptors, proposed to be central in MMN generation (Ritter et al., 1995), may govern experience-dependent synaptic plasticity in hippocampus and throughout the neocortex (Kirkwood et al., 1993).

It has been shown that the MMN is completely abolished in healthy subjects by masks interpolated at 0 to 50 msec after stimulus offset (Cowan, 1984; Winkler and Nääätänen, 1995; Winkler et al., 1993). By widening the gap between the masks and the tones, the masking effect gradually decreases, and vanishes within 150 to 300 msec (Cowan, 1984; Hawkins and Presson, 1986; Winkler and Nääätänen, 1995; Winkler et al., 1993). Here, the masks were imposed 100 msec after standards and deviants, to avoid the possible ceiling effect in the control subjects and to reduce the time required for the measurement. In addition to the investigation of auditory sensory-memory impairment in alcoholics, the effect of backward masking on MMN generation was correlated with behavioral working-memory performance. To date, this is the first clinical study that capitalizes on backward masking of MMN generation.

Methods

Subjects

Twenty consecutive male alcoholics (age, 19-55 years; mean age, 40 years; SD, 10.6 years), from the Järvenpää Social Hospital, who met DSM-IV criteria for alcohol dependence and 20 age- and education-matched healthy male social drinkers (age, 21-59 years; mean age, 37 years; SD, 11.7 years) were studied. The alcoholics, who had between 1 and 35 years (mean, 11 years; SD, 9.2 years) of chronic drinking (self-reported ethanol consumption, 336-2520 g/week; mean, 636 g/week; SD, 648.4 g/week), had been abstinent for 7 to 45 days (mean, 20 days; SD, 10.4 days) and were without acute withdrawal symptoms (according to Clinical Institute Withdrawal Assessment for Alcohol (Sullivan et al., 1989)). The social drinkers' self-reported consumption was 21 to 216 g/week (mean, 97 g/week; SD, 73.4 g/week). The Alcohol Use Disorders Identification Test (Seppä et al., 1995) was used. The study was approved by the Ethics Committee of the A-Clinic Foundation, Helsinki, Finland, according to the Declarations of Helsinki. An informed consent was obtained after the procedures had been fully explained to the subjects. An experienced clinician (A.H.) recruited the alcoholics from a routine treatment program and examined their medical records. Subjects with hearing loss, neurological disorders, severe psychiatric disorders other than alcoholism, or other severe diseases were excluded. The social-drinker subjects abstained from alcohol and other drugs for at least 48 hr before the measurement. Six
alcoholics used antidepressants or other central nervous system (CNS) medication (two used fluoxetine, one used mianserin, one used mianserin and promazine, one used doxepin, and one used promazine in the evenings). No statistically significant differences were observed between the results of the 14 unmedicated and the 6 medicated alcoholics; moreover, the results of this study were significant even after exclusion of these 6 alcoholics from the analysis.

**ERP Measurement**

ERPs were measured in an acoustically and electrically shielded room by using a 32-channel EEG. Mastoid-referenced EEG (sampling rate, 250 Hz) was averaged and filtered digitally (pass band, 2–12 Hz for the MMN and 1–30 Hz for the N1; prestimulus baseline, −100 msec). Epochs with artifacts at >75 μV at any electrode or at an electro-oculogram were discarded. Subjects reading self-selected material and ignoring the stimulation were binaurally presented with trains of 600-Hz standard tones (p = 0.80) that were randomly replaced by 670-Hz deviant tones. Both the standards and the deviants (total, 1294 stimuli per block) were sinusoidal tones of 25-msec duration with 2.5-msec rise and fall times. The stimuli were presented 60 dB over subjective hearing threshold. Stimulus onset asynchrony was 300 msec. In one of these conditions, we interposed randomly varying masking tones (300, 400, 900, or 1000 Hz; duration, 25 msec; 2.5 msec rise and fall time) starting 100 msec after each stimulus offset to interfere with memory-trace formation for the standards (the backward-masking condition) (Cowan, 1984; Winkler and Näätänen, 1995; Winkler et al., 1993). During the other condition (the baseline condition), the standard and deviant tones were presented without masking tones. The MMN amplitude was determined from subtraction curves (the deviant-stimulus ERP minus standard-stimulus ERP) by using a signal-space projection (Usatilo and Ilmoniemi, 1997). Specifically, the spatial distribution of the MMN was estimated from the within-group grand-averaged ERP wave forms at the MMN peak latency. This estimate was used to dissociate the MMN signal from the noise at the individual level, which resulted in an improved signal-to-noise ratio. The signal-space projection of MMN was calculated from signals obtained at seven electrode positions centered around the frontal electrode (Fz), where the MMN is usually largest in amplitude (Näätänen, 1992).

**Neuropsychological Testing**

To measure the auditory-verbal working memory, we used the Wechsler Memory Scale digit span (Lezak, 1995; Wechsler, 1945) and the Brown-Peterson procedure termed, “auditory consonant trigrams” (ACT), in which a distractor task is interpolated between encoding and recall of three consonants (Lezak, 1995; Peterson and Peterson, 1959). In the ACT, the subject was presented with three consonants, and after hearing them, during either 3, 9, or 18 sec of distraction, he was to count backward by 3s from a given number, until signaled to report the consonants. A total number of correct consonants of 20 trials, including an additional baseline without distraction, was scored. In addition, two neuropsychological tests were used to assess attention and executive dysfunction (here, termed frontal tests), Trail-Making Test part A and part B (TMT; originally in Army Individual Test Battery, 1944) (Lezak, 1995) and Stroop Color and Word Naming Test (SCWT) color patch naming (part I) and false color word naming (part II) (Lezak, 1995; Stroop, 1935). The frontal test performance was defined as a sum score of the following standardized difference and error scores: TMT B–A, time; TMT-B, errors; SCWT I–I, time; SCWT-II, errors.

**Statistical Analysis**

Group and treatment differences in the ERP were statistically analyzed by two-way analyses of variance (two groups by two MMN conditions) with two a priori contrasts (using the error term of the overall effect) to determine the group MMN differences within the MMN conditions (Statistica 4.1 software, Stat Soft Inc., Tulsa, OK). Neuropsychological data were analyzed statistically by using multivariate analysis of variance (years of formal education entered as a covariate) with contrasts to determine the group differences in the distinct neuropsychological tests. The neuropsychological and ERP data were correlated by using Pearson's correlation coefficient, and to analyze the factors affecting working-memory performance of the alcoholics, a multiple regression analysis was used.

**RESULTS**

**MMN With and Without Backward Masking**

The cortical auditory-sensory memory function was measured under two separate ERP conditions (with and without backward masking). Figure 1 shows the deviant and the standard ERPs under these conditions, and the grand-average scalp distributions of MMN and subtraction curves are presented in the Fig. 2. Under the baseline condition without backward masking, the deviant tones elicited MMN in both groups (Figs. 1 and 2; Table 1). This baseline MMN was larger [F(1,38) = 6.00, p < 0.020] and earlier [F(1,38) = 5.66, p < 0.023] in the alcoholics, compared with that in the social drinkers. In addition, the N1 deflection to the standard stimuli was larger in the alcoholics [F(1,38) = 7.62, p < 0.009].

Under the backward-masking condition, the alcoholics' MMN was abolished by the masking tones, interposed after each stimulus offset to interfere with sensory-memory function, but the social drinkers showed no such effect. There was a significant group-by-stimulus condition interaction in the analysis of variance [F(1,38) = 10.48, p < 0.003], with the masking condition MMN amplitude being larger in the social drinkers than in the alcoholics [F(1,38) = 4.53, p < 0.040]. When the cutoff point was 0.80 μV (mean MMN reduction by masking plus 1.7 SDs), 9 of 20 of the alcoholics (sensitivity, 45%), but no social drinkers (specificity, 100%), showed impairment of the auditory sensory memory (Fig. 3). Furthermore, the MMN reduction by masking correlated significantly with self-reported weekly alcohol consumption (Pearson's r = 0.41; p < 0.01) in the whole study group.
Fig. 2. (a) Surface potential maps of mismatch negativity (MMN) (from grandaverage subtraction curves, deviant minus standard event-related potentials, at the MMN peak latency) of social drinkers and alcoholics, both with (right) and without (left) backward masking projected on a model head. (b) Deviant minus standard subtraction curves from electrode Fz. Maps and curves demonstrate between-condition double dissociation of MMN amplitude (indicated by shading in Fig. 1) in alcoholics and social drinkers.

Neuropsychological Tests

The function of auditory-verbal working memory was studied by using the ACT, in which a distractor task was interposed between encoding and recall of three consonants (Lezak, 1995; Peterson and Peterson, 1959). Figure 4 and Table 1 show that, as expected, the alcoholics performed significantly worse in the ACT than the social drinkers [F(1,37) = 14.5; p < 0.001]. In addition, two neuropsychological tests, TMT and SCWT, were used to assess attentional and executive dysfunction (here, termed frontal dysfunction). Figure 4 and Table 1 indicate that the alcoholics showed marked frontal dysfunction (measured with a sum score of TMT and SCWT) compared with the social drinkers [F(1,37) = 17.8; p < 0.001]. Both the frontal test performance (Pearson's r = -0.48; p < 0.002) and the ACT score (Pearson’s r = -0.56; p < 0.001) correlated negatively with the self-reported weekly alcohol consumption in the whole study group. The backward digit span of the alcoholics was significantly reduced [F(1,37) = 10.4; p < 0.003], but no between-group differences were found in the forward digit span (Table 1).

Correlation Between MMN and Neuropsychological Test Performance

In the whole study group, the MMN reduction by backward masking correlated negatively with ACT performance (Pearson’s r = -0.61; p < 0.001) and with the frontal test performance (Pearson’s r = -0.33; p < 0.039). The ACT score also correlated with frontal test performance (Pearson’s r = 0.65; p < 0.001).

Figure 5 indicates the association between pronounced distractibility of sensory-memory and working-memory dysfunction in the alcoholics. In the alcoholics, the MMN reduction correlated with impaired ACT performance (Pearson’s r = -0.56; p < 0.012), and the ACT score correlated with frontal test performance [Pearson’s r = 0.49; t(16) = 2.43; p < 0.026]. The MMN reduction by masking did not, however, significantly correlate with frontal test performance in the alcoholics.

In the social drinkers, no significant correlations emerged between the MMN masking effect (this MMN effect being, notably, statistically insignificant in the social drinkers) and the neuropsychological test scores.

When both the alcoholics and the social drinkers were considered, a linear regression analysis showed a significant multiple correlation [adjusted R² = 0.62; F(3,36) = 21.9; p < 0.001] between the ACT performance and three independent variables, i.e., (1) the MMN amplitude reduction by backward masking [partial r = -0.52; t(36) = -3.66; p < 0.001], (2) the frontal test performance [partial r = 0.56; t(36) = 4.08; p < 0.001], and (3) the Wechsler Memory Scale digit span score [partial r = 0.35; t(36) = 2.21; p < 0.034].

In the alcoholics, correspondingly, a significant multiple correlation emerged between the ACT performance and MMN masking effect, frontal test performance, and Wechsler Memory Scale digit span score [adjusted R² = 0.42; F(3,16) = 5.47; p < 0.009]. Significant partial correlations were detected between ACT and MMN reduction by masking [partial r = -0.55; t(16) = -2.62; p < 0.019] and between ACT and frontal test performance [partial r = 0.50; t(16) = 2.33; p < 0.034].

DISCUSSION

In conclusion, backward masking abolished the MMN in the abstinent alcoholics whereas only a weak trend was observed in the social drinkers. The decrement of MMN amplitude by backward masking is believed to reflect disruption of memory trace formation at the auditory cortices (Cowan, 1984; Winkler and Näätänen, 1995; Winkler et al.,
Table 1. Results of MMN Measurement and Neuropsychological Testing in Alcoholics and Social Drinkers

<table>
<thead>
<tr>
<th></th>
<th>Social drinkers</th>
<th>Alcohols</th>
<th>MMN, without masking</th>
<th>MMN, backward masking</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SE</td>
<td>CI (-0.95)</td>
<td>CI (+0.95)</td>
</tr>
<tr>
<td>Peak latency (msec)</td>
<td>186.6</td>
<td>6.5</td>
<td>172.9</td>
<td>200.2</td>
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<tr>
<td>Peak latency (msec)</td>
<td>156.1</td>
<td>6.2</td>
<td>143.0</td>
<td>169.1</td>
</tr>
<tr>
<td>Amplitude (μV)</td>
<td>-0.8</td>
<td>0.1</td>
<td>-0.9</td>
<td>-0.6</td>
</tr>
<tr>
<td>MMN, backward masking</td>
<td>0.19</td>
<td>0.08</td>
<td>0.03</td>
<td>0.35</td>
</tr>
<tr>
<td>N1 to standard tones</td>
<td>127.7</td>
<td>4.5</td>
<td>118.3</td>
<td>137.1</td>
</tr>
<tr>
<td>Amplitude (μV)</td>
<td>-0.2</td>
<td>0.1</td>
<td>-0.4</td>
<td>0.0</td>
</tr>
<tr>
<td>Neupropsychological tests</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>ACT (z score units)</td>
<td>0.57</td>
<td>0.12</td>
<td>0.31</td>
<td>0.83</td>
</tr>
<tr>
<td>Frontal tests (z score units)</td>
<td>0.61</td>
<td>0.08</td>
<td>0.43</td>
<td>0.78</td>
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<tr>
<td>Digit span (forward)</td>
<td>6.5</td>
<td>0.2</td>
<td>6.0</td>
<td>6.9</td>
</tr>
<tr>
<td>Digit span (backward)</td>
<td>5.2</td>
<td>0.2</td>
<td>4.7</td>
<td>5.7</td>
</tr>
</tbody>
</table>

MMN, mismatch negativity; ACT, auditory consonant trigrams (test).

Data are mean, standard error of mean (SE), and confidence interval (CI) values. *p < 0.05; **p < 0.01; ***p < 0.001.

Fig. 3. Reduction of mismatch negativity (MMN) amplitude by backward masking. Nine of 20 alcoholics but no social drinkers showed sensory-memory deficit (cutoff mean + 1.7 SD). Boxes represent SEM values; whiskers are SDs.

Fig. 4. (A) Group average mismatch negativity (MMN) amplitude. (B) Group average MMN peak latencies, without (Baseline) and with backward masking (Mask). (C) Group average z scores of auditory consonant trigrams (ACT) test and frontal test performance (*p < 0.05; **p < 0.01; ***p < 0.001, error bars are SEM values).

As a result of chronic alcohol abuse, the formation of cortical auditory-sensory memory traces appears to be abnormally vulnerable to interference by closely succeeding auditory stimuli. The masking effect is normally most evident during the 0- to 50-msec poststimulus period, after which it gradually decreases, and vanishes within 150 to 300 msec (Hawkins and Presson, 1986). During the critical poststimulus period, the temporal window of integration (normally, 150–200 msec), successive stimuli are encoded as an integrated unit (represented by an integrated memory trace) and a masking stimulus falling within this temporal window dominates this integrated unit to the extent that all other information is lost (Nättänen, 1992; Yabe et al., 1993). As a result of chronic alcohol abuse, the formation of cortical auditory-sensory memory traces appears to be abnormally vulnerable to interference by closely succeeding auditory stimuli. The masking effect is normally most evident during the 0- to 50-msec poststimulus period, after which it gradually decreases, and vanishes within 150 to 300 msec (Hawkins and Presson, 1986). During the critical poststimulus period, the temporal window of integration (normally, 150–200 msec), successive stimuli are encoded as an integrated unit (represented by an integrated memory trace) and a masking stimulus falling within this temporal window dominates this integrated unit to the extent that all other information is lost (Nättänen, 1992; Yabe et al., 1997). It appears that this temporal window may be widened in the alcoholic brain.

The significant positive correlation between MMN reduction by masking and self-reported alcohol consumption supports the assumption that this disorder may indeed be related to severity of drinking history. Moreover, the correlation coefficient ($r = 0.4$) detected is at the same level as the ones obtained by using routine laboratory markers of alcohol abuse (Sillanaukee, 1996). This was supported by the observed 45% sensitivity with 100% specificity, which should be, however, confirmed later with larger patient populations.

Although there is evidence that MMN decreases significantly even with low blood alcohol concentration (Jääskeläinen et al., 1995), a recent magnetoencephalographic study indicated that 2 to 6 weeks after withdrawal of chronic drinking, the MMN generation may even be somewhat enhanced (Pekkonen et al., 1998). Correspondingly, significant augmentation and acceleration of MMN without the masking, and augmentation of N1 elicited by the stan-
was a particularly valid predictor and absolute reduction of mismatch negativity (MMN) amplitude by backward masking within the alcoholic group. Reduction of MMN by backward masking was a particularly valid predictor of working-memory dysfunction in alcoholics (Pearson's $r = -0.55; p < 0.011$; confidence limits $p = 0.95$).

standards, was observed in the alcoholics. This may reflect reduced neural inhibition in the alcoholic brain, because reduced benzodiazepine binding has been evidenced even in alcoholics abstinent for 3 months (Lingford-Hughes et al., 1998). However, in contrast to the recent finding of augmented middle-latency auditory evoked potentials in alcoholics (J. Ahveninen et al., 1999), neither the MMN nor N1 enhancement correlated with abstinence duration in the alcoholics in the present study. Hence, whether the MMN and N1 enhancement reflects CNS hyperexcitability after alcohol withdrawal (Buck and Harris, 1991; Tsai et al., 1995), or results from more permanent or premorbid CNS changes, must be confirmed by later studies. Nevertheless, it appears that the MMN enhancement without masking probably reflects sensitized response to the detected difference between the standard tone trace and deviant tone in alcoholics, rather than strengthened sensory-memory traces. The pronounced MMN masking effect and the subsequent correlation with impaired working-memory performance supports this assumption.

One may question whether the overlapping components elicited by the tones and the masks could have affected the results. For instance, the negative N1 deflection to masks, peaking $\sim 100$ msec after mask onset, and, thus, 225 msec after the standard or deviant onset, could have overlapped with the positive P2 to the standard or deviant tones (peaking $\sim 200$ msec after tone onset). Given that the varying masks followed both the standards and the deviants with similar probability, the components elicited by the masks, and their possible effects on standard and deviant responses, should, however, be canceled out in the subtraction of deviant and standard ERPs. In addition, the masks were substantially different from the standards and the deviants in tone frequency to activate different frequency-specific neuron populations (Näätänen, 1992), respectively, which minimizes the possibility that group differences in the refractoriness of these frequency-specific neurons would have confounded the results.

The present results demonstrated that the abolition of MMN by backward masking correlated significantly with the impaired behavioral working-memory performance in the alcoholics. This implicates that the accelerated forgetting at "higher" cognitive stages of the memory system could, in part, be attributed to the initially impaired formation of preattentive sensory-memory traces.

As previously observed in alcoholic Korsakoff patients (Leng and Parkin, 1989), the accelerated forgetting during the distraction task correlated also with frontal dysfunction in alcoholics. In the alcoholic group, however, no significant correlation emerged between the frontal dysfunction and MMN reduction by masking, which suggests that these factors may predict distinct aspects of working memory. It has been proposed that in Korsakoff patients, frontal deficits may impair the ability to switch from the counting task to retrieval of the target information (Leng and Parkin, 1989). It can thus be speculated that frontally induced retrieval problems may also contribute to working-memory impairment in non-Korsakoff alcoholics. The abolition of MMN by masking, reflecting impaired buildup of cortical memory traces, may, in turn, be a predictor of impaired neural representations, also at the higher levels of memory system in alcoholics.

Given that the working-memory impairment may be one of the first neurocognitive deficits caused by alcohol abuse (MacVane et al., 1982), and the exacerbating nature of alcohol-related changes in cognitive function in general (Lishman, 1990), early detection of these memory deficits is essential in the chain of treatment. Unlike most behavioral and ERP measures of neurocognitive disorders, the MMN is not modulated by the subject's higher order cognitive processes associated with expectancy, confidence, or attention (Näätänen, 1992, 1995; Ritter et al., 1995). The MMN paradigm applied in the present study may provide an objective method for research on the early phase changes in alcohol-induced CNS disorders.

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