Acute and Chronic Effects of Alcohol on Preattentive Auditory Processing as Reflected by Mismatch Negativity

Jyrki Ahveninen, Carles Escera, M. Dolores Polo, Carles Grau, Ilpo P. Jääskeläinen

Cognitive Brain Research Unit, Department of Psychology, University of Helsinki, and BioMag Laboratory, Helsinki University Central Hospital, and Department of Neurology, University of Helsinki, Helsinki, Finland; Neurodynamics Laboratory, Department of Psychiatry and Clinical Psychobiology, University of Barcelona, Spain

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Abstract
Chronic alcoholism, a major worldwide health problem, is associated with a variety of neurocognitive changes in the affected individuals. The precise neurophysiological basis of these changes is not yet understood. Mismatch negativity (MMN) is a preattentive event-related potential component indexing cortical auditory memory traces and automatic change detection in the brain that can be used to study the neural basis of cognitive impairments in various neurodegenerative diseases. MMN studies have revealed that even a low dose of acute alcohol significantly impairs automatic change detection and involuntary attention shifting. Recent MMN results on chronic alcoholism in turn suggest that auditory sensory traces decay slightly faster and are substantially more vulnerable to the distracting effect of backward masking in alcoholics than in healthy subjects. Furthermore, chronic alcohol abuse might accelerate the age-related impairment of automatic change detection. There is also evidence that the MMN changes might predict impaired performance in behavioral memory and attention tasks in alcoholics. In MMN studies of detoxified alcoholics, however, many confounding factors have to be taken into account. For instance, postwithdrawal brain hyperexcitability might be associated with a slightly enhanced or accelerated MMN/MMNm (the magnetic equivalent of MMN). In sum, MMN and MMNm provide an objective noninvasive tool for exploring the neurophysiological functional deficits related to both acute alcohol intoxication and chronic alcoholism.

By any measure, alcohol (ethanol) abuse constitutes a worldwide social and health problem. It has been estimated that in the USA alone, approximately 13 million individuals need treatment for alcohol use disorders [Institute of Medicine, 1990], the annual costs exceeding US$ 100 billion [Holden, 1987]. In rough numbers, 20–40% of all persons admitted to urban hospitals are esti...
only in alcoholics suffering from Korsakoff's syndrome [Butters and Cermack. 1980]. following prolonged thiamine deficiency and subsequent Wernicke's disease [Victor et al., 1989]. Subtle but significant memory deficits have also been observed in alcoholics without a history of Wernicke's disease [Ryan et al., 1980; Brandt et al., 1983; Acker et al., 1987; Knight and Longmore, 1994]. Notably, the auditory short-term memory performance of alcoholics is deficient only when the active rehearsal of the information is prevented with a distractor task [Ryan et al., 1980; Brandt et al., 1983; Knight and Longmore, 1994]. This working-memory vulnerability to interference correlates with the amount of alcohol consumption even in social drinkers [MacVane et al., 1982], thus suggesting that this type of neurocognitive deficit might be among the first to develop with alcohol abuse.

**Acute Effects of Alcohol on Mismatch Negativity**

Since alcohol ingestion significantly depresses CNS function [Freed et al., 1978; Nestoros, 1980; Lovinger et al., 1989; Weight et al., 1992; Korpi, 1994; Tsai et al., 1995], many event-related potential (ERP) components, such as auditory N1, are attenuated and delayed by acute alcohol challenge [Gross et al., 1966; Porjesz and Begleiter, 1993; Jääskeläinen et al., 1996b]. Correspondingly (fig. 1), an acute alcohol challenge with doses of 0.50–0.85 g/kg reduces the amplitude [Jääskeläinen et al., 1995a, b, 1996c, 1998] and increases the peak latency [Jääskeläinen et al., 1995b, 1998] of mismatch negativity (MMN), a preattentive ERP component elicited by infrequent changes in auditory stimulation [Nättänen et al., 1978, 1997; Nättänen, 1992, 1995; Titinen et al., 1994; Ritter et al., 1995]. Increases in the MMN peak latency are observed already with doses as low as 0.30 g/kg [Jääskeläinen et al., 1999a].

With respect to response amplitude, the alcohol effects are somewhat similar in N1 and MMN [Jääskeläinen et al., 1995a, b, 1996c, 1998]. There is, however, tentative evidence that small doses of alcohol might produce a larger peak latency delay in MMN than N1 [Jääskeläinen et al., 1995b, 1998, 1999a]. The alcohol-induced latency delay in MMN might be augmented by the opioid receptor blocker naltrexone [Jääskeläinen et al., 1998] and reversed by caffeine, a selective adenosine receptor subtype A1 and A2 antagonist, although no such reversibility has been observed in P3b or processing negativity [Hirvonen et al., in press]. Taken together, more studies on the neurotransmitter systems underlying MMN generation are needed to determine the specificity of the alcohol effects cited above.

As shown in figure 2, the effects of acute alcohol might be specifically strong on the frontal MMN subcomponent [Jääskeläinen et al., 1996c] that is related to involuntary attention shifting to task-irrelevant sound changes [Nättänen, 1992]. This finding is supported by our reaction time results [Jääskeläinen et al. 1996a, 1999a] indicating reduced distractibility by task-irrelevant sound changes following an acute alcohol challenge (fig. 3). Moreover, the P3a deflection following MMN, also related to involuntary attention shifting [Nättänen, 1992], is attenuated in amplitude during alcohol intoxication [Campbell and Lowick, 1987; Grillon et al., 1995; Jääskeläinen et al., 1999a]. Given that the above-mentioned effects were observed with relatively low doses, thus disclosing the alcohol sensitivity of their neural substrate, one might suspect that these mechanisms would be especially prone to the development of neuroadaptive changes or damage during chronic alcohol drinking.

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**Fig. 1.** The MMN amplitude, measured in three latency ranges as indicated on the abscissa, in the placebo and alcohol conditions. The reduction of the MMN amplitude and the increase in the MMN latency by alcohol are evident *p < 0.05. Adapted from Jääskeläinen et al. [1995a].
might, however, be anatomical dissociation in the alcohol-withdrawal-related functional changes in the CNS. Díaz et al. [1990] observed that despite the delayed BAEP in 4-week-abstinent human alcoholics, suggesting delayed auditory transmission in their brainstem, the peak latencies of their cortically generated middle-latency auditory evoked potentials were reduced. In other words, despite the delayed transmission from the ear to the thalamus, the auditory signals might have reached the primary auditory cortex more rapidly in the alcoholics than in the controls. One possible explanation might be dysfunction in inhibitory GABAergic neurons that are hypothesized to gate the cortical input in the thalamus [Yingling and Skinner, 1976; Skinner and Yingling, 1977]. Moreover, the N1–P2 amplitude was enhanced in 1-month-abstinent alcoholics [Cadaveira et al., 1991], and the first published magnetoencephalography (MEG) study on alcoholism revealed significant acceleration of N1m ipsilateral to the ear stimulated in alcoholics with 2–6 weeks of abstinence [Pekkonen et al., 1998]. There is also evidence that the post-withdrawal acceleration and/or augmentation of auditory responses might be predicted by the duration of alcohol abstinence [Pekkonen et al., 1998; Ahveninen et al., 1999a].

Several studies [Pfefferbaum et al., 1991; Katbamna et al., 1993], however, failed to report any acceleration or augmentation of the exogenous auditory ERP in abstinent alcoholics who had been sober for approximately a month. This inconsistency might be partially due to wide differences between the studies in the predisposing factors (e.g., the severity of drinking) that affect the postwithdrawal syndrome of alcoholics. Furthermore, pharmacological agents commonly used in withdrawal treatment, e.g., benzodiazepines, may reduce ERP amplitudes [Meador, 1995], whereas disulfiram may increase them [Peeke et al., 1979].

**MMN and Other Endogenous ERP Components in Chronic Alcoholics**

The cognitive ERP components elicited in an attended auditory oddball paradigm have been extensively studied in chronic alcoholics, with the most consistent result being the amplitude reduction of P3b [Patterson et al., 1987; Porjesz et al., 1988; Pfefferbaum et al., 1991; Realmuto et al., 1993]. Delayed P3b peak latencies have also been frequently reported in chronic alcoholics [Pfefferbaum et al., 1979, 1991; Steinhauer et al., 1987; Cadaveira et al., 1991]. Generally, the P3b changes appear to become particularly evident when the discrimination of the deviants becomes more difficult [Porjesz and Begleiter, 1985; 1993]. There is also evidence that the auditory N2b, preceding P3b, might be delayed in chronic alcoholics [Sandman et al., 1987; Cadaveira et al., 1991].

As for the MMN studies [Realmuto et al., 1993; Kathmann et al., 1995; Pekkonen et al., 1998; Ahveninen et al., 1999a; Polo et al., 1999] on chronic alcoholism, the results have been partially inconsistent, possibly because of some substantial methodological differences between these studies. For instance, Realmuto et al. [1993] reported that the 'N2', elicited by unattended deviants, was significantly reduced in the frontal electrode F2, implying that this was possibly due to the MMN reduction. In contrast to the typical method of determining MMN from subtraction curves (deviant stimulus ERP–standard stimulus ERP), the MMN amplitude was, unfortunately, analyzed directly from the deviant curves by applying P2/N2 peak-to-peak analysis (MMN usually overlaps P2). In the figures, the baseline corrected grand-average deviant curves were clearly more negative at ~100–250 ms from stimulus onset in the alcoholics than controls. Moreover, the controls were, on the average, 11 years younger than the alcoholics were. Kathmann et al. [1995], in turn, reported that MMN was significantly delayed in alcoholics and schizophrenics. Alcoholics were not separately compared with controls in the statistical analysis, but on the average, the MMN peak latencies appeared to be greater in alcoholics than controls.

In their recent magnetoencephalography (MEG) study, Pekkonen et al. [1998] found no differences in the magnetic MMN (MMNm) amplitude between alcoholics and controls, neither with interstimulus intervals (ISIs) of 0.5 nor of 2.5 s. Furthermore, in contrast to the result of Kathmann et al. [1995], MMNm peaked significantly earlier in the alcoholics than controls [Pekkonen et al., 1998]. This finding was further supported by our EEG data [Ahveninen et al., 1999a] showing a significant MMN enhancement and acceleration in abstinent alcoholics. In these studies [Ahveninen et al., 1999a; Pekkonen et al., 1998], the alcoholics had been abstinent for a relatively short period (1–6 weeks); therefore, it was concluded that the MMN/MMNm acceleration and MMN augmentation might have been related to the postwithdrawal brain hyperexcitability. Given that the reduced GABA-benzodiazepine binding coexists with the long-term postwithdrawal syndrome in human alcoholics [Lingford-Hughes et al., 1998], this hypothesis is supported by a trend of MMN enhancement (on the average, from 0.4 to 1.2 μV at Fz) observed in healthy humans after administration of...