Electromagnetic Studies of Auditory Processing in Abstinent Alcoholics

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Ahveninen J, Jääskeläinen IP, Pekkonen E, Hallberg A, Hietanen M, Mäkelä R, Näätänen R, Sillanaukee P. Suppression of mismatch negativity by backward masking predicts impaired working-memory performance in alcoholics. Alcoholism: Clinical and Experimental Research 23, 1507–1515 (1999).

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Ahveninen J, Jääskeläinen IP, Pekkonen E, Hallberg A, Hietanen M, Näätänen R, Schröger E, Sillanaukee P. Increased distractibility by task-irrelevant sound changes in abstinent alcoholics. Alcoholism: Clinical and Experimental Research, in press.

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ABBREVIATIONS

ACT	Auditory Consonant Trigrams
ANOVA	Analysis of variance
AUDIT	Alcohol Use Disorders Identification Test
BAEP	Brain-stem auditory evoked potential
CAR	Common average reference
CIWA-A	Clinical Institute Withdrawal Assessment for Alcohol
CVLT	California Verbal Learning Test
DSM-IV	Diagnostic And Statistical Manual of Mental Disorders, 4th edition.
ECD	Equivalent current dipole
EEG	Electroencephalography
EOG	Electro-oculogram
ERF	Event-related magnetic field
ERP	Event-related potential
GABA	γ-aminobutyric acid
GFP	Global field power
HR	Hit rate
ISI	Inter-stimulus interval
KS	Korsakoff's sydrome
MAEF	Middle-latency auditory evoked field
MAEP	Middle-latency auditory evoked potential
MANOVA	Multivariate analysis of variance
MEG	Magnetoencephalography
MMN (m)	Mismatch negativity (magnetic)
NMDA	N-methyl-D-aspartate
PN	Processing negativity
RON	Reorienting negativity
RT	Reaction time
SCWT	Stroop Color and Word Naming Test
SD	Standard deviation
SOA	Stimulus-onset asyncrony
SQUID	Superconducting quantum interference device
TMT	Trail-Making Test
WMS (-R)	Wechsler Memory Scale (-Revised)

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ABSTRACT

Alcohol (ethanol) dependence is a major worldwide health and social problem, associated with a variety of brain function and cognitive deficits in afflicted individuals. These well-described cognitive deficits are, however, poorly understood at the neural level. Here, the neural processes underlying various stages of auditory perception, memory, and attention were investigated with electroencephalographic (EEG), magnetoencephalographic (MEG), and neuropsychological measures, in abstinent alcohol-dependent (DSM-IV) male inpatients (i.e., alcoholics) and matched healthy controls. EEG and MEG indicated post-withdrawal enhancement of early cortical auditory responses, interference in subsequent formation of cortical representations, and impaired control of attention shifting to task-irrelevant tonal changes in the alcoholics. The electromagnetic abnormalities predicted impairment in the neuropsychological attention and memory tasks in the alcoholics. The enhancement of the earliest auditory responses correlated with short abstinence duration, suggesting the role of brain hyperexcitability, caused by neural adaptation to alcohol and subsequent detoxification, in the post-withdrawal brain dysfunction of the alcoholics. These functional changes might at least partially recover with prolonged abstinence. The abnormalities in involuntary attention in turn correlated with an early age at onset of alcohol drinking (< 25 years), which will guide future studies towards the examination of the contributions of early alcohol exposure and precipitating attention deficits to the development of alcohol dependence. Finally, the potential of the present EEG and MEG methodology in clinical research was indicated by a good test–retest reliability of the N1/N1m component at the individual level in healthy subjects. Taken together the present findings might thus pave the way for future research and development of clinical markers for alcohol-related functional cerebral changes.

Keywords: Alcoholism, Attention, Auditory Sensory Memory, Brain, Ethanol, EEG, Event-Related Potentials, MAEP, MEG, Mismatch Negativity, N1, N1m, and Neuropsychological tests.

LITERATURE REVIEW

Alcoholism is one of the leading health problems in the Western world with a high incidence, vast economic costs, and notably, a poor treatment response (McCrady and Langenbucher 1996). Despite the high clinical need and profusion of intensive research, satisfactory clinical applications for detection and monitoring of alcohol-related functional changes in the brain have not yet been developed. Further, better understanding of the brain-function changes in patients who have been successfully detoxified is essential, since the first few months after the cessation of drinking constitute the period of highest risk for relapse. Given the incidence of the disorder, alcohol problems might also camouflage other deficits. Research on cognitive and neural deficits underlying this disorder is thus clearly needed. This study was launched to elucidate the brain function changes in abstinent alcoholics using magnetoencephalography (MEG), electroencephalography (EEG), and neuropsychological assessments.

Neurochemical Effects of Ethanol

Ethanol (alcohol), unlike most psychoactive drugs, has no specific receptors, but it affects a wide variety of neurotransmitter systems, which is supposed to mediate its functional effects (for reviews, see Deitrich et al. 1989; Samson & Harris, 1992). For instance, the release of noradrenaline and dopamine probably mediate the acute enlivening effects, and the euphoria and reinforcing actions may reflect a mixture of dopamine and endogenous opioid release, interacting with the serotonin system (see Nutt 1999). Low brain serotonin function has in turn been linked to a subtype of alcoholism with an early onset of drinking and poor impulse control (see Virkkunen and Linnoila 1990). The major intoxicating effects of ethanol are, however, believed to be caused by its inhibitory actions on the amino acid receptors (for reviews, see Korpi 1994; Tsai et al. 1995).

Acute Actions of Ethanol

A variety of neural ion channels are sensitive to ethanol (Figure 1). Ethanol enhances the inhibitory Cl^- influx induced by the γ-aminobutyric acid (GABA) subtype-A receptor agonists (Korpi 1994; Nestoros 1980). In addition, the excitatory cation currents induced by the N-methyl-D-aspartate (NMDA) receptor agonists are reduced by ethanol and, to some extent, the glutamatergic kainate receptors are antagonized as well (Lovinger et al. 1989). At higher concentrations, ethanol has a direct inhibitory action on the $GABA_A$ receptor (Ticku et al. 1992), and also the excitatory Ca^{2+} influx in voltage-dependent large-conductance (L-type) channels is reduced (Little 1991). In addition to these major inhibitory actions, acute ethanol may have some activating effects mediated by certain serotonin (Lovinger and White 1991) and acethylcholine (Forman et al. 1989) receptor subtypes.

Neural Adaptation to Chronic Ethanol

The dual actions of increased inhibition and decreased excitation are followed by compensatory changes in neurons during prolonged alcohol drinking (Figure 1). Reduction in the ethanol-induced inhibition might reflect adaptive changes in the $GABA_A$ receptors (Korpi 1994). Enhanced sensitivity to pharmacological antagonism of the GABA-mediated Cl^- influx (Hu and Ticku 1997), increased binding of $GABA_A$ inverse agonists (Ticku 1990), and alterations in molecular subunit compositions of the $GABA_A$ receptors (Mahmoudi et al. 1997) have been observed after chronic ethanol administration. Furthermore, the excitatory NMDA receptors appear to increase in number during long-term ethanol exposure (Grant et al. 1990). There is also evidence of adaptive changes in the L-type Ca^{2+}-channels (Buck and Harris 1991) and gene expressions of certain NMDA receptor subunits after long-term ethanol ingestion and withdrawal (Darstein et al. 2000).

Withdrawal Hyperexcitability

After withdrawal, the reduced inhibition and augmented excitability of neurons, caused by the neuroadaptation to chronic ethanol (Figure 1), result in brain hyperexcitability (for reviews, see Glue and Nutt 1990; Little 1999), which may be a major factor underlying the adverse brain effects of alcoholism (Lovinger 1993). The associated neurotoxic effects of the excessive Ca^{2+} influx (the NMDA excitotoxicity; Rothman and Olney 1995) may be further potentiated by the poor nutritional state of detoxified alcoholics. Depletion of the brain's natural glutamate antagonist, magnesium, that blocks the NMDA-receptor channels may increase the NMDA excitotoxicity (Nutt 1999), which might further interact with the neurodegenerative effects associated with prolonged thiamine (vitamin B_1) deficiency (Lovinger 1993).

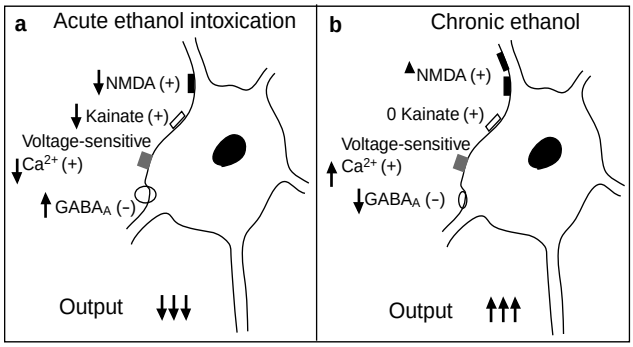

Figure 1. (a) Acute ethanol inhibits action of the excitatory NMDA and kainate receptors, inhibits the voltage-sensitive calcium channels, and enhances action of the inhibitory $GABA_A$ -receptors. Because the excitatory cation channels are inhibited and inhibitory anion channel is activated, output of the neuron is markedly decreased. **(b)** During chronic exposure to ethanol, the NMDA receptors and calcium channels increase in number, and the $GABA_A$-function is decreased. This offsets the action of ethanol and results in increased output after ethanol withdrawal. (Adapted from Samson & Harris 1992).

The withdrawal hyperexcitability is possibly intensified by previously experienced withdrawal episodes by a "kindling" mechanism (Becker 1994). It has been proposed to be a central factor in the development of alcohol dependence as well (Hunter et al. 1975; MacDonnell et al. 1975; Meyer 1996). The overt signs of withdrawal hyperexcitability (e.g., tachycardia, elevated blood pressure, seizures, or delirium tremens) are usually maximal 24–72 hours after detoxification and generally subside within the following 3–8 weeks. However, the receptor abnormalities associated with the neuroadaptation to chronic ethanol are detectable even months after detoxification in human alcoholics (Lingford-Hughes et al. 1998). Given that memory and learning have been linked to experience-driven changes in patterns of the NMDA-mediated excitability (Kirkwood et al. 1993) and GABAergic inhibition (Iijima et al. 1996), the post-withdrawal abnormalities could have an impact on cognitive funtioning *per se* in abstinent alcoholics, even after cessation of acute withdrawal symptoms.

Structural and Functional Brain Changes in Alcoholism

The structural and functional brain deficits caused by chronic alcoholism are well documented. Computerized tomography studies have indicated ventricular dilation and cortical atrophy in alcoholics (Carlen et al. 1981; Ishii 1983; Lishman et al. 1987). Brain-weight reduction, loss of white matter, and enlargement of the ventricles have been found in *post-mortem* neuropathological studies (de la Monte 1988; Harper and Blumbergs 1982; Harper and Kril 1990; Harper et al. 1985; Torvik 1987). Magnetic resonance imaging studies have indicated significant loss of both subcortical and cortical cerebral gray matter in alcoholics (Jernigan et al. 1991; Pfefferbaum et al. 1995; Sullivan et al. 1995). The gray-matter loss appears to be relatively homogeneous across the cortex, whereas the white-matter deficits are concentrated in the prefrontal and temporal-parietal regions (Sullivan et al. 1998). Functional brain-imaging studies have in turn shown reduced cerebral blood flow (Melgaard et al. 1990; Nicolás et al. 1993) and glucose utilization (Gilman et al. 1990; Volkow et al. 1992). Notably, blood-flow reduction has also been found in alcoholics without clear-cut structural abnormalities (Melgaard et al. 1990).

On the cellular level, nerve-cell death and gliosis in the frontal lobes, and neuronal shrinkage in several other cortical regions, have been observed in alcoholics (Harper et al. 1987; Kril and Harper 1989). Some recent well-controlled pathological studies have, however, failed to show loss of cerebral neurons in humans despite clear signs of atrophy, for instance, in the hippocampus (Harding et al. 1997) or neocortex (Jensen and Pakkenberg 1993).

Moreover, the alcohol-related dilation of brain ventricles and sulci (Carlen and Wilkinson 1987; Lishman et al. 1987; Schroth et al. 1988), cerebral hypoperfusion (Berglund et al. 1987), and perhaps also the white-matter loss (Pfefferbaum et al. 1995; Shear et al. 1994) might partially recover with prolonged abstinence. The possibility of such recovery by abstinence might be an important motivating factor, for both patients and professionals, to enhance the treatment response of alcoholism.

Neuropsychology of Alcoholism

The clinical presentation of alcohol-related neuropsychological deficits is heterogeneous, ranging from minimal cognitive impairment to amnesia, and in some cases, to alcoholic dementia. The most profound neuropsychological deficits such as the amnesia are observed in alcoholics suffering from Korsakoff's syndrome (KS). The characteristic brain lesions of KS can be found, for instance, in the diencephalon and limbic system that are crucial for memory functions (Joyce and Robbins 1991; Kopelman 1995; Victor et al. 1989). Atrophy of the frontal cortex and consequent attentional and executive dysfunction are also present in many cases. KS follows from acute Wernicke's disease, which is caused by prolonged thiamine deficiency. This can result from a combination of inadequate dietary intake, reduced gastrointestinal absorption, decreased hepatic storage, and impaired utilization of thiamine (Hoyumpa 1980). The thiamine deficiency might also be a major factor underlying alcohol dementia (Joyce 1994) and the associated (Arendt 1994) pathology of the nucleus basalis (Cullen and Halliday 1995), which gives rise to the cholinergic afferentation of the neocortex. In addition, the cerebellar Purkinje cells may be selectively vulnerable to the thiamine deficiency (Baker et al. 1999).

Although the overall intellectual performance is not necessarily degraded, specific neuropsychological deficits, for instance, in visuospatial and memory functions, can be detected in alcoholics without KS as well (Eckardt and Martin 1986; Grant et al. 1984; Knight and Longmore 1994; Parsons 1998; Parsons and Leber 1981). The most frequent and salient neuropsychological deficits may perhaps be related to the "frontal" impairments, as indexed by tasks that measure attention, executive functions, and those generally concerned with the management of human goal-directed behavior. This was suggested, for instance, by a retrospective study of 641 Australian patients with suspected alcohol-related brain damage (Tuck and Jackson 1991). The frontal (i.e., attentional and executive) neuropsychological impairments also appear to correlate quite consistently with metabolic abnormalities, expectedly, in the frontal lobes in alcoholics (Adams et al. 1993; Dao-Castellana et al. 1998; Nicolás et al. 1993).

Notably, difficulties in executive tasks that mimic "everyday" problem solving have been found in alcoholics with relatively unimpaired memory or intelligence (Ihara et al. 2000). Furthermore, behavioral abnormalities such as aggressiveness and poor adaptation to socio-professional or family life, typically accompanying frontal lesions (Eslinger and Damasio 1985), are common in alcoholics. One might thus hypothesize that the frontal dysfunction might also be a factor preventing alcoholics from achieving full recovery and benefiting from rehabilitation. The frontal dysfunction has, further, been identified as an important etiologic substrate for disorders of behavioral excess-disinhibition such as alcoholism (Giancola and Moss 1998). Investigation of the underlying neural abnormalities is, therefore, clearly needed.

The memory impairments in alcoholics without KS are typically evident in tests that measure free recall of verbal episodic material or learning of word lists (for a review, see Knight and Longmore 1994). These impairments have been shown to correlate with increased fluid volume in the cerebral ventricles (Acker et al. 1987; Jernigan et al. 1991), which is, however, a rather non-specific measure and does not reveal the underlying neural deficits. The auditory short-term memory performance of alcoholics (even in the amnesics with KS) is only deficient when active rehearsal of information is interfered with a distractor task (Brandt et al. 1983; Knight and Longmore 1994; Ryan et al. 1980). The distractibility of working memory may correlate with alcohol consumption even in social drinkers (MacVane et al. 1982), thus suggesting that it might be a sensitive marker of brain deficits in alcohol abusers, already in the early phase of the disorder.

Non-Invasive Measurement of Changes in Brain Electromagnetic Activity

Many aspects of the alcohol-induced changes in human information processing are not readily detected with the methods used in the studies described above. For instance, the imaging of brain regional metabolism or hemodynamics is temporally limited to seconds, which is not adequate to detect the arrangement of brain events related to perception and cognition. Such millisecond-scale neural events, and related abnormalities arising from alcoholism, can be studied non-invasively with event-related potentials (ERP), which are averaged EEG changes time-locked, for instance, to the presentation of external stimuli (Figure 2). The source localization of the brain electromagnetic activity is, however, difficult because any given external signal can be explained by an infinite number of equiprobable underlying source configurations (also termed the "inverse problem"; von Hemholz 1853). The source localization of ERPs is

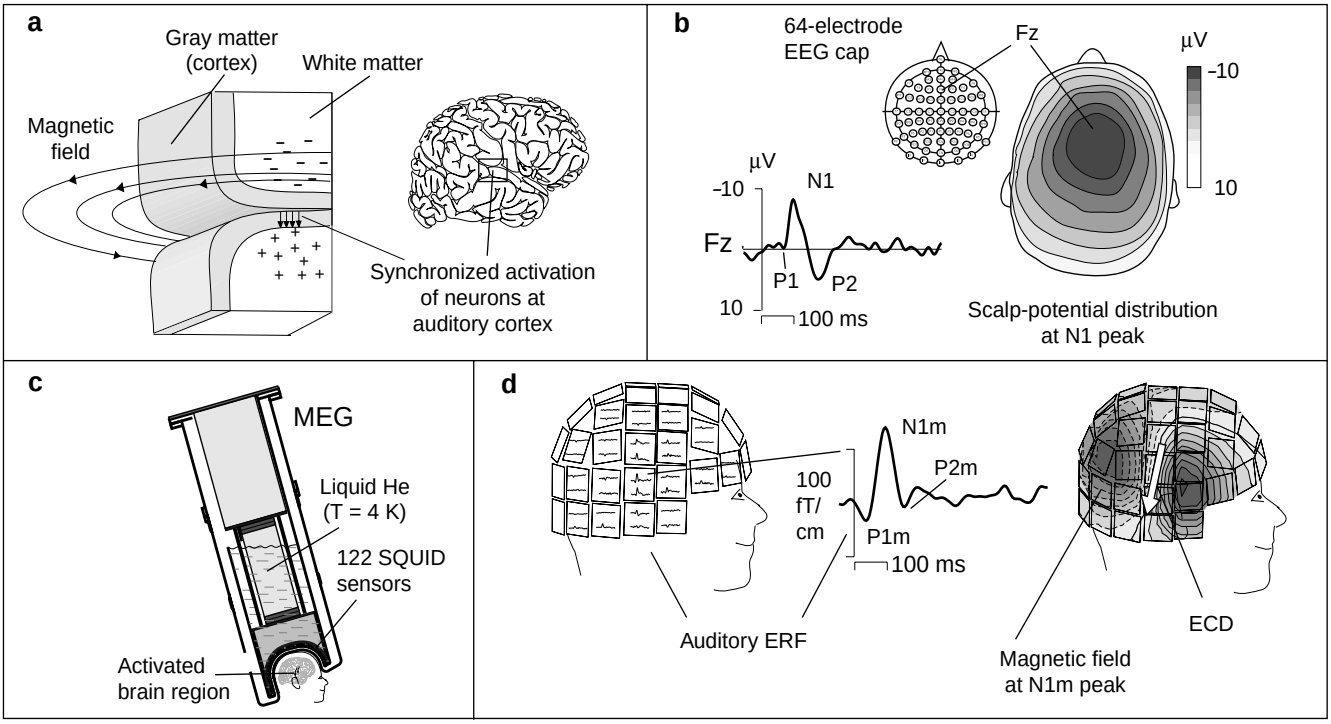

Figure 2. Schematic illustration of measurements of electromagnetic auditory responses. **(a)** Cross-sectional view of the cortex around the Sylvian fissure. The arrows, representing neural activation at the supratemporal plane (near the auditory cortices), correspond to the primary current, which gives rise to the charge distribution indicated by the + and – signs, and to the magnetic field illustrated by the circles. **(b)** This activation, a negative auditory ERP component N1, is detected from the background activity by averaging hundreds of stimulus-locked EEG epochs. The potential field, corresponding to the ERP components generated in the auditory cortex, is largest at the frontocentral EEG electrodes. **(c)** MEG device with 122 planar gradiometers (based on superconducting quantum interference device, SQUID, sensors) that detect the strongest signal right above the cerebral source. **(d)** ERF waveform obtained by averaging the simultaneously collected MEG epochs. The arrow represents an equivalent current dipole (ECD), a source for the extracerebral magnetic field that is used for localization of cerebral generators of ERF components. MEG is most sensitive to superficial sources that are tangential to the skull (see also Melcher and Cohen 1988), detecting specifically the activation in the cortical sulci. The neural activation at the supratemporal plane (a) causes the largest MEG signal (the gradient of magnetic field) directly above the active source. Differentiation of the parallel auditory activity at the left and right hemisphere is easier with MEG than EEG.

further complicated by their irregular distortion by the skull and tissue. The magnetic counterparts of ERPs, event-related magnetic fields (ERF), obtained with MEG, however, are less distorted by such factors, and their sources can thus be more easily localized (Figure 2; for a review, see Hämäläinen et al. 1993).

Auditory ERP and ERF Components

The auditory ERP and ERF are composed of different components, which are generally named by their polarity and succession (or approximate latency). ERF components are generally indicated by an additional subscript m (i.e., magnetic). The auditory ERP and ERF components are thought to reflect different aspects of information processing in the auditory system (Figure 3). They are classified as brain-stem, middle-latency, and long-latency components depending on the range of their elicitation (see below). Further, certain components are termed "exogenous", based on their strong reliance on stimulus features, whereas certain long-latency components have been labeled "endogenous", meaning that they appear to be dependent on factors such as attention and motivation (Figure 4).

The brain stem auditory evoked potentials (BAEP) and magnetic fields (Erné et al. 1987) are generated 1–10 ms from stimulus onset (Figure 4). The earliest cortical responses, middle-latency auditory evoked potentials (MAEP) and fields (MAEF), are generated 10–70 ms from stimulus onset. MAEPs are composed of several distinct deflections, with the most invariable (Deiber et al. 1988) components N_a and P_a peaking at approximately 25 ms and 30 ms post-stimulus, respectively (Figure 4). Intracranial recordings suggest that their generators lay near the primary auditory cortices (Liégeois-Chauvel et al. 1994). This claim has, in principle, been supported by the source-location results on the simultaneously elicited MAEF components N_am and P_am (Gutschalk et al. 1999; Mäkelä et al. 1994).

The exact functional role of MAEP and MAEF still remains to be elucidated. They have been suggested to be clinically useful for assessing anaesthetic adequacy (Schneider and Sebel 1997) and in coma monitoring (Kaga et al. 1985). The human P_a (Buchwald et al. 1991) and the magnetic counterpart P_am (Jääskeläinen et al. 1999) have been shown to be slightly enhanced by the cholinergic muscarine-receptor antagonist scopolamine, despite the suggested

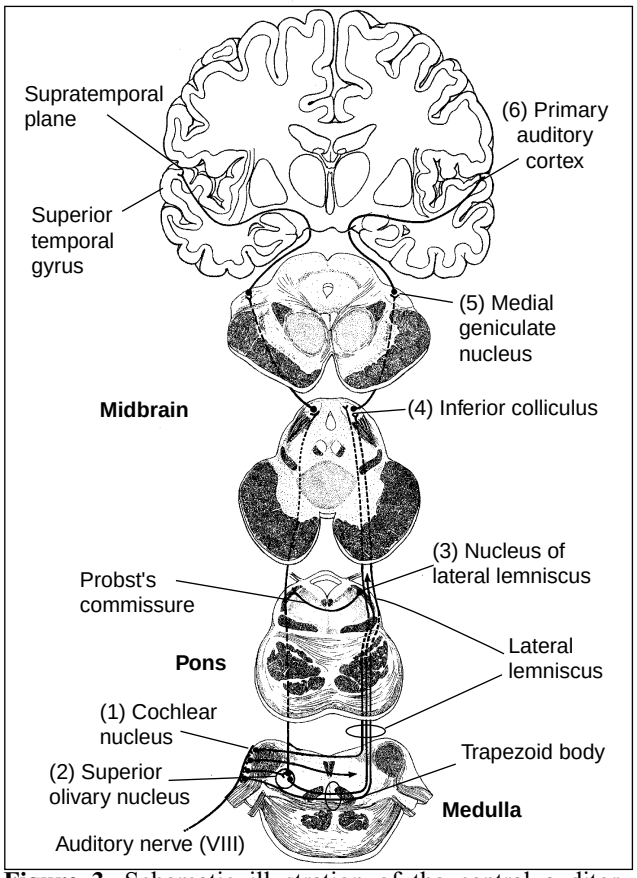

Figure 3. Schematic illustration of the central auditory pathway. Sequences of neural events encoded from sound air pressure at the inner ear ascend *via* the brain stem nuclei (1, 2, 3, 4) and the thalamus (5) to the primary auditory cortex. The major outputs (~ 3/4 of the fibers) from the cochlear nuclei project to the hemisphere contralateral to the ear stimulated. First binaural interactions occur in the superior olives (2). For clarity, the descending auditory pathways are not presented.

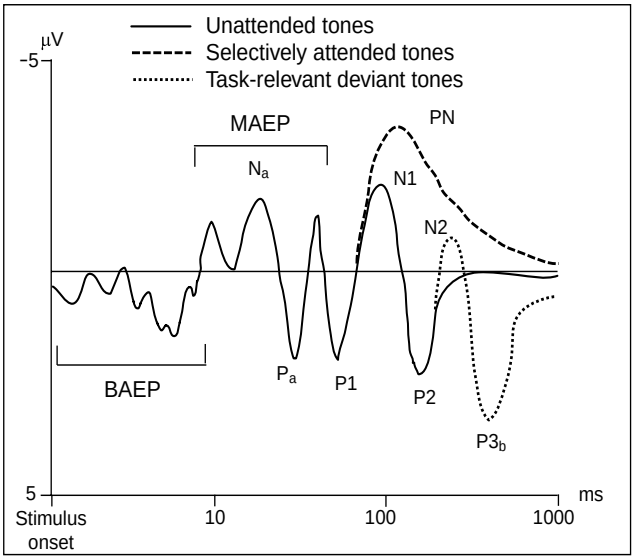

Figure 4. Idealized auditory ERP. The solid line represents the components elicited without attention (e.g., BAEP; the MAEP components P_a and N_a; the late components P1, N1, and P2). The dashed tracing represents the "endogenous" processing negativity (PN) elicited to tones that have been selectively attended. The dotted tracing represents the endogenous N2 and $P3_b$ components elicited to attended task-relevant deviant stimuli (e.g., pitch changes that are to be counted), embedded within a train of task-irrelevant standard tones. Note logarithmic time base. (Adapted and modified from Picton et al. 1974.)

facilitation of thalamocortical synaptic transmission by acethylcholine (Metherate and Ashe 1993). Low doses of the dopamine D_2-receptor antagonist haloperidol in turn showed no effect on the human MAEF (Kähkönen et al. submitted-b). The MAEP generation, further, might be regulated by GABAergic inhibition, as suggested by reduced amplitudes or increased peak-latencies during sedation induced by the $GABA_A$-receptor agonist midazolam (Morlet et al. 1997; Schwender et al. 1997), although in certain studies the MAEP suppression or delay has been statistically insignificant (Schwender et al. 1993).

The long-latency components occur at 50–800 ms after stimulus onset. On average, P1 peaks at 50 ms, N1 at 100 ms, and P2 at 200 ms (Figure 4). Their main sources lay near the supratemporal auditory cortices (Hari et al. 1980; Näätänen and Picton 1987). In addition, N1 may have a lateral subcomponent, and after longer period without discrete stimuli, the modality non-specific N1 subcomponent is generated (Hari et al. 1982; Näätänen 1992). The ERF components P1m, N1m, and P2m (Figure 2) reflect predominantly the tangential components of the supratemporal sources of their electric counterparts elicited at about the same latencies (Hari et al. 1980; Näätänen and Picton 1987). The parallel peaks of these ERF components are usually generated slightly earlier at the hemisphere contralateral to the ear stimulated (Pantev et al. 1998). The delay between the ipsilateral and contralateral N1m peaks appears to be increased with aging, and especially in Alzheimer's or Parkinson's diseases (Pekkonen et al. 1995a, 1996, 1998).

P1(m), N1(m), and P2(m) are believed to be strongly dependent on stimulus features and generated attention independently. Activation of overlapping cortical processes might, however, modulate N1 and P2 to attended stimuli (Näätänen 1990). During selective attention an increased negativity overlaps both N1 and P2, in other words, N1 is augmented and P2 reduced. This negative difference (Hansen and Hillyard 1980) between the task-relevant and task-irrelevant channels is believed to be caused by a distinct endogenous ERP component termed processing negativity (PN; Näätänen et al. 1978; see Fig. 4). However, MEG studies indicate that the supratemporal N1 *per se* may also be enhanced by attention (Fujiwara et al. 1998; see also Hillyard et al. 1973).

The functional significance of P1(m), N1(m), and P2(m) is still not fully clear, although several illustrative proposals have been put forth. For instance, Näätänen and Picton (1987) proposed that the supratemporal N1 might reflect build-up of an auditory sensory-memory trace (see also Tiitinen and May 1999). Further, the finding of N1m amplitude reduction

with short inter-stimulus intervals (ISI), and consequent improvement of tone-matching performance, has been interpreted to indicate neural adaptation that underlies the formation of sensory-memory traces (Lu et al. 1992). In further MEG studies, the short-term storage of auditory information has been associated with a putative anterior subcomponent of N1m (Loveless et al. 1996; McEvoy et al. 1997; Sams et al. 1993). An association with short-term memory scanning has also been presented for N1 (Conley et al. 1999). Finally, the occurrence of N1 has been observed to correlate with stimulus detection (Parasuraman and Beatty 1980), and it may be involved in involuntary attention shifting to sudden onsets and offsets of auditory stimuli (Näätänen 1988; Näätänen 1990). The attention shifting is, however, most clearly related to the non-specific N1 subcomponent, which may reflect triggering of an arousal burst to facilitate orienting and responding to an unexpected stimulus (Näätänen 1992; Näätänen and Picton 1987).

The generation of N1 appears to be regulated by GABAergic inhibition. N1 has been shown to attenuate in amplitude by different $GABA_A$ agonists in humans (Meador 1995; Rockstroh et al. 1991; Semlitsch et al. 1995; Sinton et al. 1986), and the apparent counterpart in monkeys was enhanced by the $GABA_A$-receptor antagonist bicuculline (Javitt et al. 1996). The effects of cathecolamines on N1 are less evident. For instance, the dopamine D_2-receptor antagonist droperidol and the α_2-adrenoreceptor agonist clonidine had no significant auditory ERP effects at 100–200 ms post stimulus (Shelley et al. 1997). Mervaala et al. (1993) in turn reported no N1 effects by the α_2-adrenoreceptor antagonist atipamezole. Similarly, the N1m waveforms, nor N1 measures, were not affected by the dopamine D_2-receptor antagonist haloperidol (Kähkönen et al. submitted-a).

Reduced serotonin levels have been proposed to increase the dependence of N1/P2 peak-to-peak amplitude on stimulus intensity (Hegerl and Juckel 1993). However, the theory of serotonergic regulation of the intensity-dependence of N1 amplitude has not been consistently supported in human studies (Dierks et al. 1999). N1 or P2 amplitudes were not significantly affected *per se* by the serotonin depleting agents methysergide (Meador et al. 1989) or fenfluramine (Meador et al. 1995) either. Finally, the histamine H_1-receptor antagonist chlorpheniramine (Serra et al. 1996) or the cholinergic muscarine-receptor antagonist scopolamine (Meador et al. 1989, 1995) had no significant effects on N1, although preliminary evidence of increased N1m peak-latencies by scopolamine has been found (Pekkonen et al. 1999b). Taken together, the most consistent drug effects on N1 have been indicated by substances acting on the $GABA_A$-receptors, which present with the significant changes after chronic ethanol exposure as well (Buck and Harris 1991; Korpi 1994). However, more studies are needed to elucidate the exact neurochemical basis of this component.

Auditory ERP and Alcoholism

The current literature suggests that the EEG and MEG signals mainly reflect temporally overlapping postsynaptic currents in the apical dendrites of cortical pyramidal neurons (Hämäläinen et al. 1993; Martin 1991). Hence, ERPs and ERFs provide direct access to alcohol-related abnormalities in neural transmission at the cortex. Despite the numerous EEG studies, no MEG reports on ethanol or alcoholism have been published prior to the present investigation.

During acute challenge, the inhibitory effects of ethanol (Buck and Harris 1991; Korpi 1994) result in attenuated and delayed elicitation of auditory ERP components (for a review, see Porjesz and Begleiter 1985). The human BAEP (Church and Williams 1982) and late components, such as N1 (Jääskeläinen et al. 1996b), are affected already at relatively low doses. Few studies on the human MAEP have been published, however, N_a and P_a are reportedly reduced and delayed in rats during chronic intoxication (Floyd et al. 1997).

After withdrawal of chronic ethanol ingestion, in turn, decreased peak latencies and increased amplitudes of different ERP components have been frequently observed in laboratory animals (Porjesz and Begleiter 1993). In healthy human subjects, the BAEP acceleration can accompany even hangover caused by acute ethanol drinking (Church and Williams 1982). The effects of withdrawal hyperexcitability on ERP, however, tend to subside with abstinence. After prolonged sobriety (over at least 3 weeks), the BAEP components may be delayed and decreased in human alcoholics (Begleiter et al. 1981), reflecting structural lesions (e.g., demyeliniation) that result in cerebral "hypoexcitability" (Porjesz and Begleiter 1985, 1993). However, Díaz et al. (1990) observed that despite the delayed BAEP, the peak latencies of the cortically generated MAEP components were reduced in alcoholics with about one month of abstinence. Furthermore, reduced GABA-benzodiazepine binding was found in alcoholics who had been abstinent for at least three months (Lingford-Hughes et al. 1998). This suggests that residual deficits in neural inhibition, following from neural adaptation to chronic ethanol, might affect brain function for several weeks after detoxification.

There are, however, also some discrepancies with respect to the withdrawal hyperexcitability in previous ERP studies of detoxified human alcoholics. For instance, only a few indices of post-withdrawal hyperexcitability in the auditory N1 have been reported (Cadaveira et al. 1991; Realmuto et al. 1993; Romani and Cosi 1989). The aforementioned MAEP results indicating facilitated responses (Díaz et al. 1990) have also been challenged by a finding of delayed latencies in abstinent alcoholics (Katbamna et al. 1993).

These discrepancies could, however, be explained by a number of factors. For instance, the alcoholics have often been medicated with inhibitory agents (e.g., see Katbamna et al. 1993; Lille et al. 1987; Pfefferbaum et al. 1991) that may reduce ERP generation. Further, there might be a wide variability and individual differences in disease-related factors, which might have confounded the post-withdrawal syndrome in different patient samples. Therefore, further studies on the post-withdrawal ERP changes in human alcoholics are justified.

The majority, and the most influential, of human ERP studies on alcoholism have concentrated on cognitive components such as $P3_b$ elicited 300–500 ms after task-relevant stimuli (Figure 4). These studies have indicated deficits in both visual and auditory $P3_b$ (see Porjesz and Begleiter 1993). The preceding negative N2 (Figure 4) might also be delayed in alcoholics (Cadaveira et al. 1991; Porjesz et al. 1987b). In the auditory system, the $P3_b$ amplitude reduction is perhaps the most consistent result (Patterson et al. 1987; Pfefferbaum et al. 1991; Porjesz and Begleiter 1993; Realmuto et al. 1993). Delayed $P3_b$ latencies have also been frequently reported (Cadaveira et al. 1991; Pfefferbaum et al. 1979, 1991; Steinhauer et al. 1987). In addition, $P3_b$ has been extensively studied in risk groups for alcoholism. For instance, 7–15-year-old sons of alcoholics have been shown to have a reduced $P3_b$ in response to both visual (Begleiter et al. 1984) and auditory stimulation (Begleiter et al. 1987), and these results have been frequently replicated (see Farren and Tipton 1999). In one study, children from high-risk families were also characterized by enhanced N2 amplitudes (Hill et al. 1995a). Importantly, the $P3_b$ abnormalities may predict subsequent adolescent and young-adult substance abuse (Berman et al. 1993; Hill et al. 1995b).

Despite the profound information obtained in the $P3_b$ studies, their drawback is that $P3_b$ is, obviously, also affected by motivational aspects that might impair the ability to actively sustain information processing (Porjesz et al. 1987a). Therefore, factors that are not directly related to the neurophysiological effects of alcohol might also confound the results. Novel studies on cognitive ERP and ERF components, not modulated by motivation and attention to that extent, might enhance the understanding of neurophysiological abnormalities in alcoholism.

MMN: An Index Of Involuntary Attention and Sensory Memory

The neural basis of cognitive processes such as sensory memory and involuntary attention can be indexed with an ERP component termed mismatch negativity (MMN), and the magnetic counterpart MMNm, which are generated without the subject's active engagement to the study (Figure 5). More specifically, MMN is elicited when an unattended series of homogenous standard stimuli is interrupted by a deviant stimulus, MMN activity usually peaking at 100–300 ms after stimulus onset (Näätänen 1992; Näätänen et al. 1978; Sams et al. 1985; Tiitinen et al. 1994). MMN presumably has several overlapping sub-components that reflect different phases of detection and orienting to novel stimulus features (Näätänen et al. 1978; Näätänen 1990, 1992). As interpreted by Näätänen (1992), MMN resembles the neuronal-mismatch process postulated by Sokolov (1963) to account for initiation of the orienting response.

The existence of the supratemporal MMN subcomponent with origins in the auditory cortices has been verified by intracranial studies in humans (Kropotov et al. 1995) and monkeys (Javitt et al. 1992). MMNm is assumed to reflect predominantly the tangential aspects of the supratemporal MMN generators (Hari et al. 1984). The supratemporal MMN subcomponent is presumably a response to the difference between the deviant stimulus and a cortical memory trace of the standard tone (Näätänen 1992; Näätänen et al. 1978). MMN is thus suggested (Näätänen et al. 1989) to reflect the operation of the auditory sensory (or "echoic") memory, the earliest memory system wherefrom the relevant information is selected for attentional processing in working memory (Baddeley 1986). Consequently, MMN might provide neurophysiological information of the accuracy of auditory sensory-memory traces. For instance, MMN amplitude decreases as a function of ISI, and the fact that a significant MMNm is generated with an ISI of 9 seconds implies that these memory traces can last up to 10 seconds in healthy young subjects (Sams et al. 1993; see, however, Jääskeläinen et al. 1999a). Furthermore, MMN studies have suggested that the decay of auditory sensory-memory traces accelerates with aging (Pekkonen et al. 1993), and particularly in neurodegenerative diseases such as Alzheimer's disease (Pekkonen et al. 1994).

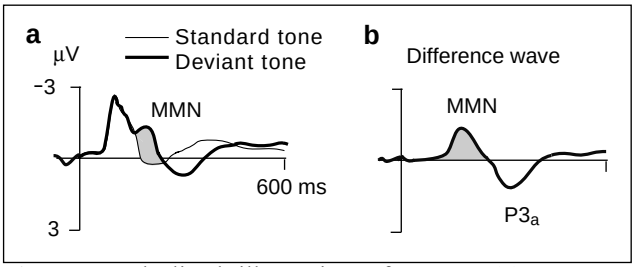

Figure 5. Idealized illustration of MMN. **(a)** ERPs to frequent standards and occasional deviants superimposed. The frequently repeated standard is presumed to form a memory trace in the auditory cortex. When the deviant tone is presented within the train of the standards, an automatic detection of the difference between this memory trace and the deviant tone elicits MMN (Näätänen et al. 1978). **(b)** The difference wave (ERP to the deviants minus ERP to the standards) represents MMN, which increases in amplitude and decreases in peak-latency as the magnitude of the stimulus deviance increases (Tiitinen et al. 1994). MMN is followed by the positive $P3_a$ component.

Behavioral studies of auditory sensory memory have shown that a backward-masking stimulus following a test stimulus at a short interval may deteriorate the memory of the test stimulus (Hawkins and Presson 1986). Similarly, it appears that the MMN generation is clearly interfered with backward-masking tones that follow the standard and deviant tones after a silent interval of 20–150 ms (Winkler et al. 1993; Winkler and Näätänen 1995). The decrement of MMN amplitude by backward masking is believed to reflect disruption of the memory-trace formation, and when the mask is very close to test stimulus (offset-to-onset interval < 50 ms), it might also block the change-detection process (Winkler et al. 1993; Winkler and Näätänen 1995). This paradigm might provide novel information of the alcohol-related deficits in auditory working memory (Brandt et al. 1983; Knight and Longmore 1994; Ryan et al. 1980).

According to the prevailing view (Näätänen et al. 1992), the preconscious discrimination of stimulus change in the auditory cortex, eliciting the supratemporal MMN, initiates a sequence of brain events that are associated with involuntary shifting of attention, orienting, and conscious detection of this change. The initiation of involuntary attention shifting is purportedly reflected by the frontal MMN subcomponent (Giard et al. 1990; Näätänen et al. 1992). Rinne and others recently showed (2000) that the "center of gravity" of the MMN source current distribution shifts from the temporal to frontal cortex as a function of time, supporting the theory (Näätänen et al. 1992) that the frontal MMN subcomponent is generated slightly after the supratemporal subcomponent. The subsequent positive $P3_a$ (Figure 5) is in turn surmised to signal the actual attention switch to the change (Näätänen et al. 1982, 1992). This interpretation is based on the apparent attention-dependence of $P3_a$ (Näätänen 1992). For instance, the $P3_a$ to task-irrelevant deviants is smaller when the primary task demands more attention (Duncan and Kaye 1987), whereas MMN is presumably attention independent (see also Trejo et al. 1995; Woldorff et al. 1991). Furthermore, $P3_a$ is also dependent on the degree of subjective stimulus change, while MMN appears to rely predominantly on the actual physical deviation (Näätänen et al. 1989). $P3_a$ is finally followed by a slow negativity elicited at 400–600 ms after stimulus onset, termed reorienting negativity (RON), which might reflect orienting back to the activity that was interrupted by the involuntary attention-shifting (Schröger and Wolff 1998a).

Involuntary attention shifting allows orienting to unexpected, potentially harmful, changes in the environment, but it might also distract concentrating on an ongoing cognitive task. For instance, task-irrelevant stimulus changes impair both speed and accuracy of reaction-time (RT) performance, if the subject tries to concentrate on duration discrimination and to ignore frequency changes in the same tones (Schröger and Wolff 1998a, 1998b). Impaired control of involuntary attention shifting might thus distract maintenance of concentration and have a detrimental impact on goal-directed functioning. Such deficit might also accompany alcoholism that often comes with a variety of attentional problems. Few studies have, however, concentrated on the effect of chronic alcoholism on involuntary attention shifting.

Drug and Alcohol Effects on MMN

The neurochemical bases of MMN are not fully known, although the NMDA receptors have been suggested to play a central role (Javitt et al. 1996; see also May et al. 1999). In their intracranial monkey study, Javitt et al. (1996) found that MMN was abolished by microinjections of different NMDA antagonists, while the preceding early components were not affected. A very recent preliminary result, obtained with the non-competitive NMDA antagonist ketamine in humans, supported these findings (Kreitschmann-Andermahr et al. 2000). However, there are also some discrepancies; according to Oranje et al. (2000), a sub-anaesthetic dose of ketamine failed to produce significant MMN effects.

Preliminary results suggest that MMN might be reduced by the $GABA_A$-receptor agonist temazepine (Hirvonen et al. 1998). The cholinergic system might also modulate MMN, as suggested by the MMNm amplitude reduction after scopolamine administration (Pekkonen et al. 1999a). The pattern of this modulation, however, appears to be quite complex, given that the cholinesterase inhibitor tacrine, surprisingly, decreased MMN in Alzheimer's patients (Riekkinen et al. 1997), despite that this drug is supposed to alleviate the cholinergic deficits in these patients. The histamine H_1-receptor antagonist chlorpheniramine in turn decreased the later phase of MMN (Serra et al. 1996), and MMN might also be slightly modulated by the dopamine D_2-receptors (Kähkönen et al. submitted-a; Pekkonen et al. submitted). The α_2-adrenoreceptor antagonist atipamezole (Mervaala et al. 1993) or the α_2-adrenoreceptor agonist clonidine (Duncan and Kaye 1987) had no MMN effects. With respect to neuromodulators and hormones, vasopressins have been shown to increase the MMN amplitude in humans (e.g. Born et al. 1986), while adrenocorticotropic hormone (e.g. Born et al. 1987a, b) or cholecystokinin analog ceruletide (Schreiber et al. 1995) produced no significant effects. Finally, elevated plasma cortisol levels, induced by hydrocortisone, have been observed to suppress MMN (Born et al. 1987).

Acute actions of ethanol on MMN are consistent with effects that have been observed in the preceding components. Relatively low doses of acute ethanol attenuate and delay MMN (for a review, see Jääskeläinen et al. 1996b).

It appears that this effect is particularly strong on the frontal MMN subcomponent (Jääskeläinen et al. 1996c). Consequently, acute ethanol has been observed to reduce involuntary attention shifting to unattended stimulus changes in behavioral experiments as well (Jääskeläinen et al. 1996a, 1999b). Finally, the ethanol-induced latency delay in MMN might be augmented by the opioid-receptor antagonist naltrexone (Jääskeläinen et al. 1998) and reversed by caffeine, an adenosine receptor subtype A_1/A_{2a} antagonist (Hirvonen et al. 2000).

Chronic MMN effects of ethanol have been studied much less extensively than the acute actions. Realmuto et al. (1993) found that the "N2" elicited by unattended deviants was significantly reduced in the frontal electrode Fz. This result was, however, obtained directly from the deviant curves by applying P2/N2 peak-to-peak analysis, which might confound the results since MMN usually overlaps P2 (Näätänen et al. 1992). Furthermore, the control group was considerably younger than the patients (11 years on the average), which also obscures the clarity of the results, because MMN has been shown to be reduced by aging (for a review, see Pekkonen 2000). Kathmann et al. (1995), in turn, reported that MMN was significantly delayed in a combined patient group of alcoholics and schizophrenics. The alcoholics were not compared with the controls separately in the statistical analysis, which is surprising, since the well-documented MMN deficits in schizophrenia (for a review, see Javitt 2000) might have biased the results with respect to these alcoholics.

In summary, the above mentioned methodological inconsistencies warrant more extensive MMN studies focused on alcoholism. Moreover, inhibitory drugs or other methodological factors might have confounded some of the previous results on the cortical auditory ERP components preceding MMN, and only a few studies on MAEP and human alcohol abuse have been published. Finally, there is a lack of MEG studies on alcoholism.

AIMS OF THE STUDY

This study was guided by the assumption that comparisons of ERP and ERF in abstinent alcoholics and healthy controls would enhance the understanding of cognitive deficits in alcoholism. The auditory ERP and ERF components were assumed to measure the post-withdrawal neurochemical changes, such as residual brain hyperexcitability. Further, one of the basic premises was that the neurophysiological abnormalities in the early phases of stimulus processing might culminate in deficits at higher levels of cognition. For instance, assuming that the neural principles of memory-trace formation are basically similar at different levels of the nervous system, MMN was presupposed to index the neural bases of memory dysfunction in alcoholics. Furthermore, experiments at the level of involuntary attention were assumed to elucidate neurophysiological aspects of alcohol-related attention and executive dysfunction. The specific hypotheses and aims of this study are presented below.

(I) (a) MEG was used to investigate whether the post-withdrawal cerebral changes such as neural hyperexcitability could affect processing of auditory stimuli in abstinent alcoholics. (b) Further, given the resemblance of alcohol-related functional deficits and the cognitive changes in aging and neurodegenerative diseases, the temporal persistence of auditory sensory memory traces that impairs with aging and in neurodegenerative diseases was studied with MMNm.

(II) Neuropsychological studies suggest that working-memory representations are particularly vulnerable to interference in alcoholics. (a) Backward masking of MMN was used to study whether such vulnerability to interference is also detected in pre-attentive sensory memory. (b) The account of sensory-memory interference to the suppressed working-memory performance in alcoholics was also studied.

(III) Chronic alcoholism is accompanied by frontal neuropsychological deficits, such as an inability to maintain focus of attention. The present hypothesis was that such attention deficits in alcoholics might be associated with pronounced involuntary attention shifting to task-irrelevant stimulus changes. Therefore, the ERP components disclosing different phases of detection and orienting to stimulus changes during behavioral performance were studied in alcoholics.

(IV) The post-withdrawal hyperexcitability may affect thalamic–cortical auditory processing in abstinent alcoholics. These changes were studied with MAEP, and results were correlated with demographic variables including abstinence duration.

(V) The functional brain changes associated with possible residual withdrawal symptoms were assumed to have an impact on higher-order cognitive functions. Therefore, the post-withdrawal changes in auditory processing were indexed with the pre-attentive auditory ERP components, and the results were correlated with neuropsychological measures of memory and learning.

(VI). One of the main rationales for the present study was the lack of objective neurophysiological measures of alcohol-related brain function changes. For the future development of neurophysiological tools, the test–retest reliability of the pre-attentive electromagnetic auditory responses was assessed in healthy subjects.

METHODS

Subjects

Experienced clinicians recruited 33 inpatients meeting DMS-IV criteria for alcohol dependence (samples A and B, Table 1), consecutively from a routine treatment program at the Järvenpää Addiction Hospital, A-Clinic Foundation, Finland. This non-profit private hospital receives a representative sample of alcoholic patients from the entire nation. Only male alcoholics were studied, because alcohol might produce rather different effects on females, and these effects may depend on the phase of the menstrual cycle (Eriksson et al. 1994, 1996; Sarkola et al. 2000), thus complicating the matching of control subjects.

The exclusion criteria were acute withdrawal symptoms, hearing deficits, heart diseases, liver diseases, diabetes mellitus, dependence on a drug other than alcohol, serious head trauma, Korsakoff's syndrome, and psychiatric or neurological diseases unrelated to alcoholism.

The exclusion and inclusion of patients, as well as the collection of demographic data of the severity of alcohol history and family history of alcoholism, was based on a semi-structured interview of the patients conducted by the experienced clinicians. In Sample B, the cessation of acute withdrawal symptoms was also controlled using the Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar; Sullivan et al. 1989). The Alcohol Use Disorders Identification Test (AUDIT; Seppä et al. 1995) was also used for patients in Sample B. The alcoholics were not treated with benzodiazepine, anticonvulsive, disulfirame, or naltrexone medication for at least three days before the measurements. Antidepressants (or related agents) were used by 7 patients in Sample A (3 had citalopram, 2 had mianserin, 2 had fluoxetine) and 6 patients in Sample B (2 had fluoxetine, and 1 had mianserin, 1 had mianserin and promazine, 1 had doxepin and 1 had promazine in evenings). In each study, the results were similar in the medicated and unmedicated subjects. A written informed consent was obtained after the procedures had been fully explained to the patients. The studies on alcoholism were approved by the Ethics Committee of the A-Clinic Foundation, Helsinki, Finland.

The 30 male control subjects were healthy social drinkers (without a history of alcohol or drug abuse) whose self-reported alcohol consumption did no exceed 18 standard drinks (12 g of ethanol/drink) per week (Table 1). They were instructed to abstain from alcohol and other drugs at least 48 hours before the measurement. In the methodological Study VI, 5 paid healthy subjects (3 females) without hearing deficits were investigated (Sample C, Table 1).

Measurements of Brain Function

General Methodology in ERP and ERF Measurements

Studies I (MEG) and VI (MEG and EEG) were conducted in a magnetically shielded room (Euroshield Ltd., Eura, Finland) at the BioMag Laboratory, Helsinki University Central Hospital, Finland. During the MEG recordings (Table 2), the subjects sat in a comfortable chair with their head placed inside a helmet-shaped whole-head MEG instrument with 122 planar gradiometers (Ahonen et al. 1993; Neuromag Ltd., Finland; see Fig. 2). Each two-channel MEG sensor unit measures two independent magnetic-field gradient components, $\partial B_z/\partial x$ and $\partial B_z/\partial y$, the z-axis being normal to the local helmet surface (Figure 6). Before each measurement block, the position of the subject's head in relation to the MEG instrument was determined by measuring magnetic fields produced by three marker coils attached to the scalp.

Table 1. Means (range) of the demographic variables. Sample A participated in Study I, Sample B in Studies II–V, and Sample C in Study VI.

	Sample A		Sample B		Sample C
Demographic Variable	Controls (N = 10)	Alcoholics (N = 13)	Controls (N = 20)	Alcoholics (N = 20)	(N = 5)
Age (years)	41 (32–59)	40 (33–55) *	37 (32–59)	40 (33–55) *	22–34
Abstinence (days)	**	27 (13–43)	**	20 (7–45)	**
Self-reported					
Years of abusive drinking	0	17 (5–25)	0	11 (1–35)	
Onset age of alcoholism		26 (16–42)		29 (14–50)	
Weekly alcohol consumption (g)	<216	1836 (300–3156)	97 (12–216)	1213 (336–2520)	
Formal education (years)			14 (11–18)	12 (8–18) *	

* No significant differences between the controls and alcoholics.

** Instructed to avoid alcohol for 48 hours before the measurements

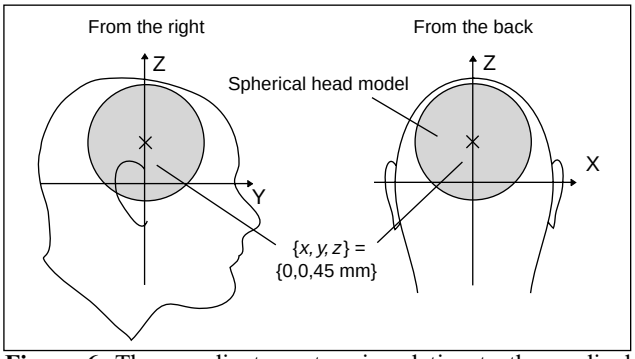

Figure 6. The coordinate system in relation to the cardinal points of the head, and the spherical head model used in the ERF source localization (Studies I, VI).

Before the measurement, the location of the marker coils in relation to the cardinal points of the head (nasion, left, and right pre-auricular points; see Fig. 6) were determined using an Isotrak 3D-digitizer (Polhemus, Colchester, VT). In Study VI, a bite-bar was used to keep the head steady while the locations were measured. MEG dipole modeling (Sarvas 1987) was performed using a spherical head model (Figure 6). The radius of the head model was 70 mm and center of symmetry at $\{x, y, z\} = \{0, 0, 45 \text{ mm}\}$. Equivalent current dipoles (ECD) were fitted separately for the left and right auditory cortices using a subset of 34 channels above each hemisphere. The ECD parameters were determined to explain the measured data optimally in the least-squares sense.

The methodological details of the EEG recordings are presented in Table 2. In Studies II–V, EEG measurements were performed in an acoustically and electrically shielded room at the CBRU laboratory, University of Helsinki, Finland. The 32-channel EEG was measured using the software of NeuroScan Inc., USA. An electrode cap with 32 Ag/AgCl electrodes was used (based on Virtanen et al. 1996). In Study VI, the 64-channel EEG was recorded in the magnetically shielded room with a biopotential amplifier specifically designed for simultaneous use with MEG (Virtanen et al. 1997), using an electrode cap with 64 Ag/AgCl electrodes (Virtanen et al. 1996). The EEG sources were modeled with the BESA program (Megis Software GmbH, Germany; Scherg 1990). The 4-layer model sphere was scaled and moved for the best fit with the electrodes. In the model, the thicknesses of the scalp, the skull, and the cerebrospinal fluid were 6, 7, and 1 mm, respectively, and the conductivities 0.33, 0.0042, and 1 S/m, respectively. The conductivity of the brain was 0.33 S/m. A pair of dipoles with symmetric locations with respect to the *y–z* plane was fitted to common-average referenced (CAR) signals at the latency of maximum amplitude of N1 at the electrode location FCz. The model sphere was rotated so that five electrodes labeled according to the extended 10–20-system matched with the BESA standard locations, and all the electrodes were projected on the surface of the sphere.

In each ERP and ERF measurement, the auditory stimuli were delivered at 60 dB above the subjective hearing threshold determined before the experiment, *via* headphones (Studies II–V) or plastic tubes and earpieces (Studies I, VI). The responses to the first few stimuli of each sequence, as well as epochs containing electro-oculogram (EOG), EEG, or MEG peak-to-peak changes exceeding the current artefact rejection criteria (Table 2), were automatically rejected in each study. In studies II and VI, the subjects were administered with a short neuropsychological test battery.

Bilateral Cortical Auditory Processing and Auditory Sensory Memory (Study I)

In four separate blocks, the subjects (Sample A, Table 1) were presented with monaural 700-Hz pure tones that were either 50-ms standards ($p = 0.8$) or 25-ms deviants (each with 5-ms rise and fall times), to both left and right ears with a stimulus-onset asynchrony (SOA; termed ISI in the original publication) of 500 ms or 2500 ms. The subjects were instructed to ignore the stimulation and to concentrate on a video movie. The MEG was digitized, and epochs with a minimum of 100 (500-ms SOA) or 40 deviant responses (2500-ms SOA) were averaged (Table 2). The averaged epochs were digitally filtered (see Table 2), and the peak amplitudes and latencies of P1m, N1m, and MMNm were quantified from the channel pair showing the highest amplitude response over the left and right temporal areas. The MMNm measures was analyzed for the left-ear stimulation from the hemisphere that showed the largest response. The amplitudes were determined as a square root of sums of squares of the amplitudes at the same latency from the orthogonal sensor pair ($a = [(\partial B_z/\partial x)^2 + (\partial B_z/\partial y)^2]^{1/2}$). The ECDs were modeled for P1m, N1m, and MMNm.

Backward Masking of MMN and Working Memory (Study II)

The subjects (Sample B, Table 1) were binaurally presented with trains of 600-Hz standard tones ($p = 0.8$) that were randomly replaced by 670-Hz deviant tones. Both the standards and the deviants (a total of 1294 stimuli/ block) were sinusoidal tones (duration 25 ms, 2.5 ms rise and fall time) presented with a SOA of 300 ms. In one of these conditions, backward-masking tones (duration 25 ms; 2.5 rise and fall time) were presented 100 ms after the offset of each stimulus in order to interfere with the MMN generation (the backward-masking condition). The frequency of the masks (300, 400, 900, or 1000 Hz) was varied randomly to prevent the confounding effects of possible MMN elicited to the mask-standard and mask-deviant pairs (Hari et al. 1992). During the baseline condition, the standard and deviant tones were presented without the maskers. In each condition, the subjects were instructed to ignore the stimulation and

to read self-selected material. The mastoid-referenced EEG was digitized, averaged and digitally filtered (see Table 2). The N1 peak latencies and amplitudes were determined from the standard-tone ERP. The MMN peak latencies and amplitudes were determined from difference waves (deviant ERP minus standard ERP), as an average signal obtained at seven electrode positions around the electrode site Fz, weighted by the spatial distribution estimated from the within-group grand-averaged ERP waveforms at the MMN peak latency. This estimate was used to dissociate the MMN signal from the noise at the individual level. The N1 peak latencies and amplitudes were determined at the electrode site Fz.

In the neuropsychological assessment, attention and executive function (here, termed frontal) were studied with the Trail-Making Test part A and part B (TMT) and the 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 II–I time, and SCWT-II errors. The Wechsler Memory Scale (WMS) digit span (Lezak 1995; Wechsler 1945) and the Brown-Peterson procedure termed "auditory consonant trigrams" (ACT), where a distractor task is interposed between encoding and recall of three consonants (Lezak 1995; Peterson and Peterson 1959), were used to test auditory-verbal working memory. In the ACT, the subject was presented with three consonants, and upon hearing them, during either 3, 9, or 18 seconds of distraction, he was to count backwards by threes from a given number, until signaled to report the consonants.

Neurophysiological and Behavioral Changes in Involuntary Attention Shifting (Study III)

The subjects (Sample B, Table 1) were presented with random sequences of binaural pure tones (5-ms rise and fall times) that equiprobably were either 100 or 200 ms in duration with a 1000-ms offset-to-onset ISI. In the forced-choice RT task, the subjects were instructed to press one button as rapidly as possible with their left-hand thumb to the 100-ms tones and another button with their right-hand thumb to the 200-ms tones. They were instructed to disregard occasional frequency changes that occurred independently of the tone duration. Either 700-Hz standards (p = 0.8), 750-Hz "slight deviants" (p = 0.1), or 1200-Hz "wide deviants" (p = 0.1) were presented. A total of 2000 stimuli were presented in four blocks with short resting periods of about 30–60 s between the blocks. The RTs and hit rates (HR) were measured to the standards (discounting stimuli occurring immediately after deviants), slight deviants, wide deviants, and to the standards presented immediately after the slight or wide deviants. The RT lag to slight deviants (RT to slight deviants minus RT to standards), RT lag to wide deviants (respectively), RT lag to standards after slight deviants, and the RT lag to standards after wide deviants were calculated.

Table 2. EEG and MEG settings.

Study	*Method*	*Sampling rate (Hz)*	*Recording passband (Hz)*	*Averaged epoch (ms) **	*Rejection cut-off point*	*Component of interest*	*Data-analysis filter (Hz)*	*Filter slope (dB/octave)*	*Baseline (ms) **
I	MEG	397	0.03–100	–150–600	3 pTcm^{-1}(MEG) 150 μV (EOG)	P1m, N1m, MMNm	1–30	12	–50
II	EEG	250	0.1–40	–100–300	75 μV (EOG, EEG)	N1 MMN	1–30 2–12	24	–100
III	EEG	250	0.1–40	–100–800	75 μV (EOG, EEG)	MMN, P3a, RON	1–30	24	–100
IV	EEG	10^3	1–500	–50–70	75 μV (EOG, EEG)	Na, Pa	10–250	24	**
V	EEG	250	0.1–40	–100–400	75 μV (EOG, EEG)	N1, P2	0.5–30	24	–100
VI	MEG & EEG	397	0.03–100	–150–600	3 pTcm^{-1}(MEG) 150 μV (EEG) 150 μV (EOG)	N1, N1m	0–20	12	–50

* With respect to the stimulus onset, ** 10-Hz high-pass filter used.

The EEG was digitized, averaged and digitally filtered (see Table 2). The ERPs were determined against CAR. The peak latencies and amplitudes of P1, N1, and P2 were determined from the averaged standard–tone ERP. The measures of MMN, $P3_a$, and RON were analyzed from difference waveforms for the slight and wide deviants (ERP for slight deviants minus standard ERP, ERP for wide deviants minus standard ERP, respectively). The MMN amplitudes for deviants were determined as an average response during two consecutive 50-ms periods. For the slight deviants, 140–189 ms (early) and 190–239 ms (later) post-stimulus periods were used, and since MMN latency decreases as the magnitude of stimulus deviance increases (Tiitinen et al. 1994), the respective periods were 80–129 ms (earlier) and 130–179 ms (later) for the wide deviants. In addition to the peak amplitudes, the average $P3_a$ amplitudes at 250–399 ms and the average RON amplitudes at 480–549 ms (Schröger and Wolff 1998a) from stimulus onset were analyzed. The MMN amplitude was determined from signals obtained at the frontal electrode (Fz), where MMN usually is largest in amplitude (Näätänen 1992).

Post-Withdrawal Changes in MAEP (Study IV)

A block of 4000 click stimuli (80-ms offset to onset ISI) was presented binaurally to a subgroup of 14 alcoholics (29–55 years, mean 43) and 13 controls (21–55 years, mean 37) of Sample B. The alcoholics had been abstinent for 7–37 days (mean 20 days), their duration of heavy drinking was 1–35 years (mean 13 years), and self-reported ethanol consumption was 336–2520 g/week (mean 1232). The extra-cerebrally referenced EEG measured from bilateral mastoids and electrode sites C5, C6, and Cz (10-20 system) was averaged and digitally filtered (Table 2). The peak amplitudes and latencies of the MAEP components N_a and P_a were analyzed. The MAEP were correlated with the demographic data in the alcoholics.

Pre-Attentive Auditory Processing and Verbal Memory (Study V)

The subjects (Sample B, Table 1) were presented binaurally with a block of 256 pure tones (frequency 700 Hz, duration 50 ms, rise and fall times 5 ms) with a 2500-ms SOA (i.e., 2450-ms ISI). The mastoid-referenced EEG was digitized, averaged, and digitally filtered (Table 2). The N1 and P2 peak-amplitudes and latencies were determined at the electrode site Fz. In addition, the peaks of global field power (GFP), representing maxima of the total brain activity that contributes to the surface potential field at a given moment (Skrandies 1989), were determined during 80–150 ms (corresponding to N1) and 150–250 ms (corresponding to P2) post-stimulus periods. The ERP data of two alcoholics were not quantified due to excessive extracerebral artefacts. In the neuropsychological assessment, auditory verbal memory and learning was assessed using the Logical Memory task (immediate and delayed recall) of the Wechsler Memory Scale Revised (WMS-R) and the California Verbal Learning Test (CVLT). In addition, the WMS-R Digit Span was used to study verbal short-term memory.

Test–Retest Reliability of Auditory ERP and ERF (Study VI)

The subjects (Sample C, Table 1) participated in repeated measurements of simultaneous 122-channel MEG and 64-channel EEG (Table 2). In two sessions separated for at least two days, three blocks of 700-Hz pure tones (rise and fall times 5 ms) that were either 50-ms standards (p = 0.8) or 25-ms deviants were presented with a SOA of 2500 ms (termed onset-to-onset ISI in the original publication) to the left ear. The MEG and EEG were digitized, averaged, and filtered (Table 2).

The peak amplitudes and latencies of N1m were quantified from the channel pair showing the highest amplitude response over the left and right temporal areas. The amplitude was determined as a square root of sums of squares of the amplitudes at the same latency from the orthogonal sensor pair ($a = [(\partial B_z/\partial x)^2 + (\partial B_z/\partial y)^2]^{1/2}$). The N1 peak amplitudes and latencies were determined at the electrode location FCz against the nasion (Nz) and CAR. The mean values of ERP, ERF, and ECD amplitude and latency measures, and ECD location measures of the N1/N1m components in each stimulus blocks (2 sessions, 3 stimulus blocks in each) were determined. The individual standard deviations were calculated within and across the sessions and averaged across the subjects.

The contribution of measurement noise to the total variation in the dipole locations was analyzed in one subject. In addition, to estimate the head movements with respect to the MEG sensors between the stimulus blocks, the relative locations of two fiducial points close to the auditory cortices ($\{x, y, z\} = \{\pm 50, 0, 40$ mm$\}$) and the MEG sensor array were calculated in the beginning of each stimulus block. Further, the magnitude of head movement during the measurement was investigated in one subject in an additional MEG recording session. A figure-of-8-shaped coil consisting of two loops of 25 mm radius, fixed on the scalp over the temporal lobe, was fed with bursts of 10 Hz sinusoidal current, and the location of the loop center in relation to the magnetometer was determined by fitting an ECD to the field pattern generated. The localization pulses were supplied 1500 ms after each standard tone (2500-ms SOA) in additional stimulus blocks. Three blocks of 100 auditory responses were averaged. Subaverages of 20 localization bursts were also collected. The ECDs were fitted to the subaverages of the epochs,

including the localization pulses, to monitor the head-position changes during the recording off-line.

Statistical Analysis

In Study I, the ERF differences between the alcoholics and controls were analyzed using (group by SOA, repeated measures) multivariate analyses of variance (MANOVA), and *a priori* comparisons of means (Winer et al. 1991) were calculated with the Student's *t*-tests (SPSS/PC+ software, SPSS Inc., Chicago, Illinois, USA). In studies II–V, the ERP differences between alcoholics and controls were analyzed using analyses of variance (ANOVA) for repeated measures with *a priori* contrasts (Winer et al. 1991) (Statistica 4.1 software, Stat Soft Inc., Oklahoma, USA). Although a tendency towards less education was found in the alcoholics, this was not statistically significant (Table 1). Nonetheless, to ensure this did not affect the results, the years of formal education of the subjects were entered as a covariate in the statistical analysis of the neuropsychological data. The correlations between the ERP/ERF, behavioral and demographic variables were calculated by using the Pearson's and Spearman's (Study III) correlation coefficients (r and ρ, respectively). In addition, factors affecting working-memory performance of the alcoholics were analyzed using a multiple regression analysis (Study II).

To compare the results in the patients of Sample B, correlations (the Pearson's r) between the main measures of brain function in Studies II–V were calculated (Table 3). For clarity, this analysis was based on sum-score variables that were calculated within each study. The variable "Distractibility" (Study III) was defined as a sum score of standardized values of the eight RT-lag and HR variables associated with the deviants and standards following deviants (HR variables transposed). The later phases of MMN to slight and wide deviants were collapsed. The variable "Logical memory" (Study V) was defined as a sum score of standardized values of the delayed and immediate WMS-R Logical Memory. The variable "Immediate learning" (Study V) was defined as a sum score of the standardized free recall of the CVLT lists A (only the first trial) and B. These variables were compared with one-way ANOVAs, and the years of formal education of the subjects were entered as a covariate in the analysis of the neuropsychological data.

RESULTS

MEG Experiments

Bilateral Cortical Auditory Processing and Auditory Sensory Memory (Study I)

The post-withdrawal changes in bilateral auditory processing was studied with the auditory P1m and N1m to monaural tones. The temporal persistence of auditory sensory-memory traces was studied with MMNm (SOAs of 500 and 2500 ms). The N1m recorded from the hemisphere ipsilateral to the ear stimulated peaked significantly earlier in the alcoholics than controls (Figure 7) in the right-ear ($F_{1,21} = 4.66$, $p < 0.05$) and left-ear conditions ($F_{1,21} = 4.93$, $p < 0.05$). The N1m amplitudes were, on the average, larger in the alcoholics in 7 out of the 8 conditions but the differences failed to reach statistical significance. The acceleration of the ipsilateral N1m peak latency correlated with the duration of abstinence in the alcoholics. This correlation was significant for the collapsed right- and left-ear conditions ($r = 0.66$, $p < 0.05$) and for the right-ear condition separately ($r = 0.80$, $p < 0.001$). Furthermore, MMNm peaked significantly earlier in the alcoholics than controls with the 2.5-s SOA ($t_{21} = 2.86$, $p < 0.05$). No significant group differences were found in the MMNm amplitude with the SOA of 500 or 2500 ms, nor in the ECD for P1m, N1m, or MMNm.

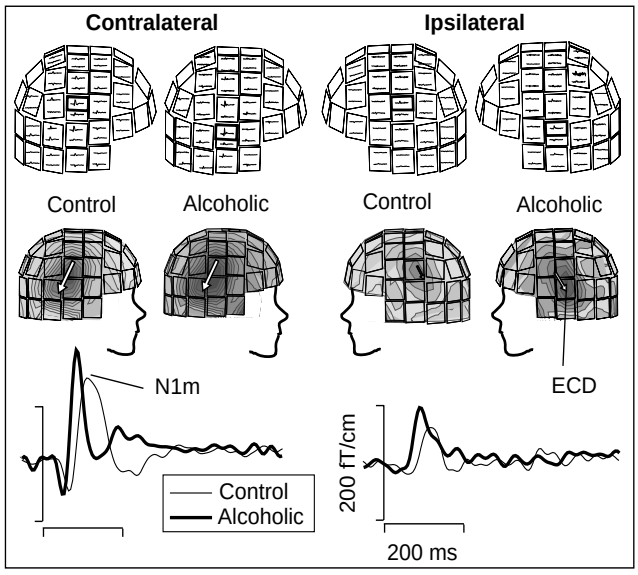

Figure 7. The gradient field maps (5 fT/cm isocontour lines) of the N1m elicited by the left-ear tones with the SOA of 2.5 s from one control and alcoholic, over the helmet-shaped sensor array viewed from the left and right sides. The arrows represent the equivalent current dipoles (ECD) of the N1m. The enlarged maximum responses over both hemispheres indicate that the N1m peaked earlier in the alcoholic than in the control.

EEG and Neuropsychological Studies

Backward Masking of MMN and Working Memory (Study II)

The auditory sensory-memory function was measured in two separate ERP conditions (with and without backward masking). In the baseline condition, MMN was elicited by the deviants within standard tones. In the backward-masking condition, the masking tones were interposed after the offset of each stimulus to interfere with sensory-memory function. The decrement of MMN by backward masking was correlated with the working-memory performance.

The baseline MMN without backward masking was larger ($F_{1,38} = 6.00$, $p < 0.05$) and earlier ($F_{1,38} = 5.66$, $p < 0.05$) in the alcoholics as compared with the controls (Figure 8). N1 was also enhanced in the alcoholics ($F_{1,38} = 7.62$, $p < 0.01$). The main result was, however, an abolition of MMN in the alcoholics by the masking sounds, while only a trend of amplitude suppression was observed in the controls (Figure 8). The ANOVA indicated a significant group by stimulus-condition interaction ($F_{1,38} = 10.48$, $p < 0.01$) , and the masking-condition MMN amplitude was significantly ($F_{1,38} = 4.53$, $p < 0.05$) larger in the controls than alcoholics. When the cut-off point was 0.80 μV (mean MMN reduction by masking plus 1.7 standard deviations), 9 out of the 20 alcoholics (sensitivity 45%), but no controls (specificity 100%) had auditory sensory-memory impairment.

As compared with the controls, the alcoholics, further, indicated impairments in the working-memory performance measured with the ACT ($F_{1,37} = 14.5$, $p < 0.001$) and in the frontal functions measured with a sum score of TMT and SCWT ($F_{1,37} = 17.8$, $p < 0.001$). In the alcoholics, the impaired ACT performance was predicted ($r = –0.56$, $p < 0.05$) by the decrement of MMN amplitude by masking (Figure 8). Further, a significant multiple correlation emerged between the ACT performance and the MMN masking effect, frontal-test performance, and WMS digit span (adjusted $R^2 = 0.42$, $p < 0.01$). The MMN reduction by masking did not, however, correlate with the frontal test performance in the alcoholics. Finally, the MMN reduction by masking correlated significantly with the self-reported alcohol consumption ($r = 0.41$, $p < 0.01$) in the whole study group.

Neurophysiological and Behavioral Changes in Involuntary Attention Shifting (Study III)

The neural abnormalities underlying attentional deficits in alcoholism were explored. The subjects were to differentiate equiprobable 100- and 200-ms tones in the RT task and to ignore the occasional slight or wide frequency changes. Involuntary attention shifting to the task-irrelevant frequency deviants was indexed with the RT lag and HR to deviants. The underlying neural processes were measured with the simultaneously elicited ERP components disclosing different phases of detection and orienting to stimulus changes.

The duration-discrimination performance in the alcoholics was significantly more distracted by the task-irrelevant changes in tone frequency as compared to the controls (Figure 9). In the ANOVA, the RT lag caused by the slight ($F_{1,38} = 11.3$, $p < 0.01$) and wide deviants ($F_{1,38} = 4.17$, $p < 0.05$) was significantly pronounced in the alcoholics. The contrasts indicated that the RT lag to slight deviants ($F_{1,38} = 6.81$, $p < 0.05$), the RT lag to standards after slight deviants ($F_{1,38} = 13.2$, $p < 0.001$), and the RT lag

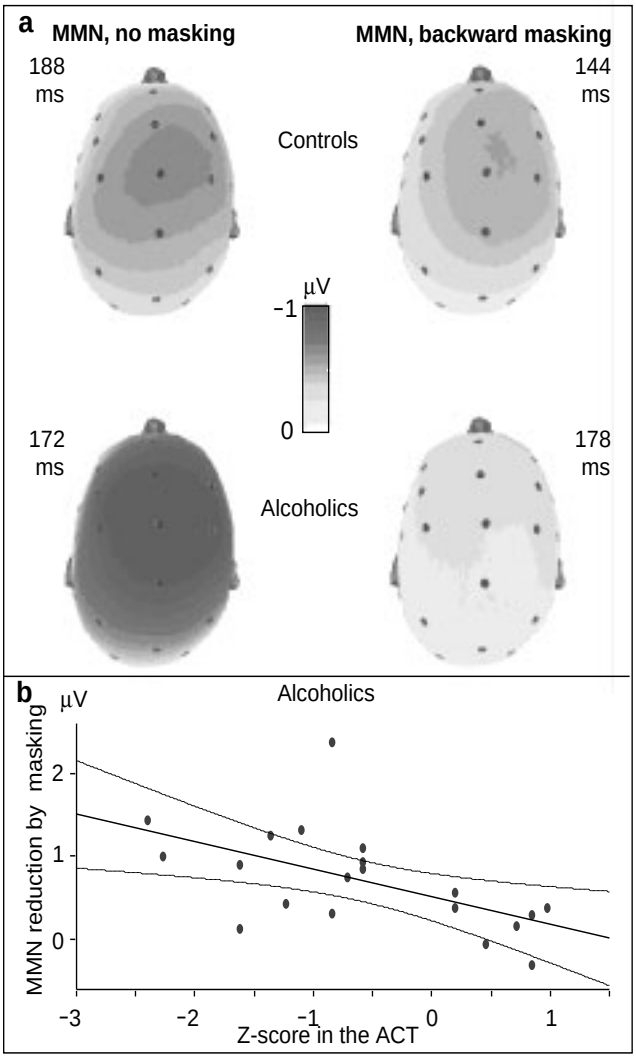

Figure 8. (a) The grand-average surface-potential maps at the MMN peak latency in the controls and alcoholics. The figure indicates that despite the slight MMN enhancement in the baseline condition, MMN is abolished by the backward-masking tones in the alcoholics. Only a trend towards MMN reduction by the backward masking was found in the controls. **(b)** The correlation plot of the Z-score in the working-memory task (ACT) and the absolute reduction of the MMN amplitude by backward masking in the alcoholics (confidence limits $p = 0.95$).

to standards after wide deviants ($F_{1,38} = 5.57$, $p < 0.05$) was significantly increased in the alcoholics.

The behavioral distractibility was accompanied by neurophysiological evidence of increased involuntary attention shifting to the unattended sound changes. The later phase (190–240 ms post stimulus) of MMN to the slight deviants was significantly ($F_{1,38} = 6.95$, $p < 0.05$) larger in the alcoholics than controls (Figure 9). No differences were, however, observed in the MMN peak latency, $P3_a$, or RON for the slight deviants. No differences were found in any ERP components elicited by the wide deviants or the standards.

The behavioral distractibility correlated with the MMN changes in the alcoholics. The increased later MMN to slight deviants correlated significantly with the increased RT lag to slight deviants

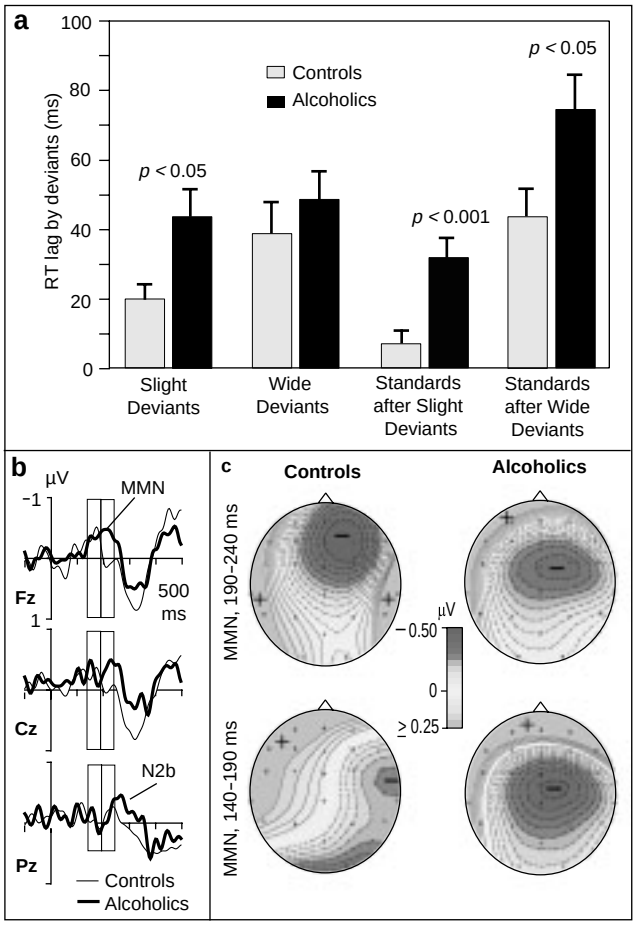

Figure 9. (a) Distractibility by the task-irrelevant deviants, shown by the reaction time (RT) lag to deviants and first standards after deviants. Error bars disclose standard error of mean. **(b)** The grand-average difference waves (ERP to slight deviants minus ERP to standards) in the controls and alcoholics superimposed, indicating the significant augmentation of the later MMN phase in the alcoholics. **(c)** The grand-average scalp distribution of MMN for the slight deviants during the earlier (140–190 ms) and later (190–240 ms) time windows in the controls and alcoholics (the distance-weighted least-squares method; McLain, 1974).

($\rho = -0.50$, $p < 0.05$), lower HR to slight deviants ($\rho = 0.67$, $p < 0.01$), and with lower HR to standards after slight deviants ($\rho = 0.61$, $p < 0.01$). Also the later MMN and low HR for the wide deviants correlated significantly ($\rho = 0.44$, $p < 0.05$). Finally, the self-reported onset age of alcoholism correlated significantly ($\rho = 0.45$, $p < 0.05$) with the amplitude of the later MMN to slight deviants. A trend towards correlation between the RT lag to slight deviants and the onset age of alcoholism was also found ($\rho = -0.4$).

Post-Withdrawal Changes in MAEP (Study IV)

The post-withdrawal changes in thalamic–cortical auditory processing were studied with MAEP, and correlated with the demographic data. The amplitude of MAEP component P_a, measured from the vertex electrode (Cz), was significantly larger ($F_{1,25} = 9.07$, $p < 0.01$) in the alcoholics than in the controls (Figure 10). There were trends, approaching statistical significance, towards an enhancement of N_a amplitude (alcoholics, –0.53 ± 0.15 μV; controls, –0.33 ± 0.05 μV), a decrease of N_a peak latency (alcoholics, 18.3 ± 0.78 ms; controls 19.9 ± 0.42 ms), and a decrease of P_a peak latency (alcoholics, 31.2 ± 1.36 ms; controls, 34.0 ± 1.28 ms) in the alcoholics.

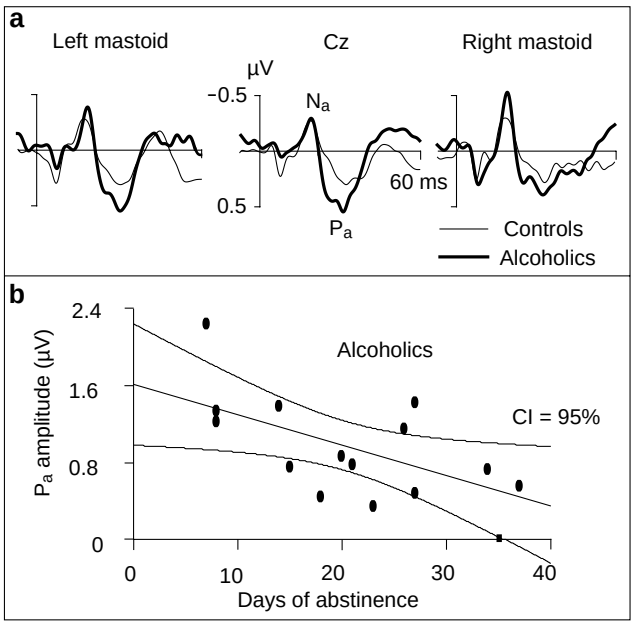

Figure 10. (a) The grand-average MAEPs measured from the alcoholics and controls at the electrode site Cz and bilateral mastoids, indicating that the P_a amplitude was significantly larger in the alcoholics than controls. **(b)** The correlation plot showing the significant negative correlation between the abstinence and P_a amplitude in the alcoholics (confidence interval 95%).

The increased P_a amplitude appeared to be predicted by short duration of ethanol abstinence in the alcoholics (Figure 10). The P_a amplitude correlated significantly with the days of abstinence ($r = -0.57$, $p < 0.05$). This correlation was also significant for the logarithmic transformation of the days of abstinence ($r = -0.65$, $p < 0.05$). The P_a amplitude did not, however, correlate with other demographic variables in the alcoholics.

Pre-Attentive Auditory Processing and Verbal Memory (Study V)

The post-withdrawal changes in auditory processing were studied with N1 to unattended stimuli. The response amplitudes were determined with the GFP of the 32 EEG channels. The ERP data was correlated with the neuropsychological test performance. The GFP maximum during 80–150 ms post-stimulus period, approximately at the N1 peak latency, was significantly larger ($F_{1,36} = 8.42$, $p < 0.01$) in the alcoholics than controls (Figure 11). The N1 augmentation in the alcoholics ($F_{1,36} = 10.30$, $p < 0.01$) was also detected in the mastoid-referenced N1 at the frontal Fz electrode (Figure 11). No differences were observed in the N1 peak latency, the GFP maximum during 150–250 ms, the P2 amplitude, or the P2 peak-latency (Figure 11).

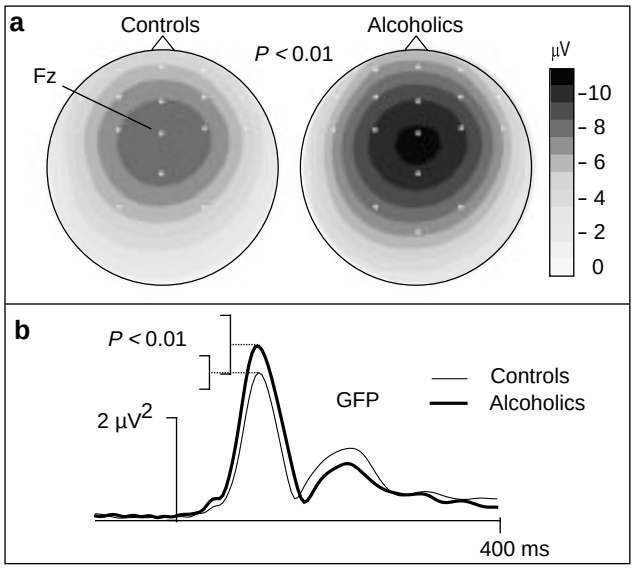

Figure 11. (a) The grand-average distribution of the scalp-potential field at the N1 peak, indicating the significant N1 enhancement in the alcoholics as compared to the controls. **(b)** The grand-average global field power (GFP) in the alcoholics and controls superimposed (error bars disclose SD).

The performance of the alcoholics was significantly impaired in the immediate ($F_{1,37} = 19.62, p < 0.001$) and delayed recall ($F_{1,37} = 24.01, p < 0.001$) of the WMS-R Logical Memory task. The learning performance was impaired in the free recall after first presentation of the CVLT List A ($F_{1,37} = 5.38, p < 0.05$) and List B ($F_{1,37} = 7.53, p < 0.01$) in the alcoholics. However, after repetition, the group differences in the number of recalled or recognized items of the CVLT List A were not statistically significant. Finally, the increased 80–150 ms GFP maximum (~ at the N1 peak latency) correlated significantly with the impaired Delayed WMS-R Logical Memory ($r = –0.53, p < 0.05$) and impaired total score (immediate plus delayed recall) of the WMS-R Logical Memory ($r = –0.48, p < 0.05$) in the alcoholics.

Meta-Analysis of the EEG Results

To compare the results in the patients of Sample B, correlations between the main measures of brain function in Studies II–V were calculated (Table 3). In addition, the main results and their correlations with the main demographic variables are summarized in Table 4. The results revealed that the impairments in the reproduction of verbal material correlated with the suppressed working-memory and attentional performance in the alcoholics. As indicated in Table 3, the logical memory and immediate learning correlated significantly with the frontal-test performance in the alcoholics. The immediate learning was also dependent on the auditory-verbal working memory performance measured with the ACT. These findings were not statistically significant in the controls. Corroborating the results in Study III, the analysis of sum-score variables indicated a highly significant correlation between the behavioral distractibility and the MMN augmentation in the alcoholics ($r = –0.7$). However, as for correlation between the ERP and behavioral variables across studies, only few trends that did not reach statistical significance were found. A trend towards correlation between the increased GFP of N1 and the impaired working memory performance was detected in the alcoholics. The enhanced GFP of N1 (positive value) also tended to correlate with the increased amplitude of the collapsed later phase of MMN in the alcoholics. In the controls, the Immediate learning correlated negatively with P_a-amplitude ($r = –0.57, p < 0.05$), and the Distractibility correlated negatively with GFP of N1 ($r = –0.46, p < 0.05$), but other significant correlations were not found.

Test–Retest Reliability of Auditory ERP And ERF (Study VI)

Table 5 presents the mean N1/N1m amplitudes and latencies, as well as the ECD amplitudes and locations, in each stimulus block and for both sessions. The standard deviations (SD), expressed as percentages of the mean values for the amplitudes, were calculated for each subject separately and then averaged, within and across sessions. The positions of the fiducial points (near the auditory cortices) in relation to the magnetometer were determined at the beginning of each stimulus block for all subjects. The average SD of the *x*, *y*, and *z* coordinates calculated both across and within the three blocks of stimuli were 2.5 and 1.1 mm, respectively. In the additional session with one subject, the average SD of the localization loop center coordinates (including the 3 stimulus blocks) was 0.3 mm, whereas the average SD of the ECD coordinates for the contralateral N1m from the corresponding three stimulus blocks was 1.7 mm.

Table 3. Correlation coefficients (*r)* between the main findings in Studies II-V in the alcoholics. Correlations within each study on shaded backgroud.

Study		Study II			Study III		Study IV	Study V		
		MMN-masking effect	Working memory	Frontal tests	Later MMN, collapsed [1]	Distractibility sum-score	P_a amplitude	GFP of N1	Logical memory	Imm. learn.
II	MMN-masking effect									
	Working memory	–0.56*								
	Frontal tests	–0.13	0.50*							
III	Later MMN, collapsed[1]	–0.25	0.23	–0.04						
	Distractibility, sum score	0.28	–0.29	–0.24	–0.68**					
IV	P_a amplitude	–0.31	0.29	–0.05	0.03	–0.19				
V	GFP of N1	0.30	–0.46[§]	–0.17	–0.42[§]	0.37	0.02			
	Logical memory	0.10	0.36	0.45*	0.03	0.00	–0.20	–0.47*		
	Immediate learning	–0.12	0.45*	0.51*	–0.18	0.25	–0.03	–0.31	0.55*	

[1]Note that the MMN response is negative. [§] $p < 0.10$; * $p < 0.05$, ** $p < 0.01$

Table 4. Correlation coefficients (*r*) between the main findings in Studies II–V and demographic variables in the alcoholics. (As in the original publication, Spearman's ρ used in Study III.)

Variable	Mean ± SD		Correlations in alcoholics					
	Controls	Alcoholics	Age	Abstinence	Ethanol consumption	Years of alcohol abuse	Onset age of alcoholism	Years of Education
Study I								
MMN-masking effect (μV)	0.2 ± 0.34	0.7 ± 0.62**	–0.37	0.39	0.08	0.02	–0.23	–0.17
Working memory	0.6 ± 0.55	–0.6 ± 1.03***	0.16	–0.13	–0.26	–0.05	0.02	0.54*
Frontal tests (Z-score)	0.6 ± 0.37	–0.6 ± 1.07***	–0.34	–0.01	0.00	–0.01	–0.35	0.47*
Study III								
Amplitude of later MMN phase (μV)[1]								
Slight deviants	0.1 ± 0.58	–0.5 ± 0.73*	0.38	0.11	0.04	0.11	0.45*	–0.06
Wide deviants	0.0 ± 1.06	–0.5 ± 0.86	0.08	–0.04	0.16	–0.15	0.24	–0.06
Collapsed	0.0 ± 0.63	–0.5 ± 0.64*	0.29	–0.11	0.21	0.02	0.38	0.01
Behavioral distractibility								
Sum score	–0.4 ± 0.89	0.4 ± 0.93**	–0.22	0.12	0.04	0.08	–0.23	–0.24
Study IV								
P_a amplitude (μV)	0.5 ± 0.32	1.0 ± 0.52**	–0.01	–0.57*	0.02	0.36	–0.43	0.04
Study V								
GFP of N1 (μV^2)	3.1 ± 0.65	4.0 ± 1.34**	0.18	0.05	–0.16	0.13	0.02	–0.32
Logical memory (Z-score)	0.6 ± 0.66	–0.6 ± 0.86***	–0.32	0.30	–0.27	–0.04	–0.18	0.30
Immediate learning (Z-	0.5 ± 0.85	–0.5 ± 0.90***	–0.17	–0.06	0.11	0.04	–0.31	0.18

[1]Note that the MMN responses are negative. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 5. Average amplitudes, latencies, and dipole locations of N1 and N1m, with standard deviations.

		MEG		EEG	
WAVEFORMS		Contra	Ipsi	Nasion	CAR
Amplitude		(fT/cm)		(μV)	
Mean		64.8	34.3	5.4	3.8
SD within (%)		14.3	10.6	20.9	13.7
SD across (%)		23.1	13.0	20.4	14.0
Latency (ms)					
Mean		105.0	112.3	102.7	105.5
SD within		1.8	3.2	3.8	3.1
SD across		2.3	3.7	4.5	3.5
DIPOLES		Contra	Ipsi	Nasion	CAR
Amplitude (nAm)					
Mean		24.2	12.8	5.8	3.8
SD within (%)		18.8	16.3	17.3	19.0
SD across (%)		19.5	20.1	20.9	21.5
Location (mm)					
Mean	*x*	53.8	–52.1	40.5	–41.3
	y	8.3	4.4	3.6	5.7
	z	46.4	47.5	58.3	53.6
SD within	*x*	1.7	3.4	4.5	4.5
	y	1.3	3.9	5.1	5.0
	z	1.4	3.5	5.3	5.3
SD across	*x*	2.0	4.6	4.5	4.4
	y	2.1	4.2	5.8	4.9
	z	2.3	4.4	5.4	5.7

The standard deviations within sessions ("SD within") and across sessions ("SD across") in the amplitude measures expressed as percentages of the mean.

DISCUSSION

In the present study, neurophysiological and behavioral measures of brain function were compared in the alcoholics and controls. Further, the reliability of the methodology was studied. The results of the clinical EEG and MEG studies revealed indices of interdependent abnormalities at pre-attentive and higher levels of cognitive processing in the alcoholics. Firstly, the abnormalities in neural transmission after chronic drinking and abrupt detoxification were revealed by the enhancement of P_a amplitude, the decreased peak latency of N1m, the increased GFP of N1, and the facilitated MMN and MMNm generation in the alcoholics. The P_a and N1m changes in the alcoholics correlated with short duration of abstinence, and the N1 enhancement also predicted impaired verbal memory performance. Secondly, increased interference in sensory memory was indicated by the abolition of MMN by backward masking in the alcoholics, which further predicted their impaired working-memory performance. Finally, the increased behavioral distractibility by the task-irrelevant deviants, predicted by the significant augmentation of the later phase of MMN, suggested impaired control of involuntary attention shifting in the alcoholics. This finding appeared to correlate with the onset age of alcohol abuse. Finally, a relatively good test–restest reliability of the present ERP and ERF methodology was indicated. These findings are discussed below.

Sensitized Auditory Responses Suggested Neural Hyperexcitability

One of the main findings of the present study was the consistent pattern of acceleration and enhancement of the pre-attentive auditory responses in the alcoholics (Studies I–V). At the earliest level of cortical processing (Study IV), the amplitude of MAEP component P_a was significantly increased in the alcoholics. In the long-latency range, the N1m measured from the hemisphere ipsilateral to the ear stimulated peaked significantly earlier in the alcoholics than controls. The MAEP and MEG results were, generally, supported by the significant enhancement of N1 to binaural tones, presented either with 0.3-s (Study II) or 2.5-s SOA (Study V), in the alcoholics. The N1 peak-latencies were, however, similar between the groups (Studies II, V). Tentatively, the radial aspects of N1 sources that are not clearly detected by MEG (Huotilainen et al. 1998) and, perhaps, the different temporal activation patterns of the bilateral N1 generators for binaural (Studies II, V) versus monaural (Study I) stimulation could account for this slight difference between the N1 and N1m results.

In principle, the present results agree with previous studies showing neural hyperexcitability at the cellular-level (e.g, see Little 1999) and consequent facilitation of different ERP components in laboratory animals after withdrawal of chronic alcohol administration (Begleiter and Porjesz 1977, 1979; Chu et al. 1978; Porjesz and Begleiter 1985, 1993). Support for the present MAEP (Díaz et al. 1990) and N1 findings (Cadaveira et al. 1991; Realmuto et al. 1993; Romani and Cosi 1989) can be found in human ERP studies as well. However, many studies have shown either no (Patterson et al. 1987; Pfefferbaum et al. 1979, 1980, 1991) or even opposite effects for the auditory N1 (Steinhauer et al., 1987; Kaseda et al. 1994; Lille et al. 1987) and MAEP in abstinent alcoholics (Katbamna et al. 1993). A number of factors could account for these discrepancies. Firstly, certain earlier results on N1 to unattended stimuli (Lille et al. 1987; Pfefferbaum et al. 1991) or MAEP (Katbamna et al. 1993) might have been affected by the inhibitory medication that was reportedly administered to the studied alcoholic patients. Further, N1 for attended stimuli is, in turn, often overlapped by attentional ERP components (Näätänen et al. 1992), which might be specifically suppressed in alcoholics (Lille et al. 1987; Porjesz and Begleiter 1993). This might partially explain the difference with the present results (Studies I, VI) and the earlier findings obtained with N1 to attended stimuli (e.g., Kaseda et al. 1994; Pfefferbaum et al 1979, 1980; Steinhauer et al., 1987). This speculation is supported by the fact that the enhancement of N1 to attended stimuli was not statistically significant in this study either (Study III).

The present findings of the post-withdrawal facilitation of the pre-attentive components were also seemingly discrepant with the previous $P3_b$ studies indicating, relatively consistently, either reduced amplitudes or increased peak latencies in abstinent alcoholics (for a review, see Porjesz and Begleiter 1993). However, $P3_b$ might have more complex generators, both neurochemically and anatomically, than the pre-attentive components (Birbaumer et al. 1990; Frodl-Bauch et al. 1999; Rebert et al. 1986). One might thus speculate that the post-withdrawal neural abnormalities could impair the arrangement of higher-order cognitive functions underlying $P3_b$ generation.

The decreased ipsilateral N1m peak latency (Study I) and the increased P_a amplitude (Study IV) correlated with short duration of abstinence. These results lend further support to the interpretation that a gradually recovering phenomenon, such as the post-withdrawal hyperexcitability, might underlie the facilitation of ERP and ERF generation in the alcoholics. The neuroadaptation to alcohol, underlying the post-withdrawal hyperexcitability, is associated with decreased inhibition mediated by the $GABA_A$-receptors (Hu and Ticku 1997; Mahmoudi et al. 1997; Ticku 1990), which, in turn, appear to regulate the generation of early auditory ERP components such as N1 (Meador 1995; Rockstroh et al. 1991; Javitt et al. 1996). The decreased GABAergic inhibition after adaptation to alcohol might thus have influenced the present results. However, it should be pointed out that the neurotransmitter abnormalities in alcoholism are heterogeneous. For instance, *post-mortem* studies of alcoholics have also demonstrated reductions of temporal muscarine receptors (Freund and Ballinger 1991) that are suggested to inhibit the P_a generation (Buchwald et al. 1991; Jääskeläinen et al. 1999). Furthermore, the post-withdrawal state is also associated with a marked imbalance in the catecholamine systems and neuroendocrine regulation in alcoholics (Becker 1999; Glue and Nutt 1990). Therefore, the elucidation of specific neurochemical factors underlying the neurocognitive deficits in alcoholism must be addressed in the course of future efforts.

Backward-Masking of MMN Indicated Sensory-Memory Interference

The second main result suggested that the transient memory system eliciting MMN might be profoundly vulnerable to the effects of sensory interference in the alcoholics (Study II). The randomly varying backward-masking tones, commencing 100 ms after the offset of each standard and deviant tone, abolished MMN in the alcoholics, while only a slight amplitude decrement was observed in the controls. The backward-masking effect, correlating ($r = 0.4$) with the self-reported alcohol consumption in the whole subject group, demonstrated sensory-memory impairment in 9 out of the 20 alcoholics (sensitivity 45%) when the cut-off point for MMN reduction was 0.80 μV (mean plus 1.7 SDs). Each control subject was unimpaired (specificity 100%). Furthermore, the pronounced backward-masking effect correlated significantly with the impaired behavioral working-memory performance, measured with the ACT, in the alcoholics. However, unlike the P_a and N1m changes, the backward-masking effect was not exaggerated in the alcoholics with the most recent detoxification, suggesting that this effect might not be directly related to the post-withdrawal symptoms. (The tendency was, in fact, to the opposite direction.)

The effect of backward-masking on MMN (with stimulus-mask intervals > 50 ms) is believed to reflect disruption of memory-trace formation in the auditory cortex (Winkler et al. 1993; Winkler and Näätänen 1995), which is in turn suggested to occur normally during a period termed the temporal window of integration (Näätänen 1992). During this period, at approximately 150–200 ms from stimulus offset, the stimulus is, presumably, encoded as an integrated unit (Näätänen 1992; Yabe et al. 1997, 1998). A masking stimulus commencing during this temporal window thus occurs before the integration is finished and may interfere with the memory-trace formation to the standard tone. The fact that the MMN generation was profoundly vulnerable to interference by closely succeeding sounds suggests that this temporal window of integration could be extended in alcoholics. However, relatively specific explanations for the backward-masking effect are also emerging from cellular-level studies on different sensory systems. These studies suggest that the backward maskers might block a transient response to the offset of the target stimulus (Macknik and Livingstone 1998; see also Rolls et al. 1999). Tentatively, the present result could also be speculated to result from abnormal function of neurons that process temporal events such as stimulus onsets and offsets. Therefore, future studies of alcoholics, for instance, using the omission-MMN paradigm that is presumed to give an estimate of the duration of the temporal window of integration (Yabe et al. 1997) could be informative.

The correlation between the backward-masking effect and the impaired ACT performance suggests that the previously reported (Brandt et al. 1983; Ryan et al. 1980) distractibility of working memory in alcoholics could partially reflect impaired formation of sensory-memory traces. However, the impaired ACT performance also correlated with dysfunction in the frontal tests, measuring attention and shifting of mental set. This supports previous results in alcoholics with Korsakoff's syndrome, interpreted to reflect an inability to switch from the counting task to retrieval of the target information (Leng and Parkin 1989). Tentatively, the present results thus revealed two

factors that might influence working-memory performance in alcohol-dependent individuals. Firstly, the build-up of cortical memory traces might be impaired already in pre-attentive sensory memory. Secondly, the distracted retrieval of relevant information might further impair the performance.

Despite the pronounced backward masking effect, no significant group differences were found in the decrement of MMNm amplitude when the SOA was prolonged from 0.5 to 2.5 s (Study I). This suggests that the temporal persistence of auditory sensory-memory traces is not significantly impaired during the time window of 0.5–2.5 s after stimulus onset in alcoholics. This result is supported by recent EEG findings (Polo et al. 1999), which were published shortly after the present MEG results. However, a very recent study suggested that after prolongation of ISI to 5 seconds, MMN may be absent in alcoholics, although a significant response can still be found in controls (Grau et al. in press).

Without the backward masking, the MMN amplitude was increased and the peak latencies of both MMN and MMNm were decreased (Studies I, II). This suggests that the present MMN and MMNm results may also have been affected by the effects of the post-withdrawal hyperexcitability, associated with the decreased GABAergic inhibition and increased NMDA-mediated excitability (Buck and Harris 1991), which are suggested to play a specific role in the MMN generation (Javitt et al. 1996). These neurochemical abnormalities would seem to result in sensitized response to the difference between the standard-tone trace and deviant tone in the alcoholics. However, based on the pronounced backward-masking effect, this response facilitation probably does not reflect strengthening of sensory representations in the alcoholics.

MMN and Distractibility Implied Abnormalities in Involuntary Attention Shifting

Study III linked the aforementioned sensitization of the automatic change-detection responses (Studies I, II) to impaired control of involuntary attention shifting in the alcoholics. More specifically, the task-irrelevant frequency changes delayed the task-relevant discrimination of the tone duration significantly more in the alcoholics than controls. The increased RT lag for trials succeeding frequency deviants further suggests that the reorientation to the relevant task was also impaired in the alcoholics. These behavioral abnormalities were accompanied by the significant enhancement of the later phase of MMN for the slight frequency deviants. Furthermore, this MMN enhancement correlated significantly with the pronounced RT lag to slight deviants, lower HR to slight deviants, and lower HR to the first standards after deviants in the alcoholics. This association was corroborated by the correlation analysis of the sum-score variables ($r = –0.7$). In sum, these results suggest pronounced involuntary attention shifting to stimulus changes in alcoholics, occurring even when this change is repetitive and small, and thus would not require orienting.

According to Näätänen's (1992) theory, the detection of an unattended sound change in the auditory cortex is followed by the initiation of involuntary attention shifting, reflected by the frontal MMN subcomponent (Alho 1995; Giard et al. 1990; Näätänen 1992). The frontal MMN sources were recently shown to be activated a few milliseconds later than the supratemporal generators (Rinne et al. 2000). Similarly, it can be argued that the later phase of MMN reflected predominantly activation of the frontal subcomponent. This interpretation is supported by the correlation between the enhanced later phase of MMN and the increased behavioral distractibility in the alcoholics. Further support can be found from results indicating that the frontal MMN sources are specifically affected by the actions of acute alcohol as well (Jääskeläinen et al. 1996c). One might thus speculate that the present results reflect long-term effects of ethanol on the neural networks generating the frontal MMN and underlying involuntary attention shifting. However, the later phase of MMN might also have been partially overlapped by $N2_b$ (although see Fig. 9), the change-detection response that is most pronounced in voluntary attention tasks (Loveless 1986). Hence, the contribution of the different MMN subcomponents will have to be confirmed with further studies, for example, by using combined EEG and MEG measurements.

Interestingly, it was recently shown that the $P3_b$ to both task-relevant and irrelevant tones in a Go/No Go task is decreased in alcoholics (Cohen et al. 1997b). This was interpreted to reflect impaired inhibition of task-irrelevant processing. Similarly, the enhancement of the later phase of MMN in the alcoholics might reflect an inability to inhibit the frontal-temporal neural network involuntarily activated by frequency changes. The loss of this task-relevant inhibition could then explain the pronounced distractibility by task-irrelevant sound changes in the alcoholics. One might expect that such deficit could impair an alcoholic's ability to concentrate to the cognitive activities of daily living as well. This merits future studies on neural abnormalities underlying pronounced distractibility.

Pre-Attentive Abnormalities and Verbal Memory

Taken together, the present ERP and ERF findings revealed a consistent pattern of abnormalities at the different levels of auditory processing, and the MMN changes were linked to the behavioral impairments in working memory and involuntary attention. Study V provided further evidence of the association of pre-attentive and higher-order cognitive abnormalities,

as suggested by the correlation between the impaired memory performance and the enhanced GFP of N1 in the alcoholics. Notably, the verbal-memory impairment, itself, has been previously well reported (for a review, see Knight and Longmore 1994), and other significant factors, including alcohol-related structural brain lesions, could undoubtedly result in such functional deficits (Acker et al. 1987; Jernigan et al. 1991). Nonetheless, the N1 enhancement might be a general marker of the degree of post-withdrawal state, which might overlap the effects of possible neural lesions. Importantly, a number of the neurochemical or neuroendocrine abnormalities accompanying the post-withdrawal syndrome (Becker 1999) could impair memory performance in alcoholics. For instance, elevated plasma cortisol levels, observed for weeks after withdrawal in alcoholics (Glue et al. 1989), have been shown to impair verbal memory performance in healthy subjects (Newcomer et al. 1999). Furthermore, GABAergic inhibitory neurons have been shown to play a significant role in memory processing (Wilson et al. 1994). Hence, it can be speculated that the possible abnormalities in the GABA system, associated with the post-withdrawal symptoms (Korpi 1994; Lingford-Hughes et al. 1998), might also have a detrimental impact on memory function.

In the final part of the data analysis, the results were compared across studies II–V. Despite that the correlations between the ERP and behavioral variables across studies remained statistically insignificant in the alcoholics, the results were generally in line with those that were found within each separate study. In addition, a few significant correlations emerged between the neuropsychological variables. As expected, the verbal memory and learning correlated with the frontal-test performance in the alcoholics, further, the basic premises of the human memory system were supported by the correlation between the working-memory and verbal learning performance in the alcoholics.

Test–Retest Reliability of Auditory ERP and ERF

The reliability of ERP and ERF at individual level was studied using N1 and N1m elicited by monaural stimulation to the left ear (Study VI). Their replicability was also supposed to give an estimate of the maximum level of reliability that can be reached with MMN and MMNm, which have been shown to be well replicated at the group level (Kathmann et al. 1999; Pekkonen et al. 1995b; Tervaniemi et al. 1999). The results corroborated previous findings (Pekkonen et al. 1995b; Yamamoto et al. 1988) by demonstrating a good reproducibility of N1/N1m waveforms and source location at the individual level.

The N1m source localization had the best replicability in the contralateral hemisphere, and the accuracy of the EEG dipole localization was comparable with the ipsilateral N1m. The fact that the variability of the MEG source locations was larger across than within the sessions probably reflects errors caused by head movements and inaccurate digitization of the cardinal points and the marker coil locations. However, physiological noise appears to be the dominant source of variation in the present dipole modeling, for both N1 and N1m, as suggested by the fact that the within-session head movement, studied in one subject, explained only a small portion of the variation. Further, the confidence volume that was estimated from the noise level for another subject was large enough to explain the measured range of the dipole coordinates.

The peak latency of N1m and N1 was approximately as well reproduced in MEG and EEG, indicating less than 5 ms of individual SD within and across different sessions. The N1m amplitude measures were also reasonably well replicated (mean SD of 10–24%). The variability was, however, generally larger across than within sessions. It can be speculated that this reflects variance in the head locations in relation to the measurement device across sessions. However, the subjects repeatedly positioned their heads inside the magnetometer with only an average SD of 2.5 mm in the coordinates of the fiducial points. Further, the reproducibility of the response amplitude across the sessions was not generally improved with N1m dipole source modeling (mean SDs ~20%). Thus, the present observations encourage the direct analysis of the ERF waveforms when only the relative amplitudes and latencies are of interest.

In EEG, the most reliable amplitude measures were obtained for the N1 determined with CAR, associated with mean individual SD of 14% both within and between sessions. For the nose-referenced data these values were around 20%. The superiority of CAR suggests that the signal-to-noise ratio of ERP amplitude measurements can be improved by using multiple electrodes and, further, by using weighted sums of multiple electrodes.

Possible Limitations

The specificity of studies on alcoholism is, in general, limited by the fact that the substance use disorders are seldom the only health problem in the afflicted individual, for instance, psychiatric comorbidity might be a problem (Alaja et al. 1998). The present patients were interviewed by experienced clinicians, and the cases with severe psychiatric illnesses such as schizophrenia or major depression were excluded. However, structured psychiatric interview would have probably improved the reliability of the present study. For instance, 40% of patients with a diagnosis of alcohol

dependence have been estimated to have comorbid depression (Kolodziej and Weiss 2000). However, according to a recent review (Raimo and Schuckit 1998), a majority of the mood disorders seen in alcoholic persons are substance-induced and resolve within several weeks of abstinence. This invites the interpretation that the exclusion of each patient with signs of depression during withdrawal might have considerably compromised the generalizability of the present results. This assumption is, for instance, supported by a recent study indicating that tight exclusion criteria can result in samples that are more heavily composed of economically stable and higher functioning individuals than the real-world samples of alcoholics (Humphreys and Weisner 2000).

Comorbid abuse of other substances than ethanol is one more obvious problem in the studies on alcoholism. Obviously, the majority of the present alcoholics have had at least some experiences of other centrally acting drugs (e.g., in the detoxification). However, the goal was to include patients whose primary diagnosis was alcohol dependence, and cases with diagnosis or self-reported chronic abuse of any other substance were excluded.

Another possible limitation to this study is the fact that 13 out of the 33 patients received either antidepressant or closely related centrally acting agents, although none had substances such as benzodiazepines, which have profound auditory ERP of ERF effects in humans (Meador et al. 1995). However, at least mianserin used by four (Bo et al. 1985; Koponen et al. 1991), doxepin used by one (Fairchild et al. 1981), and citalopram used by three patients (Neckelmann et al. 1996) might affect spontaneous EEG activity. Mild EEG effects of fluoxetine (four users) have been also reported (Saletu and Grunberger 1985). These antidepressants affect predominantly serotonergic and catecholaminergic transmission (Stahl 1996). Notably, previously reported MAEP, N1, or MMN effects of other drugs with actions on these systems have been marginal (Dierks et al. 1999; Meador et al. 1989; Mervaala et al. 1993; Shelley et al. 1997).

Some of the presently used agents might, further, have histamine H_1-receptor antagonist potency (Richelson 1992). However, N1 was not affected by histamine H_1-receptor antagonist chlorpheniramine (Serra et al. 1996), and the effects on MMN (reduction of the later phase) suggested that possible histamine H_1-antagonist effects should have reduced, rather than facilitated, the present group differences in MMN. Most importantly, the effects in the medicated and unmedicated patients were principally very similar in each study (I–V). Therefore, the probability of a systematic bias in the present ERP and ERF results, caused by the antidepressants, is relatively small.

Clinical Prospects for Future Research on Alcoholism

One of the most important aspects of the present results was that the facilitation of brain responses was clearly apparent in the alcoholics, even thought their overt signs of withdrawal hyperexcitability had subsided. This agrees with previous studies suggesting that the neurochemical and neuroendocrine abnormalities, suggested to contribute to the development of dependence and neural degeneration (Becker 1999), might be present for a significant period after detoxification in abstinent alcoholics (Eisenhofer et al. 1985; Glue et al. 1989; Lingford-Hughes et al. 1998). Importantly, the first weeks and months after withdrawal also constitute the period of highest risk for relapse in detoxified alcoholics (Meyer 1989). Therefore, the present findings of post-withdrawal ERP and ERF facilitation could be of clinical relevance. This conclusion is supported by previous results suggesting that the alcoholics with susceptibility for severe withdrawal symptoms could be identified with N1 enhancement 5 days after detoxification (Neiman et al. 1991).

The correlation between the N1 enhancement and the memory impairments in the alcoholics, further, provided evidence of the potentially harmful cognitive effects of the post-withdrawal symptoms. Notably, moderate neural hyperexcitability has been observed in BAEP a few hours after withdrawal of low doses of alcohol in social drinkers (Church and Williams 1982). Therefore, the cognitive effects of post-withdrawal symptoms, both in alcoholics and social drinkers, clearly, deserve further experimental attention.

The present results, further, indicated that the MMN results might provide information regarding more permanent deficits. Firstly, backward masking of MMN appeared to provide an attention-independent predictor of the memory-trace impairment in working memory. Given that the working-memory impairment may be one of the first neurocognitive deficits caused by alcohol abuse (MacVane et al. 1982), the present methods could be useful in the research on the earliest brain changes induced by alcohol. The abnormalities in involuntary attention in turn appeared to be most pronounced in the alcoholics with an early onset of dependence. The conclusions of this result, however, must remain tentative, since the present effects might not be alcohol-specific and, secondly, the alcohol history of the present sample was based on self-reports. Nonetheless, many of the alcoholics had, self-reportedly, begun pathological drinking in their teens, which might have interfered with their frontal-lobe maturation, known to occur still in the early adulthood. At the same time impulsiveness and attentional deficits have been associated with trait factors that precipitate the early onset of drinking (Cloninger et al. 1988; Giancola and Moss 1998). Impaired control of response inhibition has been found in individuals at risk to

develop alcoholism as well (Begleiter et al. 1984; Cohen et al. 1997a). Further elucidation of the neural basis of attentional abnormalities might, therefore, yield valuable insights for the studies on the risk factors that underlie an early onset of alcohol abuse.

The test–retest reliability of the present N1/Nm latency measures was relatively good. Furthermore, the N1 and MMN results appeared to be clearly different from the results observed in Alzheimer's or Parkinson's patients (cf. Pekkonen et al. 1996, 1998; Pekkonen 2000). These factors pave the way for the development of electrophysiological markers for dissociation of alcohol-related and other etiological factors affecting cognitive function in various clinical populations. However, elucidation of several methodological factors is still needed before the pre-attentive auditory ERP components can be readily used in the diagnostics. For instance, future studies on the exact cellular determinants of ERP amplitudes and latencies would be beneficial. Furthermore, given the well-known inter-individual variability of the ERP amplitude and latency measures, development of normative databases for different components and stimulation parameters is essential.

CONCLUSIONS

The present study demonstrated abnormalities at different levels of auditory processing in the alcoholics. (I) The acceleration and enhancement of the early auditory ERP and ERF components, correlating with short abstinence duration, suggested neural hyperexcitability, caused by neural adaptation to alcohol and subsequent withdrawal in the alcoholics. (II) The MMN results revealed that the transient memory traces in the auditory cortex might be vulnerable to sensory interference. This might also partially underlie impairments at higher levels of the short-term memory system in alcoholics. (III) Electrophysiological and behavioral evidence of pronounced involuntary attention shifting to task-irrelevant sound changes was found in the alcoholics. This abnormality correlated with an early onset of alcohol abuse, which indicates the importance of exploring the contributions of early ethanol exposure and attention deficits to the development of alcohol dependence. (IV) The correlation between the N1 enhancement and the memory impairments suggested that the post-withdrawal symptoms, possibly recovering with prolonged abstinence, might have an impact on the higher cognitive functions for weeks after detoxification. (V) Finally, the potential of the present EEG and MEG methodology in clinical research was indicated by the good test–retest reliability of the N1 and N1m components at the individual level in the healthy subjects. The present findings might thus facilitate future research, for example, in the development of clinical markers for alcohol-related functional cerebral changes.

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ERRATA

Publication VI, page 295, Table 1

5.4 mV	should be	5.4 μV
3.8 mV	should be	3.8 μV