Global field power of auditory N1 correlates with impaired verbal-memory performance in human alcoholics

J. Ahveninen, I.P. Jääskeläinen, E. Pekkonen, A. Hallberg, M. Hietanen, R. Näätänen, P. Sillanaukee

Abstract

First weeks after alcohol withdrawal, associated with profound changes in neural transmission, constitute the critical period for relapse prevention and pharmacological intervention in alcoholism. Here, 20 male alcoholics with 1–6 weeks of abstinence and 20 age-matched healthy controls were studied using auditory event-related potentials (ERP), measured with a 32-channel electroencephalogram, and neuropsychological tests of auditory-verbal memory. Global field power maximum of ERP during 80–150 ms period after presentation of unattended tones (binaural 700 Hz pure tones, inter-stimulus interval 2.5 s) was significantly larger in the alcoholics than controls. This effect, reflecting augmented N1 generation, significantly correlated with impaired memory performance in the alcoholics. The profound change in pre-attentive auditory processing, predicting impaired memory performance, might reflect impaired cerebral inhibitory transmission in alcoholics.

Keywords: Alcoholism; Auditory event-related potentials; Electroencephalograph; Memory; N1; Neuropsychological tests

Alcoholism is a major social and health problem worldwide, presented with a variety of brain lesions and cognitive deficits [8], and generally, with a poor treatment response. Specifically, first few months following cessation of chronic drinking constitute the period of highest risk for relapse [12]. This period is accompanied with post-withdrawal neural hyperexcitability following adaptation to chronic inhibitory effects of alcohol, which is suggested to contribute to both alcohol-related brain lesions and development of alcohol dependence [2]. These post-withdrawal cerebral changes might be detectable for weeks or even months after detoxification [10], accordingly, electroencephalographic (EEG) [1] and magnetoencephalographic (MEG) [14] studies have indicated enhanced auditory responses in alcoholics abstinent for 1–6 weeks.

The vertex-negative N1 deflection of event-related potentials (ERP), stimulus-locked EEG changes revealing neural processes underlying cognitive function, peaks at about 100 ms after stimulus onset, and a subsequent positive P2 deflection at about 180–250 ms, respectively. The N1 consists of several subcomponents, with a major contribution from a supratemporal source near primary auditory cortex. N1 amplitude is dependent on the inter-stimulus interval (ISI), and with different ISIs, different subcomponents govern the total scalp response [3,13]. The supratemporal N1 reaches an asymptotic level already with an ISI of 2–4 s [3], whereas a relatively large modality-non-specific N1 subcomponent is elicited only after a longer silent period [13]. Although elicited exogenously, N1 amplitude is modulated by attention [13].

In humans, acute alcohol challenge attenuates both N1 and P2 amplitude [5]. Several animal studies have in turn shown that after withdrawal of chronic alcohol ingestion ERP component latencies might be reduced and amplitudes increased [16], and recently, augmented or accelerated audi-
tery responses have been observed even for weeks after detoxification in human alcoholics [1,14]. Several earlier studies failed to report such results, however, alcoholics were often medicated with anxiolytic or anticonvulsive agents [15,16], such as benzodiazepines, inhibiting ERP generation [12].

Here, the post-withdrawal cerebral changes were studied in abstinent alcoholics by recording auditory N1 in an unattended stimulus condition with stimulus parameters that recently produced a very reliable response [19]. Global field power (GFP) [9] was used to quantify the instantaneous global activity across the spatial potential fields of the ERP, sampled over the scalp with a 32-channel EEG. In addition, ERP data was correlated with neuropsychological test performance.

Twenty male alcoholics (19–55 years, mean 40 years), abstinent for an average of 20 days (7–45 days), and 20 male education-matched controls (21–59 years, mean 37 years) participated. The age difference between the groups was statistically insignificant. The alcoholics meeting Diagnostic and Statistical Manual of Mental Disorders (4th edn.) criteria for alcohol dependence, without acute withdrawal symptoms according to Clinical Institute Withdrawal Assessment for Alcohol (CIWA-A) [18], were consecutively recruited from a routine treatment program, and those with severe psychiatric diseases, hearing deficits, neurological or other severe diseases were excluded. Written informed consent was obtained after the procedures had been fully explained. The Ethical Committee of the A-Clinic Foundation, Helsinki, Finland, approved the study. On the average, the alcoholics had been drinking (self-reportedly) 1213 g (336–2520 g) of ethanol per week for 11 years (1–35 years). A structured interview on their alcohol history and Alcohol Use Disorders Identification Test (AUDIT) [17] were used. Control subjects (self-reported weekly ethanol consumption 97 g, 12–216 g) abstained from alcohol and other drugs for at least 48 h before the measurement. Six alcoholics used antidepressants or other central nervous system medication (two had fluoxetine; one had mianserin, one mianserin and promazine, one doxepin, and one promazine at evenings). The exclusion of these six alcoholics from the analysis would have had no effect on the results of this study.

In an acoustically and electrically shielded room, a block of 256 pure tones (frequency 700 Hz, duration 50 ms, rise and fall times 5 ms) was binaurally presented 60 dB above the subjective hearing threshold with an ISI of 2450 ms. During the measurement, the subjects were reading material of their own choice and ignoring the stimulation. The mastoid-referenced 32-channel EEG (sampling rate 250 Hz) was averaged and digitally filtered (passband 0.5–30 Hz, pre-stimulus baseline −100 ms). Epochs with artefacts exceeding ±75 μV at any electrode or at an electro-oculogram (EOG) were discarded. The N1 and P2 peak-amplitudes and latencies were determined at the electrode site Fz. In addition, peaks of global field power (GFP), representing maxima of the total brain activity that contributes to the surface potential field at a given moment [9], were determined during 80–150 ms (corresponding to N1) and 150–250 ms (corresponding to P2) post-stimulus periods. Group and treatment differences in the GFP maxima, ERP amplitudes, and peak latencies were statistically analyzed with one-way ANOVAs (Statistica 4.1 software, Stat Soft Inc., OK, USA). The ERP data of two alcoholics were not quantified due to excessive extracerebral artefacts. The subjects’ memory was tested using Logical Memory (part 1) from Wechsler Memory Scale Revised (WMS-R) and California Verbal Learning Test (CVLT) [8]. The neuropsychological data were statistically analyzed with MANCOVA (years of formal education entered as a covariate) with a priori contrasts.

Fig. 1 shows the scalp-distribution maps of the grand-average ERPs at the peak-latency of N1, indicating significant augmentation \((F = 10.30 \ [d.f. = 1, 36], P < 0.01)\) of mastoid-referenced N1 in the alcoholics at frontal Fz electrode. The GFP maximum during 80–150 ms post-stimulus period was also significantly larger \((F = 8.42 \ [d.f. = 1, 36], P < 0.01)\) in the alcoholics than controls (Fig. 1b). No differences were observed in the N1 peak latency, 150–250 ms GFP maximum, P2 peak-latency, or P2 amplitude (Table 1). The alcoholics’ neuropsychological performance (Table 2) was significantly impaired in the backward digit span \((F = 10.40 \ [d.f. = 1, 37], P < 0.01)\), WMS-R immediate \((F = 19.62 \ [d.f. = 1, 37], P < 0.001)\) and
delayed logical memory ($F = 24.01$ [d.f. = 1, 37], $P < 0.001$), and in the immediate free recall of CVLT list A ($F = 5.38$ [d.f. = 1, 37], $P < 0.05$) and list B ($F = 7.53$ [d.f. = 1, 37], $P < 0.01$).

In the alcoholic group, the increased 80–150 ms GFP maximum (~at N1 peak latency) correlated significantly with impaired delayed WMS-R logical memory (Pearson $r = -0.53$, $P < 0.05$) and impaired total score (immediate plus delayed recall) of WMS-R logical memory ($r = -0.48$, $P < 0.05$). Insignificant trends towards correlation between 80–150 ms GFP amplitude and immediate WMS-R logical memory ($r = -0.41$, $P < 0.10$) and CVLT list B immediate free recall ($r = -0.42$, $P < 0.10$) were also observed in the alcoholics. No such correlations emerged in the controls.

The present result of enhanced N1 (80–150 ms GFP) in the alcoholics supports previous findings of enhanced generation of auditory magnetic or electric responses in alcoholics that have been abstinent for approximately a month [1,14]. Our previous MEG experiment [14], however, indicated significant N1m latency reduction in alcoholics, but the N1m augmentation failed to reach statistical significance. This slight discrepancy might reflect the fact that MEG and EEG detect different aspects of brain electromagnetic activity [13,19].

Alcohol withdrawal results in neural hyperexcitability caused by reduced GABAergic inhibitory and increased glutamatergic excitatory transmission [2]. In abstinent human alcoholics, GABA$_A$ receptor densities might be reduced for months after detoxification [10]. Intracranial monkey studies have shown that an administration of GABA$_A$ antagonist bicuculline enhances exogenous auditory responses closely resembling the human N1 [6]. On the other hand, auditory N1 is attenuated by several different GABA$_A$ agonists [11]. The presently observed N1 augmentation might thus be related to post-withdrawal reduction of GABAergic inhibition, and increased neural excitability in alcoholics. The lack of such results in many previous studies of auditory N1 could in turn be explained by the inhibitory anxiolytic medication used in the treatment of alcoholics (e.g. [15]).

The differences in the N1 recovery function, for instance due to shortened refractoriness of the nonspecific N1 generator, might also have caused the present result. This possibility is, however, contradicted by the fact that there were no group differences in the N1 scalp distribution (see Fig. 1a), which should have shifted backwards if the contribution of nonspecific N1 generators had increased in alcoholics [3,13]. Moreover, no such alcohol-related abnormalities in the N1m recovery function were previously observed with ISI of 0.5–2.5 s [14].

Alternatively, N1 augmentation could also indicate that the alcoholics occasionally ‘violated’ the task instruction of ignoring the tones. Attending to the tones should, however, have also increased P2 amplitude in the presently used passive paradigm, in contrast to selective attention tasks where attention-induced negative difference decreases P2 and increases N1 amplitude [13]. The lack of P2 amplitude differences implies that the present result was not related to group differences in attending to the tones. Confounding effects of attentional modulation of N1 could, however, explain why many previous studies of attended auditory N1 (for a review, see [16]) have demonstrated no differences in between abstinent alcoholics and their controls.

The present study replicated previous findings [8] of impaired memory performance in alcoholics, however, only in the tasks measuring immediate recall of verbal information (see Table 2). After repeated presentation of the material and in the delayed recall of CVLT, there were no significant group differences. This shows that the present alcoholics were not actual amnesics, but presented with a relatively mild cognitive dysfunction. Moreover, increased global field power of N1, possibly reflecting reduced inhibition and increased excitability of cortical neurons, correlated with the impaired verbal memory performance in alcoholics.
alcoholics. Cellular-level studies indicate that experience-driven changes in patterns of neuronal excitatability [7] and inhibition [4] contribute critically to adaptive plasticity (i.e. memory and learning) in the brain. Future studies are thus warranted to investigate whether the unbalanced neuronal excitability and inhibition after withdrawal [2], possibly pronouncing the effect of actual brain lesions [8], could impair memory performance in short-term abstinent alcoholics. The auditory ERP might provide a marker of this post-withdrawal impairment in alcoholics.

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