P300 Abnormality due to Chronic Alcohol Exposure in Patients with Alcohol Dependence*

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SUMMARY:
P300 ABNORMALITY DUE TO CHRONIC ALCOHOL EXPOSURE IN PATIENTS WITH ALCOHOL DEPENDENCE

Objective: Scalp recorded P300, the long latency event-related potential (ERP) occurring in response to stimulus is primarily originated from subcortical structures, has been reported to be an indicator of neuronal structure change. In this study, we aimed to examine the probable effect of chronic exposure to alcohol on ERP components in patients with alcohol dependence who had not overt cognitive dysfunction. **Method:** Twenty-six male patients (mean±SD age: 45.04±5.98 range: 26-52) with alcohol dependence diagnosed to DSM-IIIR criteria and 15 male healthy control (mean ± SD age: 43.2±6.96± range: 28-54) were included in the study. Cognitive functions were evaluated with Mini Mental State Examination and Bender - Gestalt teats. No overt structural abnormality detected in brain computerized tomography. Auditory ERPs were recorded by "odd ball two voice discrimination task" procedure in the third week of alcohol withdrawal. **Results:** We found that the patients had significantly longer P3 latency. P3 amplitude was not different from those of the controls. **Conclusions:** We concluded that our finding of delay P3 latency may indicate a neuronal structure impairment due to alcohol in patients with alcohol dependence despite the fact that obvious cognitive dysfunction is not observed.

Key words: *alcohol dependency, event-related potentials, cognitive functions.*

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ÖZET:
ALKOL BAĞIMLILARINDA KRONİK ALKOL KULLANIMINA BAĞLI P300 DEĞİŞİKLİKLERİ

Amaç: Bir uyarana cevap olarak ortaya çıkan ve primer olarak subkortikal yapılardan kaynakladığı düşünülen olaya-bağlı uzamış potansiyeller (ERP) saçlı deriden P300 dalgası şeklinde kaydedilmekte olup, bunun nöronal yapı değişikliğinin bir göstergesi olduğu bildirilmiştir. Bu çalışmada belirgin bilişsel işlev bozukluğu olmayan alkol bağımlısı hastalarda kronik alkole maruz kalmanın ERP bileşenleri üzerindeki olası etkilerini araştırdık. **Yöntem:** DSM-IIIR tanı kriterlerine göre alkol bağımlılığı tanısı alan 26 erkek hasta (ort ± SD yaş: 45.04±5.98 aralık: 26-52)ve 15 sağlıklı erkekten (ort ± SD yaş: 43.2±6.96± aralık:: 28-54) oluşan kontrol grubu çalışmaya alındı. Bilişsel işlevler Mini Mental Durum Muayenesi ve Bender-Gestalt testi ile değerlendirildi. Deneklerin hiçbirisinin bilgisayarlı beyin tomografisinde yapısal anomali tespit edilmedi. İşitsel ERP'ler alkol yoksunluğunun 3. haftasında "odd ball iki ses ayırımını değerlendirme" yöntemi ile kaydedildi. **Bulgular:** Biz P300 genliğinde hastalar ve kontroller arasında anlamlı fark olmamasına rağmen, hastalarda P300 latansında belirgin uzama bulduk. **Tartışma:** Sonuç olarak bizim bulduğumuz P300 latansındaki bu uzama belirgin bilişsel işlev bozukluğu göstermeyen alkol bağımlısı hastalarda, alkolün yol açtığı nöronal yapılardaki bozulmanın bir göstergesi olabilir.

Anahtar kelimeler: *Alkol bağımlılığı, olaya ilişkin potansiyeller, bilişsel işlevler.*

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INTRODUCTION

Alcohol abuse and dependence are the most common substance-related disorders. Long-term alcohol abuse is known to permanently impair certain cerebral functions in some individuals. The extent of the cognitive deficits may range on a continuum from mild to severe, including dementia associated with brain atrophy (1). Although some authors pointed out that there is a cortical shrinkage in an alcoholic patient's brain, they could not found any correlations between the atrophy and neuropsychological deficits, except in the frontal lobe areas; others have found that there is a modest correlation between the shrinkage and the cognitive impairments (2-5). In SPECT studies it is shown that there is a reduction in cerebral blood flow during alcohol withdrawal which is not related with brain atrophy (6,7). Some other studies have shown that there is a correlation between low cerebral blood flow and neuropsychological test scores (8, 9).

Patterns of drinking may affect the neuropsycho-

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logical findings. Alcoholic patients with more than 10 years of heavy drinking show greater cognitive deficits. Repeated withdrawals may also be associated with cortical-related neurological damage. Social drinkers show greater decrease in cognitive performance when larger amounts are consumed at one time rather than spread out over time (10).

Psychophysiological measures of brain activity in the form of event-related potentials (ERP) have been used to assess the integrity of the drinker's central nervous system (CNS) functioning. Sensorial evoked potentials (EPs) are the responses of the brain to a specific sensory stimulus. There is, however, another distinct class of evoked potential, the "endogenous" or "cognitive" potentials (ERPs), which can be recorded in response to an external stimulus or event. The term cognitive subsumes a broad range of psychological concepts, including attention, expectancy, surprise, storage and retrieval of information from memory, and linguistic processing, among others. The amplitude and latency of these potentials may depend on the motivation of the subject and the cognitive, affective or motor response to that particular stimulus and it has been accepted that these potentials originate from different cortical and subcortical structures (11).

Different authors found similar P300 (P3) patterns in alcoholic patients (6, 12-14). Alcoholics manifested significantly delayed P3 latencies and some found have smaller P3 amplitudes. These findings are similar to P3 patterns found in Alzheimer's disease, other dementias and normal aging (15-17). Although these results seem to be evidence for premature aging for alcoholic patients; Porjesz and Begleiter found very different evoked potentials between elderly individuals and alcoholic patients (18). In studies on young alcoholic men versus nonalcoholic control subjects, there was no difference among psychological findings (19). But in there reports these was no information about brain atrophy which effects cognitive functions.

In this study, we want to evaluate the effects of alcohol on cognitive functions in a homogeneous alcoholic patient group who do not have brain atrophy.

METHOD

Subjects

Twenty-six male inpatients with alcohol dependence diagnosed according to DSM III-R criteria were included in the study (mean±SD age: 45.04±5.98 range: 26-52). All patients gave written informed consent. At the time of admission, patients received a complete medical, psychiatric and neurological evaluation. Psychiatric histories were evaluated with the structured Clinical Interview for DSM III-R. No patients had overt cognitive dysfunction. Assessment of cognitive dysfunction was based on anamnestic data and impairment in neuropsychological tests including the Mini Mental State Examination, Bender (visual-motor) Gestalt Test. MADRS (Montgomery-Asberg Depression Rating Scale), CAS (Clinical Anxiety Scale) was used to evaluate depression and severity of anxiety symptoms (20, 21). Brain computed tomography (CT) scans (performed on a Toshiba 600 XT) revealed no morphological abnormality or cortical atrophy in the subjects studied. This visual evaluation was done by a experienced radiologist. The control group consisted of 15 physically and mentally healthy male volunteers (mean ± SD age: 43.2±6.96± range: 28-54). They also received complete medical, psychiatric and neurological evaluation. Exclusion criteria for patient and control subjects were:

- Current or past axis I psychiatric diagnosis (other than alcohol dependence for the patients)
- History of alcohol consumption (only for control subjects)
- Prescription drug use
- Neurological signs and/or history of neurological disease (both for control subjects and alcoholic patients)
- History of head trauma
- History of cardiovascular or endocrinological disease

- Current medical illness

All of the alcoholic patients had laboratory findings within normal limits (including complete blood count, serum electrolyte assay, liver function test, fasting blood glucose level, kidney function tests, thyroid function tests, urinalysis, serological tests for viral hepatitis and electrocardiograph, and electroencephalograph). Overall nutrition was assessed in terms of the proportion of actual weight to ideal weight; none of the patients were malnourished. The control group was matched with the group of alcoholics in age and social status.

Duration of alcohol abuse of the patients ranged from 12-35 years (mean±SD: 22.5±6.36) and daily intake of ethanol (mean±SD) was 392.31±156.59 gr/day during the month prior to the study. This was calculated as corresponding to the amount of pure ethanol (in grams). The pattern of drinking was continuously excessive alcohol intake. The daily diazepam dose administered during the withdrawal (mean±SD) was 14.62±3.31 mg/day and initial doses were successively reduced to 5 mg/pd during the next 10 to 15 days in all patients. All the alcoholic patients had minimum 3 weeks detoxification treatment before being tested.

ERPs were recorded with the 'odd-ball' two voice discrimination task . Active electrodes were placed at CZ, FZ, and earth electrode was placed at FPZ, according to the 10-20 International EEG system. Reference electrodes were placed at the mastoids and connected to each other. The electrode impedance was less than 5 kW. Subjects were instructed to count silently infrequent high-pitch tones of 2000 Hz randomly presented in a series of low-pitch tones of 1000 Hz. The ratio of high to low pitch tones was 20%. The responses to frequent and rare tones were averaged separately. A Nihon Kohden MEB-530 signal averaging computer was used. Twenty artifact-free traces were recorded with a sweep time of 1s. The peaks were evaluated by visual observation as N100, P200, N200 and P3. The latencies were measured according to the highest point by means of a cursor. If there were two peaks for P3, two lines were drawn from the descending and ascending parts of the trace and the crossing point of the lines accepted as the peak and latencies were measured from this point. The amplitude measurements were done from peak to peak. The amplitude of N1 was measured according to the baseline which is drawed automatically by the computer.

Statistical analysis was performed by using paired and unpaired Student's t test and simple correlation-regression analysis.

RESULTS

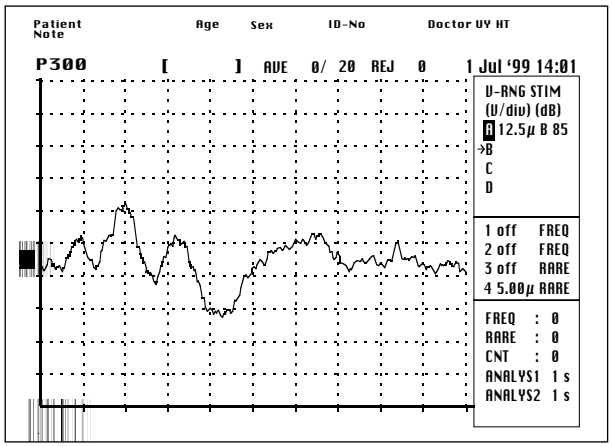
The latencies and the amplitudes which were obtained from both the alcoholic patients and the controls are given in table I. The mean P3 latency of

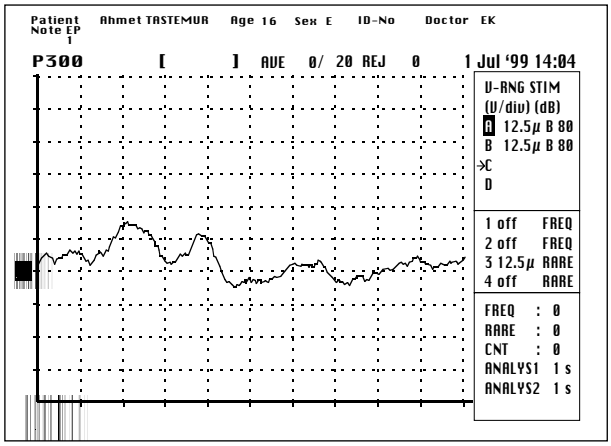
Table I. Event related brain potentials in the groups

		Alcoholics (n=26) mean± SD	Controls (n=15) mean ± SD	t
Latencies (msn)	N1	94.00 ±11.63	94.00± 16.92	0.1
	P2	180.62 ± 20.35	175.20 ±15.92	0.88
	N2	233.85 ± 28.86	220.27±16.03	1.67
	P3	342.00 ± 37.11	319.20 ± 21.26	2.18*
Amplitude(μv) (peak to peak)	N1	7.32± 3.23	5.16± 2.31	2.27*
	P2	12.07± 5.75	9.22± 3.18	1.76
	N2	7.45 ±4.87	6.60± 3.50	0.59
	P3	11.09± 6.31	9.85 ± 3.69	0.69

*p<0.05

Figure 1. Typical examples of P300 recording from a normal control (A), from an alcoholic patient





the alcoholic patients peaked at 342.00 ±37.11 msec and this result is significantly different from those of the controls which peaked at 319.2±21.26 (t=2.18, p<0.05). When we compare the mean latencies of N1, P2, N2 and the mean amplitudes of P2, N2, P3; we could not find any difference between the groups. But the mean latencies of N1, P2, N2 and the mean amplitude of P2, N2, P3 of the alcoholic patients tend to be longer and higher than the control group's values. The mean amplitude of N1 (according to baseline) is significantly higher than that of the control group. Typical examples of P3 recording from a normal control and from an alcoholic patient have shown in figure l.

Table II. Variables of drinking history and neuropsychological test scores of the alcoholic patients

Variables	Alcoholics (n=26) mean SD
Age	45.04 ±5.98
Age at start of regular drinking	26.77± 7.19
Years of regular drinking	19.00 ±11.82
Age of start heavy drinking	32.30± 6.84
Daily amount of alcohol intake (grams)	392.31±156.59
Mini mental state examination	27± 3

Mini mental state and Bender (visual-motor) Gestalt Test scores of subjects were within the normal limits (table II). None of the alcoholic patients had clinical anxiety and depression.

We also could not find any correlations between the drinking pattern, duration and quantity of drinking and the mean P3 latency of alcoholic patients. There is also no correlation between the mean amplitude of N1 and the drinking variables.

DISCUSSION

In our study when we compare the ERP components of the alcoholic patients and those of the controls, there is a tendency in prolongation of latencies and augmentation of amplitudes of all ERP components of the alcoholic patients. But only the mean P3 latency and the mean N1 amplitude of the alcoholic patients were found significantly different from those of the controls.

In the previous studies it was shown that alcoholics had significantly delayed P3 latencies and some had low P3 amplitudes (6, 12-14). We also found longer P3 latency in our alcoholic patients but in this study the amplitudes of ERP components of the alcoholic patients were higher than those of the controls which is not consistent with the previous studies. The delayed P3 latencies were found in other psychiatric patients especially patients in the with dementia (14-17). The neural origins of the P3 component are not clearly known at the present time. However, some evidence with intracranial recording implicates the medial temporal lobe as contributing to the generation of the scalp P3 (22). It has been suggested that sources within the frontal lobe are also involved in P3 generation (23). So the abnormal changes in ERP components may show pat-

hological changes in these regions.

Brain shrinkage (cortical atrophy and ventricular enlargement) is detectable by CT scanning in many patients with chronic alcoholism, and prolonged abstinence results in reversibility in some patients (24). Correlation of damage between CT findings and neuropsychological deficits is linear in some studies (2) . PET scan studies have suggested that glucose utilization may be decreased in the frontal lobe area and is correlated with severity of clinical dementia (27). SPECT scan studies detect hipoperfusion in right temproparietal, right temporal, left temporal and left frontotemporal areas in alcoholic patients (7, 8, 26, 27). In one study P3 lantency is found to be correlated with thalamic blood flow (28). Together with neuropsychological studies, neuroimaging studies confirm that alcohol destroys not only cortical but also subcortical structures.

Schuckit et al found that people with positive family history has similar P3 latencies with people without positive family history (29). Polich et al could not find any difference in P3 latencies and amplitudes between groups according to family history (30). So the difference that we have seen in alcoholics is probably due to the effects of alcohol. But opposing findings have also been reported (31).

In our alcoholic patient group, the amplitudes of ERP components have increment tendency and the mean N1 value of the alcoholic patients is significantly higher than that of controls. The amplitude of the N1 component also reflects the direction of attention to stimuli even when no behavioral response is made (32). N1 is generated when an auditory stimulus is deviant in frequency, intensity or duration from the preceding stimuli in a sequence (33). Similar pattern had been demonstrated among individuals who had antisocial personality behavior (34, 35). Although not evaluated systematically most of our patients have antisocial behavior in their history.

Our results indicate that mean P3 latencies peaked later than those of the controls. Similar results have been reported by Pfefferbaum et al and Begleiter et al (12, 13). Pfefferbaum et al found that alcoholics manifested significantly delayed P3 latencies to easy but not difficult discriminations to when compared to controls; these P3 latencies were in a range comparable to those expected for a difficult task (14). There are some reports showing reduction in P3 amplitude which we could not confirm in our study (12, 36). Johnson has suggested that more complex stimulus causes the higher P3 amplitude (11). Although there is no difficult discrimination task in our study, high ERP component amplitudes can be explained by the task that we have used is already difficult for alcoholic patients.

We conclude that our finding of delay P3 latency may indicate a neuronal structural impairment due to chronic exposure to in patients with alcohol dependence despite the fact that obvious cognitive dysfunction is not observed. However this result should be confirmed by further studies, especially done after 3 weeks of abstinence.

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