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ORIGINAL ARTICLE

The P300 event-related brain potential, relationship with functional, familial and chronic subtypes of alcohol dependence

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Abstract

The results of contemporary studies confirm that the electrophysiological characteristics of alcoholics, such as low P300 amplitude of the Event-Related Potential (ERP), are related with high risk in their offspring, and are considered to be biological endophenotypes of predisposition to develop alcohol use disorders.

The purpose of this study was to evaluate the differences in the theta (4–7 Hz) ERP occurring in the P300 response in the resting EEG of alcoholics in comparison to normal age- and gender-matched control subjects.

The study included individuals of Polish ancestry with three generations (parents, siblings, spouses, marrying into the family, and children) from families with a positive diagnosis of alcohol dependence. Next, the group of alcoholics was subdivided into five distinct groups, according to the National Institute on Alcohol Abuse and Alcoholism (NIAAA). The control group consisted of 25 unaffected individuals from families who were screened and assessed to be negative for a diagnosis of alcohol dependence.

The theta band (4–7 Hz) visual ERP occurring in the P300 response in the resting EEG were examined to explore the electrophysiological effects of alcohol on the brain in patients with alcohol addiction. The amplitude and latency of auditory P300 response was recorded in the frontal, central, occipital and temporal regions, in control and alcohol dependent individuals.

The amplitude of auditory P300 response in the central areas of the brain was lower in alcoholics in all studied groups, compared to the control subjects, except for the young adult subtype. No statistical difference in the amplitude of P300 potential in the studied brain regions was observed between the young adult subtype, and the control group. Similar P300 amplitude values in the young adult subtype and in the controls, and different values in the remaining alcoholics in the study, allow the differentiation into two subtypes of young alcoholics, based on the P300 amplitude as the biological endophenotype, and provide the background related with causative environmental and genetic factors in alcohol addiction.

Key words

Alcoholics, Endophenotypes, Evoked Potentials, National Institute on Alcohol Abuse and Alcoholism (U.S.)

INTRODUCTION

The results of contemporary studies concerning alcohol use disorder confirmed its multi-causative conditioning, including approx. 60% genetic and approx. 40% environmental [1–3]. The precise differentiation of the contribution of causative agents in the etiology of alcohol addiction, together with an introduction of the typology of the disease require integrated research approach, which connects the results of studies with the use of neurophysiological methods, experimental psychology, psychiatry and sociology, as well as genetics and epigenetics [4]. Electroencelographic methods gained a new cognitive, as well as application importance of the results of studies of the etiology of alcohol use disorder, including evoked potentials [5–8]. Event-Related Potentials (ERP) – are changes in the form of waves in electroencelophalograhic recordings when the examined persons are exposed to the effect of a sudden stimulus defined as an event. The range of stimuli contemporarily applied in studies, covers their wide spectrum, including auditory, visual, motor stimuli, sensory stimulation, as well as the performance of cognitive tasks in psychological tests [7–9].

The P300 potentials are perhaps the most-studied ERP component in the study of electrophysiology of human alcoholisms [10]. The P300 response, which is a positive potential triggered by a light or acoustic signal of high frequency of 600 Hz or 1600 Hz, and registered in electroencelographic recording within the range of delta and theta waves after the elapse of 300 milliseconds has been considered as a phenotype with an increased susceptibility to alcohol and alcohol use disorder [11]. The study shows that the value of amplitude of P300 potential remains under genetic control, and its decreased value is genetically and family connected with the existing sensitivity to alcohol and tendency towards its abuse [12]. Moreover, it is noteworthy that the amplitude of P300 has been considered as a phenotype presenting the presence of the genes of susceptibility, and even metaphorically considered as a 'electrophysiological signature' identifying this characteristics with an active alcohol use disorder, or unrevealed susceptibility to its development [12,13].

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There is much of evidence [14] to suggest that a family history of alcoholism significantly increases the risk for the development of alcohol use disorders. It was found that children from families burdened with alcohol use disorder are characterized by a developmentally impaired morphology of the structures of the cerebral cortex and cerebellum, responsible for decision-making and control executive functions. Also, in the processes of adolescent development, evaluated by the characteristics of electrophysiological phenotypes, developmental delay was revealed within the subcortical nuclei with accompanying deficit and cognitive dysfunctions, and deviations in behaviours. Compared to the control values of families and offspring free from alcohol use disorder, affective and behavioural reactions of children of parents with alcohol addiction syndrome are characterized by the suppression and balance deficit, making wrong decisions in research tests and life, as well as an impaired capability for making peer social relationships [15]. Neurophysiological dysfunctions and developmental disorders in the neuronal structures, with accompanying cognitive difficulties and anti-social behaviours in children from families burdened with alcohol use disorder, simultaneously indicate an increased risk of addiction to alcohol in adolescent development [4, 16].

Data from international reports indicating the presence of genetic factors related with susceptibility to alcohol use disorder, and the lack of such studies in Poland, justify undertaking the evaluation of P300 potential connections, as an endophenotype, with alcohol use disorder in the population of young and adult native alcoholics.

Thus, the purpose of this study was to evaluate the differences in the theta band (4–7 Hz) ERP occurring in the P300 response in the resting EEG of individuals with a positive diagnosis of alcohol dependence with three generations (parents, siblings, spouses, marrying into the family, and children), in comparison to normal age- and gender-matched control subjects

MATERIAL AND METHODS

Subjects

The participation of candidates for the study group and the control group was based on the recruitment of patients reporting for treatment in hospitals and addiction treatment centres, as well as their families, willing relatives and siblings, their children and parents. Enrolment of those addicted and their family members into the study was based on the principles of total voluntariness and expression of consent for EEG registration, with the provision of full information concerning safety and non-invasiveness of, as well as maintaining the confidentiality of personal data and results.

The addicted patients were divided into five groups, based on a detailed interview, according to the typology currently applied in studies and treatment of alcohol use disorder in the USA, and introduced by the National Institute of Alcohol Abuse and Alcoholism – NIAAA (https://www.nih.gov/news-events/news-releases/researchers-identify-alcoholism-subtypes). The NIAAA typology differentiates alcohol addicts into five groups of alcoholics: *young adult* (GR-1); *young antisocial* (GR-2); *functional*) (GR-3); *intermediate familial* (GR-4) and *chronic*) (GR-5). The control group were 25 persons with comparable characteristics classified into groups with alcohol use disorder, but not abusing and not addicted to alcohol and psychotropic substances.

P300 potential

The study of P300 potential was conducted using the Neurosoft EMG/EP system 'Neuro MEP4' in the Laboratory for Diagnosis and Treatment of Epilepsy, and in the Laboratory for early Diagnostics of Susceptibility to Addictions at the Institute of Rural Health in Lublin. The triggering and registration of P300 potentials and latency were performed using acoustic stimuli within the range 600 and 1,600Hz, in experimentally established conditions, and in cooperation with the Institute of Physiology and Pathology of Hearing at the World Hearing Centre in Kajetany.

EEG recordings were performed from eight areas of the scalp, with the use of methodologically valid positions of the electrodes at the left frontal polar region (FP1-R), right frontal polar region (FP-2R), left central region (C3-R), right central region (C4-R), left occipital region (O1-R), right occipital region (O2-R) left temporal region (T3-R), and the right temporal region (T4-R). Positions of electrodes were selected based on a pilot study of 19 sites, on the analysis of preliminary results, their repeatability, as well as methodological data from literature. P300 potential was registered in the EEG recording of patients addicted to alcohol, divided into five groups, and in the control group of persons free from alcohol addiction and not abusing alcohol.

The experimental protocols were approved by the Ethics Committee of the Institute of Rural Health in Lublin, after obtaining informed consent from all participants.

Statistical analysis

Our objective was to compare the absolute power of the theta band (3–7 Hz) in the resting EEG between alcoholic and control subjects. Data were expressed as the mean ± standard deviation (SD) or median (range) according to data Distribution. Kruskal-Wallis non-parametric ANOVA and Dunn's multiple comparisons test were applied for the analysis of data from both P300 amplitude and P300 latency in the study groups.

RESULTS AND DISCUSSION

Characteristics of the study population are detailed in Table 1.

Into Group 1 (GR-1 ***young adult***) were qualified young people who were characterized by a low indicator of addiction to other psychotropic substances, lack of pathological psychical disorders, apart from alcoholism, and a mediocre level of family alcoholism (Tab. 1). Group 2 (GR-2 ***young antisocial***) consisted of young persons who had begun consuming alcoholic beverages since early youth, at the age of 15, and by the age of 18 were already pathologically addicted. In their families, addiction of others to alcohol was frequently observed. During interview, they often mentioned addiction to nicotine and use of psychotropic drugs. Into Group 3 (GR-3 ***functional***) were classified middle-aged persons who had a stable occupational and family situation. The majority of this group were addicted to nicotine. Group 4 (GR-4 ***intermediate familial***), had characteristics similar to Group 3; however, in their families there were more alcoholics and more persons with psychical disorders. The majority of them were addicted to nicotine and

Table 1. Characteristics of alcoholics in the study, divided into five groups, divided according to the National Institute on Alcohol Abuse and Alcoholism (NIAAA), USA, and the control group

Groups	Group-1 (n=22)	Group-2 (n=24)	Group-3 (n=31)	Group-4 (n=26)	Group-5 (n=25)	Control (n=25)
Mean age in years (±SD)	31.3 ±9	32.2 ±8.0	52.6 ±6.9	57.6±7.5	59.0 ±6.3	47.0 ±7.2
Male / female	15 / 7	16 / 8	23 / 8	16 / 10	17/8	17 / 8
Cigarette smokers (%)	18.2	58.3	38.7	69.2	79.2	16.0
Treated for alcoholism (%)	4.5	25.0	12.9	23.0	58.3	0.0
Treated for psychological disorders (%)	0.0	0.0	9.7	26.9	33.3	0.0
Consuming other psychoactive substances (%)	13.6	70.8	19.4	26.9	41.7	4.0
Family alcoholism (%)	22.7	62.5	12.9	61.5	75.0	8.0
Urban inhabitants (%)	72.7	75.0	51.6	53.8	70.8	64.0
Education (>12 yrs in %)	22.7	16.7	25.8	15.4	8.3	32.0

GR-1 – '***Young adult;*** GR-2 – ***Young antisocial***; GR-3 – ***Functional***; GR-4 – ***Intermediate familial,*** GR-5 – ***Chronic severe,*** with severe chronic course and intensified pathological symptoms of addiction.

psychoactive substances. Group 5 (GR-5 ***chronic***), included persons who started alcohol consumption in early youth, and demonstrated behaviours with the features of delinquency and offence. They came from families of alcoholics with the highest indicators of psychological disorders, habitual cigarette smoking, and frequent taking of narcotics. More than a half of this group were treated for alcoholism; however, without positive results. The control group were 25 persons with comparable characteristics classified into groups with alcohol use disorder, but not abusing and not addicted to alcohol and psychotropic substances.

P300 LATENCY

The mean values of the duration of latency of evoked P300 potential for each alcoholic group and the control group are presented in Table 2.

Latency value ranged in individual groups from the lowest mean values, within the range from 287 milliseconds, to the highest – 317 milliseconds. No statistically significant differences were found between the mean values in individual groups, and between the values in individual positions of electrodes in the examined groups of alcoholics, and the control group (Tab. 2).

P300 AMPLITUDE

The mean values of amplitude of evoked P300 potential for each alcoholic group and the control group are presented in Table 3.

In the group of *young adult alcoholics* (Gr.1) with low parameters of addiction, no statistically significant differences were observed in the P300 amplitude, compared to the values in the control group (Tab. 3). In the group of *young antisocial alcoholics* (GR-2), *functional* (GR-3), *intermediate familial* (GR-4) and *chronic alcoholics* (GR-5), P300 amplitude was lower in the regions C3-R and C4-R, and in FP-2R, compared to the control group; the differences were statistically significant (Tab. 3). Also in the region T3-R, P300 amplitude was significantly higher in the above-mentioned four groups of alcoholics, compared to the control group. However, in the region T4-R, P300 amplitude was lower in the group of *intermediate familial* (GR-4) and *chronic alcoholics* (GR-5), and significantly differed from the control group (Tab.). The values of P300 amplitude in *young adult alcoholics* (GR-1) in the area C3-R and C4-R were higher than the values in *young antisocial* (GR-2), *functional* (GR-3), *intermediate familial* (GR-4) and *chronic alcoholics* (GR-5); the differences between mean values were statistically significant (Tab. 3).

A lower P300 value from single leads C3-R and C4-R, and T3-R, as well as a lower mean value from the summary value of all leads in *young social alcoholics* (GR-2), compared

Table 2. Latency of P-300 in alcoholics examined, divided into five groups, divided according to the National Institute on Alcohol Abuse and Alcoholism (NIAAA), USA, and the control group

Electrodes	Group-1 (n=22)	Group-2 (n=24)	Group-3 (n=31)	Group-4 (n=26)	Group-5 (n=25)	Control (n=25)	p
FP1-R	317.0 ±22.2	294.3 ±31.2	298.8 ±41.0	303.5 ±27.6	292.6 ±25.1	312.6 ±34.2	0.1517
FP2-R	315.4 ±22.4	292.6 ±34.5	303.2 ±40.8	298.1±25.6	301.4 ±32.2	306.0 ±32.1	0.4153
C3-R	297.3 ±22.2	287.6±28.4	305.1±30.2	293.7±23.8	290.3 ±24.2	303.0 ±28.3	0.2368
C4-R	301.4 ±25.8	289.0 ±29.5	303.1 ±25.6	294.7 ±27.6	298.2±26.2	301.4 ±25.6	0.3634
O1-R	298.9 ±20.8	306.7 ±36.6	298.6 ±31.2	303.2 ±30.5	295.6±32.6	298.0 ±31.2	0.7745
O2-R	290.7 ±21.8	299.1 ±34.1	286.9 ±23.9	288.5 ±25.3	298.5 ±30.5	308.6±22.5	0.1630
T3-R	304.0±26.1	288.1 ±29.1	305.6±44.2	288.0 ±22.9	301.1 ±24.7	302.9±30.0	0.0656
T4-R	311.0±28.9	282.7±31.7	304.3 ±35.9	296.2 ±30.8	294.6±26.7	298.6 ±26.2	0.1736

Latency [ms]; M (mean) ± SD (standard deviation); Kruskal-Wallis non-parametric ANOVA and Dunn's multiple comparisons test; p value (level of significance).
Electrodes: FP – fronto-parietal; C – central; O – occipital; T= temporal (mastoid process).
GR-1 – '*Young adult*; GR-2 – *Young antisocial*; GR-3 – *Functional*; GR-4 – *Intermediate familial;* GR-5 – *Chronic severe,* with severe chronic course and intensified pathological symptoms of addiction

Table 3. P-300 amplitude in examined alcoholics, divided according to the National Institute on Alcohol Abuse and Alcoholism (NIAAA), USA, and the control group

Electrodes	Group-1 (n=22)	Group-2 (n=24)	Group-3 (n=31)	Group-4 (n=26)	Group-5 (n=25)	Control (n=25)	p
FP1-R	4.48±2.42	3.33±2.39	3.43±1.97	3.29±1.62	3.36±1.42	4.38±1.69	0.16
FP2-R	3.97±2.03	3.19*±2.61	2.98*±1.56	3.10*±1.60	3.22*±1.34	4.99±2.57	< 0.0403
C3-R	6.72±4.29	3.24*±2.85	3.13*±1.88	2.66*±1.17	2.24*±0.79	7.37±3.46	< 0.0001
C4-R	6.24±3.68	3.17*±2.18	3.78*±2.18	3.22*±1.96	2.80*±1.67	6.74±2.51	< 0.0001
O1-R	2.58±3.05	2.86±1.44	3.21±2.63	3.83±2.26	3.62±1.88	3.27±1.68	0.13
O2-R	2.99±2.18	3.27±1.93	3.12±1.73	3.53±2.13	2.38±2.32	3.42±1.84	0.94
T3-R	5.71±3.77	4.07±1.48	3.43*±1.61	2.44*±1.50	2.22*±0.84	7.10±3.50	< 0.0001
T4-R	4.17±2.73	3.79±1.77	3.16±1.60	3.07*±1.61	2.24*±1.11	5.71±2.83	< 0.0008

Amplitude [μV]; M (mean) ± SD (standard deviation); Kruskal-Wallis non-parametric ANOVA and Dunn's multiple comparisons test; p value (level of significance);
Electrodes: FP – fronto-parietal; C – central; O – occipital; T – temporal (mastoid process).
GR-1 – *Young adult*; GR-2 – *Young antisocial*; GR-3 – *Functional*; GR-4 – *Intermediate familial,* GR-5 – *Chronic severe,* with severe chronic course and intensified pathological symptoms of addiction.

to the value in the group of *young adult alcoholics* (GR-1), indicate a high probability of the dominance of the genetic effect over the etiology of alcoholism in *young antisocial alcoholics* (Tab. 3).

A decreased P300 value, considered as an endophenotype, observed in the presented study, both in the three older age groups (GR-3,4,5) and also in intensive and long-lasting alcoholism, was also present in *young antisocial alcoholics* (Tab. 3). The possession of this electrophysiological endophenotype in *young antisocial alcoholics* indicated the presence of the genes which increase the susceptibility to alcohol in those qualified into GR-2. Considering the fact that the endophenotype characteristic P300 of those belonging to the group of *young antisocial alcoholics* was also present in the remaining three, older age groups, it may be presumed that alcoholics from GR-2 demonstrate a mutually similar or identical set of genes, which determine an increased susceptibility to alcohol, and which might have been the main cause of triggering this disease in alcoholics from GR-2. Therefore, considering the presence of endophenotype P300, the probability of the presence of a similar mechanism for triggering addiction is justifiable from the perspective of its continuation in *young antisocial alcoholics*, finally leading to alcoholics from groups GR-3, 4 and 5. It is also logical to presume that the *young antisocial alcoholics* in the presented study will, in the future, satisfy the typology conditions for qualification into GR-3, 4 or 5. An obvious precondition will be the lack of undertaking therapy, or lack of positive results of undertaking such a therapy in the future. Following this course of thinking, it may also be presumed that the majority of alcoholics classified into the last three groups (GR-3,4,5), in their youth, hypothetically belonged to *young antisocial alcoholics*, because they also demonstrate the presence of the characteristic P300, as the endophenotype of an increased genetic susceptibility to addiction. Therefore, an equation considering age of *young antisocial alcoholics* with *young adult alcoholics* is not essentially justifiable in the evaluation of the etiology of alcoholism, because the neuropsychological mechanisms lying in the background of addiction in these two groups vary, which is evidences by the differences in P300.

With respect to *young adult alcoholics* from GR-1, P300 amplitude in this group did not differ from that in the control group, and was significantly higher than the value observed in the group of *young antisocial alcoholics* (GR-2), and from the values in the remaining groups of alcoholics (Tab. 3). Therefore, the values of P300 in alcoholics from GR-1 cannot be ascribed the characteristics of an endophenotype, and the presence of genes causing an increased susceptibility to addiction to alcohol. Thus, on this basis, it may be presumed that probably in *young adult alcoholics* (GR-1.) environmental factors and conditioning, and not genetic factors, had the dominant etiological effect in triggering alcoholism. The lack of statistically significant difference while comparing P300 in the group of *young adult alcoholics* (GR-1) and the values in the control group, both in registrations from the leads C3-R and C4-R, and T3-R and T4-R, confirms the justification for such a probability (Tab. 3). It should be mentioned that the chances for positive outcomes of treatment of *young adult alcoholics,* irrespective of the types of the methods applied, are decisively higher than the perspective of obtaining positive results of therapy in *young antisocial alcoholics.* The results of the presented study indicate that *young antisocial alcoholics* will probably constitute the main pool for 'recruitment' into those who are adult and advanced in addiction and disease, represented by *functional, intermediate familial* and *chronic severe alcoholics*.

The results of the presented study of P300 are of great cognitive and practical importance in the differential and causative diagnostics, and even in targeted therapy in alcohol-related disease in young people, as well as in approaches preventing this social disease.

While presenting the results of this study and considerations of its results, it is worth mentioning the opinion expressed in a form of a therapeutic recommendation by the main researcher dealing with this problem, which have led to the typology introduced by the NIAAA which, with respect to *young antisocial alcoholics,* that exclusively abstinence may be the method of treatment [17].

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