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AGE-RELATED PARAMETERS OF P300 AUDITORY EVOKED POTENTIALS IN ELDERLY PERSONS IN THE CONTEXT OF COGNITIVE HEALTH: A STUDY IN THE EUROPEAN NORTH OF RUSSIA

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ABSTRACT

Background. Setting of norms for the parameters of P300 cognitive auditory evoked potentials (EP) in elderly people with intact cognitive functions considering their residence in certain climatic and geographical regions is an urgent problem.
The aim of the study. To determine age-related parameters of P300 cognitive auditory evoked potentials in elderly people aged 60–69 and 70–74 years, living in the European North of Russia (using the example of Arkhangelsk).
Methods. The parameters of P300 auditory EP were determined in randomly selected urban residents in the age groups of 60–69 years (n = 284) and 70–74 years (n = 115) with normal scores on the Montreal Cognitive Assessment Scale (MoCA), without depression (according to Beck Depression Inventory), with preserved ability to work and/or social functions. We calculated the 5th–95th percentile values (P5–P95) of the P300 EP parameters and assessed the relationships of these parameters with socio-demographic characteristics, lifestyle and the results on the MoCA scale and Beck Depression Inventory.
Results. Statistically significant differences in latency indicators of P300 EP were determined between groups of 60–69 and 70–74 years (P25–P90) in all studied brain regions (frontal, central). In the group of 60–69 years, the range of P25–P75 values of P300 EP latencies was 342.5–401 ms, in the group of 70–74 years – 358.5–443 ms. Age differences in P300 EP amplitudes were minimal with an interquartile range of 4–13 µV in the total sample. Participants who smoked had higher latency scores and lower amplitude scores; former smokers had higher latency scores compared to never-smokers.
Conclusion. Latency above 400 ms at the age of 60–65 years and above 443 ms at 70–74 years can be considered as a criterion for reduced cognitive reserve and an increased risk of developing cognitive disorders in elderly people living in the European North of Russia.

Key words: cognitive function, cognitive evoked potentials, North, healthy aging, cognitive health

ВОЗРАСТНЫЕ ОСОБЕННОСТИ ПАРАМЕТРОВ СЛУХОВЫХ ВЫЗВАННЫХ ПОТЕНЦИАЛОВ Р300 У ПОЖИЛЫХ ЛЮДЕЙ В КОНТЕКСТЕ КОГНИТИВНОГО ЗДОРОВЬЯ: ИССЛЕДОВАНИЕ НА ЕВРОПЕЙСКОМ СЕВЕРЕ РОССИИ

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РЕЗЮМЕ

Обоснование. *Нормирование параметров когнитивных слуховых вызванных потенциалов (ВП) Р300 у пожилых людей с сохранными когнитивными функциями с учётом проживания в определённых климатогеографических условиях является актуальной проблемой.*

Цель исследования. *Определение возрастных особенностей параметров когнитивных слуховых вызванных потенциалов Р300 у пожилых людей 60–69 и 70–74 лет, жителей Европейского Севера России (на примере г. Архангельска).*

Методы. *Определены параметры слуховых ВП Р300 у случайно отобранных городских жителей в возрастных группах 60–69 лет (n = 284) и 70–74 лет (n = 115) с нормальными показателями по Монреальской шкале оценки когнитивных функций (МоСА, Montreal Cognitive Assessment), отсутствием депрессии (по шкале депрессии Бека), сохранной трудоспособностью и/или социальными функциями. Рассчитаны 5–95-е процентильные значения (Р5–Р95) параметров ВП Р300 и оценены связи этих параметров с социально-демографическими характеристиками, образом жизни и результатами по шкале МоСА и шкале депрессии Бека.*

Результаты. *Определены статистически значимые различия показателей латентности ВП Р300 между группами 60–69 и 70–74 лет (Р25–Р90) во всех изучаемых мозговых отделах (лобных, центральных). В группе 60–69 лет диапазон значений Р25–Р75 латентностей ВП Р300 составил 342,5–401 мс, в группе 70–74 лет – 358,5–443 мс. Возрастные различия амплитуд ВП Р300 были минимальными при межквартильном диапазоне 4–13 мкВ в общей выборке. Курящие участники имели более высокие показатели латентности и более низкие показатели амплитуды, курившие в прошлом – более высокие показатели латентности в сравнении с никогда не курившими.*

Заключение. *Латентность выше 400 мс в возрасте 60–65 лет и выше 443 мс в 70–74 года может рассматриваться в качестве критерия сниженного когнитивного резерва и повышенного риска развития когнитивных нарушений у пожилых людей, проживающих на Европейском Севере России.*

Ключевые слова: *когнитивные функции, когнитивные вызванные потенциалы, Север, здоровое старение, когнитивное здоровье*

BACKGROUND

Maintaining higher mental functions at an optimal level in old age ensures the active participation of elderly people in public life. Successful cognitive activity in elderly people is also necessary for the effective transfer of accumulated work experience to the younger generation, which also ensures the stability of society. However, the individual viability of elderly people decreases, primarily due to a decrease in the indicators of the cognitive domain [1]. Modern psychodiagnostic approaches make it possible to assess the risks of cognitive impairment in elderly people, but neurophysiological tests are not always sensitive to the detection of early, pre-dementia disorders.

Parameters of event-related bioelectric potentials of the brain (evoked potentials (EP)) are promising electroneurophysiological correlates of cognitive functions both in norm and in pathology [2, 3]. At the same time, the problem of identifying the limits of fluctuations in the values of cognitive evoked potentials in elderly individuals in the context of healthy aging remains relevant. The natural age-related change in the EP P300 parameters occurs both against the background of a decrease in cognitive functions reflected in the data of neuropsychological testing, and against the background of preserved cognitive and social functions. This complicates the interpretation of the EP P300 parameters in elderly individuals in the context of the need to differentiate the characteristics of the age norm and electrophysiological correlates of the risk of developing cognitive impairment [4]. Lifestyle, his activity in society significantly determines the neurophysiological status of an elderly person.

Age-related decrease in the speed of information processing in the form of increased latency and decreased amplitude of the P300 EP is traditionally considered in 10-year periods [2]. The age of 70 as an important age limit is often used to predict various aspects of the lives of elderly people. For example, the age of 70 is used to calculate survival predictors (socioeconomic status, lifestyle, cognitive functions, etc.) [5]. Therefore, age-related features of the P300 EP parameters and their relationship with social and psychological characteristics seem important to consider taking into account the division of old age into periods before and after 70 years.

According to the concept of the "aging curve" proposed in the 1970s–90s based on the age-related dynamics of the P300 EP latency, with age the average latency increases according to the formula: Latency P300 = $1.25 \times$ age + 285 ms [2]. However, the maximum values of the P300 EP latency may differ significantly from the calculated values. That is, in older age groups, the ranges of values of the P300 latency indicators may be quite wide.

The amplitude of the P300 EP is also traditionally considered within the framework of regression models, according to which the amplitude decreases with age (P300 EP Amplitude = 11.9 µV – $0.09 \times$ Age) [6]. In this case, the spread of amplitude values in age samples can be quite wide, and the data presentation is limited to the values of the arithmetic mean for the sample and the standard deviation. There is also information on a slight age-related decrease in the P300 EP amplitude with aging [7].

Age-related changes in physiological parameters, including cognitive functions, may have regional characteristics. Thus, in a random sample of elderly people visiting outpatient clinics in one of the regions of the Arctic zone of the Russian Federation (Arkhangelsk), pre-dementia disorders according to neuropsychological testing were detected in half of the visitors [8]. In general, this is comparable with the results of assessing cognitive impairment among individuals from the all-Russian sample, when mild and moderate (pre-dementia) disorders were detected in 46.6 % of visitors to the I.M. Sechenov University of the Ministry of Health of the Russian Federation (Moscow) among individuals with an average age of 66.0 ± 15.7 years [9]. However, it is noted that when recording visual EP P300 in elderly women in Arkhangelsk, the greatest decrease in amplitude and prolongation of latency of visual EP P300 were detected in the 70–74 year age group [10].

Determination of normative ranges of the P300 EP latency and amplitude parameters taking into account the data of neuropsychological testing, as well as information on the socioeconomic status, labor and social activity of elderly people would ensure their applicability both for assessing the parameters of healthy aging and for identifying electrophysiological criteria for the risk of developing cognitive impairment in elderly people. Taking into account the nonparametric distribution of these parameters, the presentation of their normative ranges using percentile corridors (from P5 to P95) would also contribute to increasing their validity. On these grounds, the aim of this study was to determine age-related parameters of P300 cognitive auditory evoked potentials in elderly people aged 60–69 and 70–74 years, living in the European North of Russia (using the example of Arkhangelsk).

METHODS

In 2023, study participants were recruited from among residents of Arkhangelsk who had previously been included in the random population sample of the "Know Your Heart" study [11], formed on the basis of an anonymized database of the territorial compulsory health insurance fund. Random addresses were selected for visiting, and elderly men and women (according to age periodization – aged 60-74 years) living at them were invited to participate in the study. The survey was conducted at the consultative and diagnostic clinic of the Northern State Medical University of the Ministry of Health of the Russian Federation (NSMU) and the biorhythmology laboratory of the N. Laverov Federal Center for Integrated Arctic Research

of the Ural Branch of the Russian Academy of Sciences (FECIAR UrB RAS). All participants provided written informed consent for the examination, which was approved by the local Ethics Committee of NSMU (protocol No. 03/04-23 dated April 26, 2023) and carried out in compliance with the principles of the Helsinki Declaration of the World Medical Association.

The inclusion criteria for the sample of this study were age 60–74 years; residence in the Arkhangelsk region for 10 years; availability of signed informed consent for the study.

The exclusion criteria were the presence of an acute infectious disease at the time of the study; exacerbation of a chronic disease; history of mental illness.

A total of 605 people aged 60–74 years took part in the study. They were offered to undergo a full examination, including a medical examination and questionnaire (stage one), as well as cognitive-psychological testing and recording of the parameters of P300 cognitive auditory EP (stage two). Additional exclusion criteria for assessing the parameters of P300 cognitive auditory EP were the presence of epilepsy, traumatic brain injury with damage to the bones of the skull, cerebrovascular accidents accompanied by hemiparesis, and hearing loss above grade I. A total of 529 people completed both stages. The remaining participants met the exclusion criteria or refused to complete the second stage.

The questionnaire provided data on the participants' ability to work (currently employed or not employed, but could work if desired or necessary), level of education, marital status, length of residence in Arkhangelsk, financial situation, smoking and alcohol consumption, performance of functions in the family (1 – financial support of family and relatives; 2 – housekeeping; 3 – managing a summer cottage or garden plot; 4 – raising children and grandchildren; 5 – caring for elderly and/or sick relatives) and socially significant activities (volunteer work, participation in the work of political parties, public organizations, in community work at least once a year).

Cognitive functions were tested using the Montreal Cognitive Assessment (MoCA) [12]. A total score of 26 or higher was considered normal on this scale. The level of depression was determined using the Beck Depression Inventory [13]. The absence of depressive symptoms was considered at a level of less than 14 scores. In addition, the Age Is No Barrier test was used to determine signs of frailty [14, 15].

The P300 EP auditory was assessed using the Neuron-Spectrum electroencephalograph (Neurosoft LLC, Russia); the P300 EP parameters were recorded in standard electroencephalogram (EEG) leads using the international 10-20 electrode placement system with an ear referent in the frontal (F3, F4) and central (C3, C4) regions of the brain. The conditions of binaural nonverbal acoustic stimulation in the oddball paradigm with button pressing included: stimulus duration – 50 ms; intensity – 80 dB; inter-stimuli period – 1 s; tone frequency – 2000 Hz with 30 % occurrence of a significant stimulus, 1000 Hz with 70 % occurrence of an insignificant stimulus. The P300 EP latencies (ms) and the N2-P300 interpeak amplitude (µV) were determined [2, 6].

Subsequently, to examine the age ranges of the P300 EP indicators, a selection of individuals with normal cognitive function indicators according to the MoCA scale (26 scores or more), without signs of depression (less than 14 scores according to the Beck Depression Inventory), preserved ability to work, performing two or more work functions in the family and/or performing socially significant activities at least once a month, was made.

In statistical analysis, categorical variables are presented as absolute values (Abs) and percentages (%). Continuous variables are presented as arithmetic means (M) and standard deviations (SD) or medians (Me) with 25% and 75% percentiles [P25; P75]. Comparisons of groups by categorical variables were performed using the Pearson`s chi-square (χ^2) test, and by continuous variables – using the Mann – Whitney test. Normative values of the P300 cognitive auditory evoked potential for the 60–69 and 70–74 age groups are presented as percentile values (P5, P10, P25, P50, P75, P90, P95) modeled using multiple quantile regressions with age group, gender, and education as covariates, with the condition of uniform distribution of age groups by gender and education. Differences between the corresponding percentile values in the age groups were assessed based on the statistical significance of the regression coefficients for the age group variable in the described quantile regression models. The relationships between the P300 EP indices and socio-demographic characteristics, lifestyle (smoking and alcohol consumption) and the results on the MoCA scale and the Beck Depression Inventory in the analyzed sample of elderly people with normal MoCA indices, without signs of depression (on the Beck Depression Inventory) and with preserved working capacity and/or social functions were estimated using multiple linear regressions with adjustments for gender and age. The conditions for the applicability of multiple linear regression models were estimated by visual assessment of the distribution of residuals. Regression coefficients and differences between groups were considered statistically significant at $p < 0.05$. STATA 18.0 (Stata Corp., USA) was used for data analysis.

RESULTS

As a result of applying the selection criteria for participants with normal scores on the MoCA scale and the Beck Depression Inventory, with preserved working capacity and/or social functions, a group of 399 people (284 people aged 60–69 years and 115 people aged 70–74 years) was formed for the analysis of age-related characteristics of the ranges of the P300 EP parameters, which amounted to 75.4 % of the total sample size (605 people) (table 1).

According to the "Age Is No Barrier" questionnaire, the group included: 310 (77.7 %) people for whom

frailty is unlikely (0–2 points); 84 (21 %) people for whom pre-asthenia is probable (3–4 points); 5 (1.3 %) people with probable frailty (5–7 points). Taking into account the selection of participants with normal indicators on the MoCA scale [16, 17], the presence of signs of pre-asthenia and asthenia in the participants was considered to be due to a decrease in physical functions.

The study participants aged 60–69 and 70–74 were comparable ($p > 0.05$) in terms of the ratio of men to women, time of residence in Arkhangelsk, performance of family functions (except for the proportion of those working on summer cottages and garden plots, which was higher among individuals aged 70–74), participation in socially useful activities, and frequency of alcohol consumption (table 2). There were more unemployed people and those reporting that they would not be able to work if they wanted to or had to, aged 70–74 ($p < 0.001$), and there was a higher proportion of people with no more than secondary education at this age ($p = 0.037$). There were more married people aged 60–69 ($p = 0.011$), and there were more people living alone aged 70–74 ($p = 0.046$). There were more smokers among those aged 60–69 ($p = 0.005$). Income levels were lower in the 70–74 year old group due to a higher proportion of individuals reporting financial constraints on purchasing major household appliances. Participants aged 70–74 also had a lower mean score on the MoCA scale. Scores on the Beck Depression Inventory were not statistically significant between participants aged 60–69 and 70–74.

Analysis of the ranges of the P300 EP values showed an increase in the P300 EP latency values with age in all the studied EEG leads (table 3). Taking into account the maximum spread of values in the four considered EEG leads, in the 60–69 year old group, the range of P300 EP latency values at the level of average percentile values (P25–P75), reflecting the conditional "average norm", was 342.5–400.9 ms, in the 70–74 year old group – 358.5–442.9 ms. In all the considered EEG leads (C3, C4, F3, F4), higher percentile values in the P10–P95 range were determined in the 70–74 year old group compared to the 60–69 year old group. At the P90 level, the P300 EP latency increased significantly compared to the value at P75 in each age group, especially in the 70–74 age group – more than 40 ms.

The range of the conditional "average" norm (P25–P75) of the P300 EP amplitudes in the 60–69 year old group, taking into account the spread of values in the EEG leads, was 4.2–12.6 µV, in the 70–74 year old group – 3.5–12.3 µV. The differences in the P300 EP amplitudes between the age groups were insignificant and reached statistical significance only at the level of low percentiles (P5–P25) for lead C4.

In the analyzed group of participants, consisting of individuals without cognitive and psychological impairments, with preserved working capacity and/or social functions, the analyzed P300 EP indices had no statistically significant relationships with the level of education, employment, or income. Compared with those who had never smoked, current smokers had higher latency indices (lead C4: Me – 394.0 vs. 374.0 ms, $p = 0.024$; lead F4: Me – 393.4 vs. 370.1 ms, $p = 0.008$; lead F3: Me – 393.3 vs. 366.5 ms, $p = 0.004$) and lower amplitude indices (lead C3: Me – 6.5 vs. 8.5 µV; $p = 0.043$); former smokers had higher latency values (lead F3: Me – 384.8 vs. 366.5 µV; $p = 0.019$). The frequency of alcohol consumption had no statistically significant relationship with the P300 EP values.

When examining the same sample, no relationships were determined between the latency indicators of the P300 EP amplitude and the results on the MoCA scale, limited to a range of 26 to 30 points (fig. 1, 2), as well as with the results on the Beck Depression Inventory scale, considered in a range of 0 to 13 points (fig. 3, 4).

TABLE 1

RESULTS OF SELECTING STUDY PARTICIPANTS WITH NORMAL MOCA SCORES, NO SIGNS OF DEPRESSION AND PRESERVED ABILITY TO WORK AND/OR SOCIAL FUNCTIONS

Age groups	Total (*n* = 529)	60–69 years (*n* = 354)	70–74 years (*n* = 175)	*p**
	Abs (%)			
No cognitive impairment (MoCA score ≥ 26)	441 (84.2)	306 (87.2)	135 (78.0)	0.007
No depression (Beck Depression Inventory score < 14)	477 (90.7)	328 (93.2)	149 (85.6)	0.005
Maintained ability to work (a person works or could work if desired and/or necessary)	347 (65.6)	260 (73.5)	87 (49.7)	< 0.001
Maintained social functions (≥ 2 functions in the family and/or socially useful activities at least once a month)	498 (94.1)	334 (94.4)	164 (93.7)	0.770
No cognitive and psychological impairments and preservation of working capacity and/or social functions	399 (76.2)	284 (80.9)	115 (66.5)	< 0.001

Note. * – *p*-value estimated by the Pearson`s chi-square (χ^2) test.

TABLE 2

SOCIODEMOGRAPHIC, BEHAVIOURAL, COGNITIVE, PSYCHOLOGICAL AND NEUROPSYCHOLOGICAL CHARACTERISTICS OF STUDY PARTICIPANTS AGED 60–69 AND 70–74 YEARS

Characteristics	60–69 years (n = 284)	70–74 years (n = 115)	p*
	Abs (%)		
Socio-demographic			
Gender:			
– male	112 (39.4)	35 (30.4)	0.091
– female	172 (60.6)	80 (69.6)	
Residence in Arkhangelsk:			
– since birth	140 (49.3)	58 (50.4)	0.837
– more than 10 years	144 (50.7)	57 (49.6)	
Education:			
– higher education	98 (34.5)	38 (33.0)	
– secondary specialized education	158 (55.6)	55 (47.8)	0.037
– secondary and lower education	28 (9.9)	22 (19.1)	
Employment:			
– currently working	116 (40.9)	14 (12.2)	
– does not work, but could work if desired and/or necessary	100 (35.2)	54 (47.0)	< 0.001
– does not work and could not work if desired and/or necessary	68 (23.9)	47 (40.9)	
Income level:			
– not enough money for food/clothes	21 (7.4)	7 (6.1)	
– enough for food/clothes, buying large household appliances is difficult	124 (43.8)	68 (59.1)	0.046
– a person can buy large household appliances, but buying a car is difficult	106 (37.5)	29 (25.2)	
– there are no financial difficulties, it is possible to buy a car, an apartment	32 (11.3)	11 (9.6)	
Marital status:			
– married	172 (60.6)	60 (52.2)	
– divorced	42 (14.8)	13 (11.3)	0.011
– widower/widow	45 (15.9)	35 (30.4)	
– never been married	25 (8.8)	7 (6.1)	
Living alone	73 (25.7)	41 (35.7)	0.046
Functions in the family:			
– financial support of family and relatives	204 (71.8)	88 (76.5)	0.338
– housekeeping	265 (93.3)	107 (93.0)	0.924
– managing a summer cottage or garden plot	180 (63.4)	86 (74.8)	0.029
– raising children and grandchildren	186 (65.5)	78 (67.8)	0.656
– caring for elderly and/or sick relatives	72 (25.4)	29 (25.2)	0.978
Socially useful activity or volunteer work:			
– rarely or never	263 (92.6)	105 (1.3)	0.660
– at least once a month	21 (7.4)	10 (8.7)	
Lifestyle			
Smoking:			
– never	169 (59.5)	86 (74.8)	
– in the past	68 (23.9)	22 (19.1)	0.005
– in the present	47 (16.6)	7 (6.1)	

TABLE 2 (*continued*)

Alcohol consumption:			
– once a month or less	212 (74.6)	89 (77.4)	
– 2-4 times a month	59 (20.7)	16 (13.9)	0.103
– 2-3 times a week or more often	13 (4.6)	10 (8.7)	
Mental health, Me [P25; P75]			
MoCA scale, scores	28 [27; 29]	28 [26; 29]	0.001
Beck Depression Inventory, scores	4 [1; 7]	5 [2; 7]	0.060

Note. * – for quantitative characteristics, the *p*-value is estimated by the *t*-test for independent samples or the Mann – Whitney test, for categorical characteristics – by the Pearson`s test (χ^2).

TABLE 3

NORMATIVE VALUES FOR THE PARAMETERS OF P300 COGNITIVE AUDITORY EVOKED POTENTIAL IN INDIVIDUALS AGED 60−69 (*n* = 284) AND 70−74 YEARS (*n* = 115) WITH NORMAL MOCA SCORES, NO SIGNS OF DEPRESSION AND PRESERVED ABILITY TO WORK AND/OR SOCIAL FUNCTIONS

Groups	Mean	SD	P5	P10	P25	P50	P75	P90	P95
P300 EP latency, ms									
C4									
60–69 years	378.0	46.2	319.2	330.7	349.2	370.3	395.3	430.1	453.1
70–74 years	403.0	53.9	328.2	345.7*	367.2*	392.3*	440.3*	488.1*	512.1*
C3									
60–69 years	379.7	42.4	322.1	331.2	351.5	374.6	400.9	434.0	465.8
70–74 years	406.4	55.9	332.1	343.7*	371.5*	392.6*	442.9*	482.0*	514.8*
F4									
60–69 years	374.5	45.7	317.9	328.0	344.0	368.1	396.4	426.4	454.1
70–74 years	398.5	53.6	324.9	338.0	360.0*	390.1*	422.4*	469.4*	503.1*
F3									
60–69 years	374.7	45.2	317.1	326.1	342.5	369.3	395.6	429.3	467.3
70–74 years	399.2	54.7	330.1*	337.1	358.5*	384.3*	427.6*	479.3*	506.3
P300 EP amplitude, µV									
C4									
60–69 years	9.5	6.0	2.1	3.1	5.7	8.4	12.1	18.0	21.3
70–74 years	8.3	5.2	0.9*	1.4*	4.3*	8.1	11.4	15.3	18.2
C3									
60–69 years	9.9	6.2	1.9	3.2	6.2	9.0	12.6	17.0	21.1
70–74 years	9.2	4.8	2.9	3.7	5.6	8.3	12.3	16.7	19.3
F4									
60–69 years	8.5	6.3	0.9	2.1	4.3	7.4	10.5	16.0	21.5
70–74 years	8.3	6.1	0.7	1.7	3.5	7.2	12.3	17.3	21.6
F3									
60–69 years	8.4	6.5	1.1	2.2	4.2	7.2	10.9	15.2	20.2
70–74 years	7.9	5.2	1.7	2.3	4.1	6.5	11.2	14.8	19.0

Note. Percentile values were modeled and differences between them across age groups were estimated using multiple quantile regressions with age group, sex, and education as covariates, assuming that age groups were equally distributed across sex and education; * – *p* < 0.05 for differences between corresponding percentile values.

DISCUSSION

The obtained data reflect statistically significant age differences in the P300 EP latencies in elderly people in the 60–69 and 70–74 year old groups, to a greater extent in the P25–P90 percentile range, when the differences are reflected in all EEG leads, and minimal age differences in the P300 EP amplitudes.

Socio-demographic factors, as well as parameter variations within the normative ranges according to the MoCA and Beck Depression Inventory data, had no connection with the P300 EP parameters in individuals of the group with normal MoCA scores, no depression, preserved working capacity and/or social functions. This indicates that the principles of study participant selection for the formation of normative values of the P300 EP parameters were chosen correctly, as far as the survey capabilities allowed. Nevertheless, the smoking factor, even past smoking (in those who quit smoking by the time of the study), was associated with both the latency and the amplitude of the P300 EP. The obtained data are consistent with studies where, in representative samples of mentally healthy people who were smoking at the time of the study and had never smoked, the electrophysiological phenotype of a smoker with reduced P300 EP amplitude was shown, with a possible dose-response relationship [18, 19]. The latency prolongation of the auditory P300 EP is associated with the prolongation of its sensory component N1, when there is a decrease in the perception of the auditory signal due to the chronic effect of nicotine on the neuronal pathways from the inner ear to the auditory zone of the cerebral cortex [20].

Despite the fact that the issue of creating normative databases of P300 EP parameters has been raised for a long time, for more than 30 years [21], comparison of the obtained results with literature data is difficult. This is due to the different number of participants in the samples and different statistical approaches. The most commonly used method is to evaluate P300 EP indicators taking into account the average value and standard deviation (sigma) [2]. Nevertheless, focusing on the data of the P300 EP norm in the central EEG leads with pressing a button in the group of 60–69 years (383 ± 40 ms), given in the work of V.V. Gnezditsky et al. [2], it can be concluded that in our study both the average values (374.5–380 ms) and standard deviations (42.4–46.2 ms) in the 60–69 year old group are
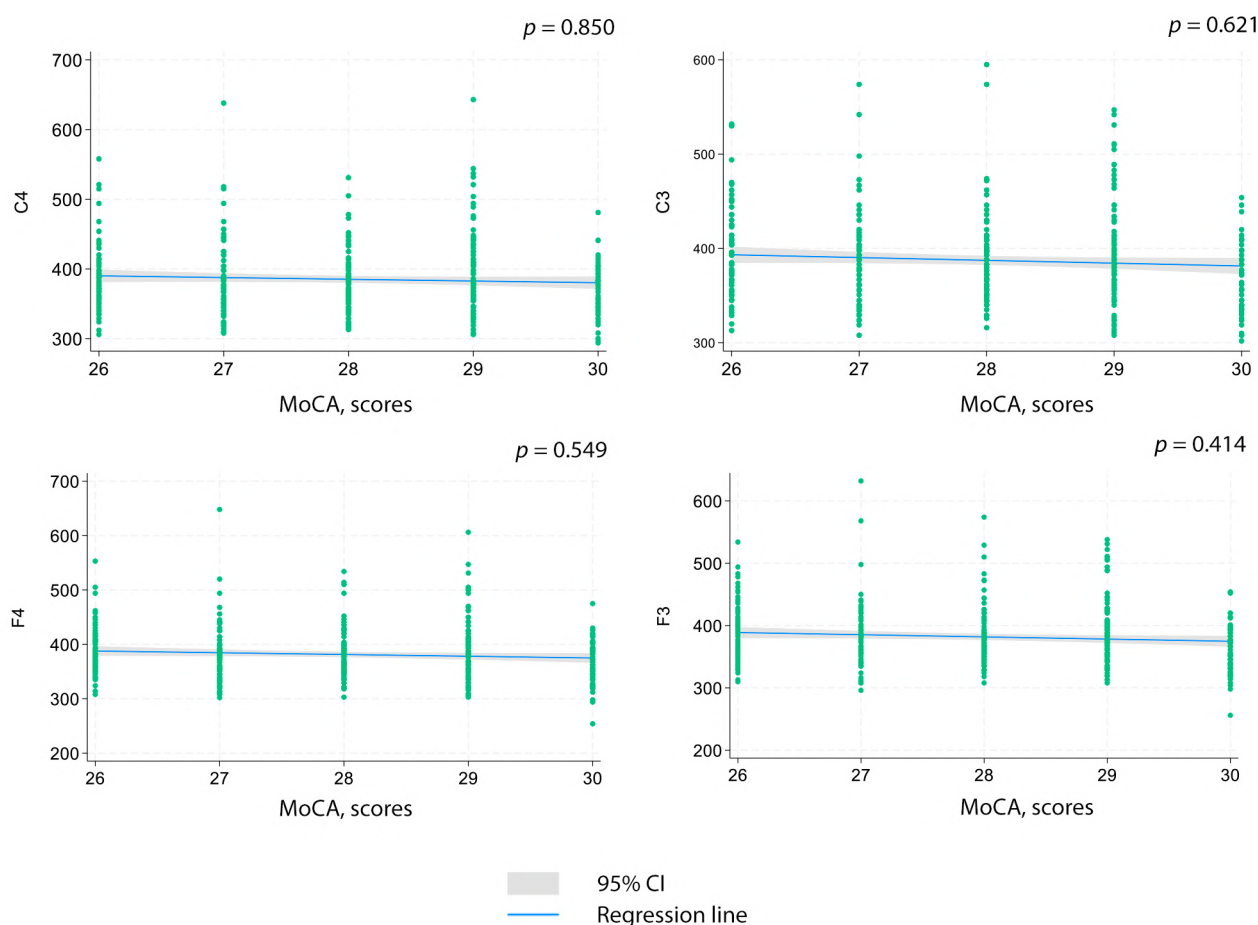

FIG. 1.
Results of multiple regression analysis showing the relationship between P300 evoked potential latency and MoCA scores ranging from 26 to 30 points in individuals with normative values of P300 evoked potential parameters: regression lines and relationships between variables are defined with correction for gender and age
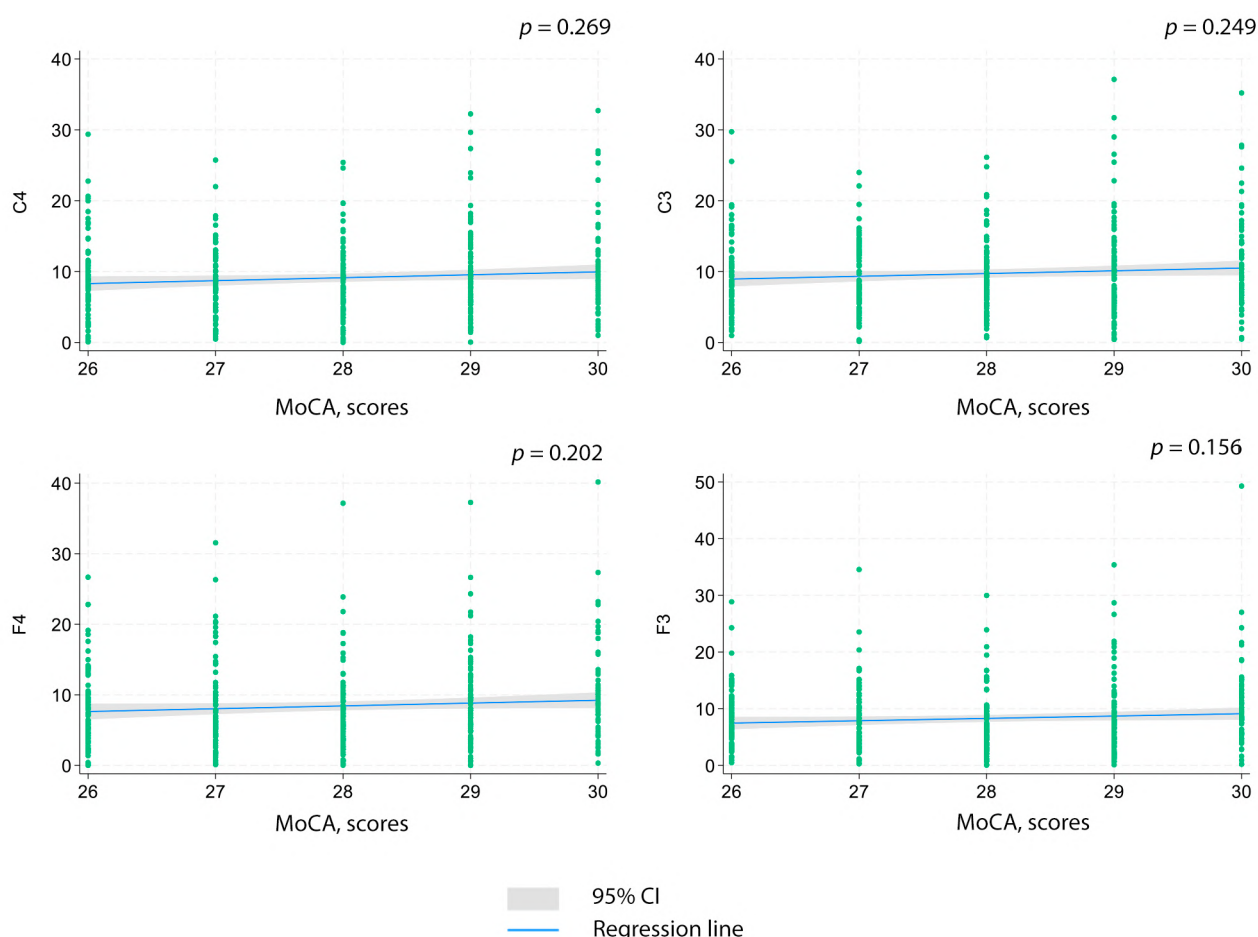
FIG. 2.
Results of multiple regression analysis showing the relationship between P300 evoked potential amplitude and MoCA scores ranging from 26 to 30 points in individuals with normative values of P300 evoked potential parameters: regression lines and relationships between variables are defined with correction for gender and age

generally comparable with the data of the above-mentioned authors. In the 70–74 year old group, the P300 EP latency in our study appears to be more prolonged (average – 399–406 ms, sigma – 54–56 ms; according to V.V. Gnezditsky et al. [2] – 392 ± 46 ms).

In another study, also conducted using auditory P300 EPs [22] in healthy elderly individuals in South Korea with an average age of 75.8 years, the P300 EP latency was 362.5 ± 44.2 ms in the median frontal EEG lead, 362.2 ± 43.5 ms in the central EEG lead (M ± sigma). In a study conducted by the authors from Japan in healthy individuals with an average age of 62.7 years, the P300 EP latency was 377–406 ms [23].

Acknowledging that a comparison of the obtained data with the data presented in the literature is only conditionally possible (differences in the electrode placement schemes, different characteristics of the samples) [4], we can state in general the correspondence of the ranges of auditory P300 EP latencies in our study with the literature data for individuals aged 60–69 years (especially at the level of P25–P75), but there is a more pronounced shift towards

an increase in the P300 EP latency in a group of Arkhangelsk residents aged 70–74 years.

Despite the recognition by various authors of the presence of extended P300 EP latencies in individuals without identified cognitive impairment, the P300 EP latency of about 400 ms is considered a threshold above which the risk of cognitive impairment and a decrease in the volume of working memory statistically significantly increases, and in individuals with both neurodegenerative and neurovascular pathology [2]. There is evidence that the P300 EP latency of more than 400 ms can be associated with cerebrovascular insufficiency and signs of dementia according to neuropsychological testing [24]. Thus, it can be stated that in elderly people of Arkhangelsk aged 60–69 years, the limit of the conditional "average" norm (P25–P75) of the P300 EP latency in all the EEG leads under consideration corresponds to 400 ms.

The results showed that age differences in the P300 EP amplitudes in the age range of 60–74 years were minimal. According to the "aging curve" calculations [6], for the age of up to 74 years, the amplitude norm
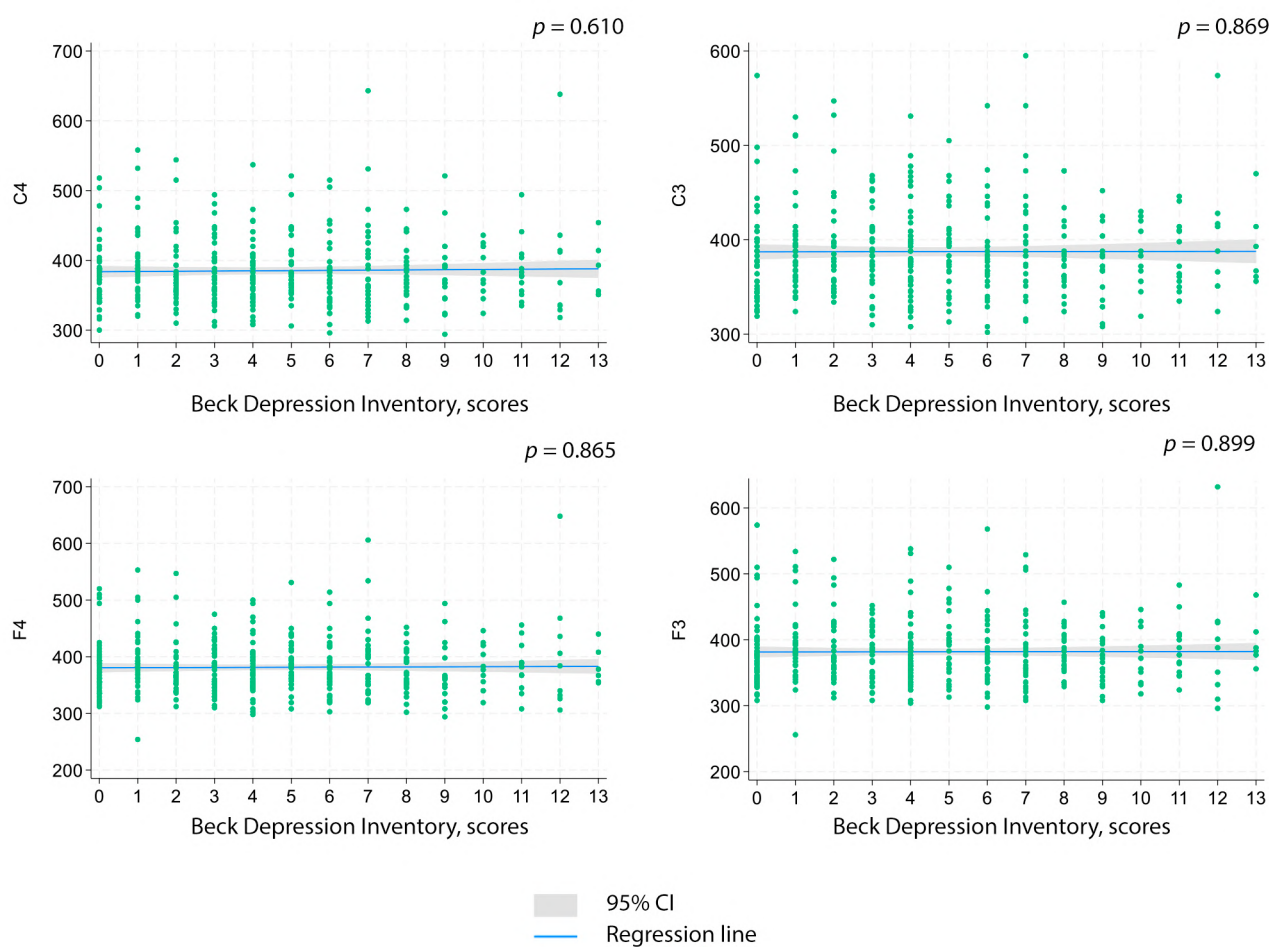
FIG. 3.
Results of multiple regression analysis showing the relationship between P300 evoked potential latency and Beck Depression Inventory scores ranging from 0 to 13 points in individuals with normative values of P300 evoked potential parameters: regression lines and relationships between variables are defined with correction for gender and age

is expected to be more than 5 µV. In our study, the lower limit of the average norm (P25) is presented slightly lower – at the level of 5 µV (4 µV), but at P10 it is significantly lower (from 1.4 to 4 µV) depending on the EEG lead. It is worth considering that the calculations of regression models for predicting the amplitude depending on age presented in the literature were carried out taking into account a large range of ages (from 18 to 80 years) and on small samples of people.

If we rely on the works devoted to the study of the auditory P300 EP parameters in elderly people, then the relationship between age and the P300 amplitude is not obvious, as in our study. In the previously presented work, in healthy individuals with an average age of 75.8 years, the amplitude in the median frontal lead was 6.5 ± 5.5 µV, in the median central lead – 4.0 ± 2.8 µV (M ± sigma) [22]. According to other data, in individuals with an average age of 62.7 years, the amplitudes were 5.2 ± 1.9 µV (M ± sigma) [25]. Some authors associate the decrease in the P300 EP amplitudes with aging not with age, but with a lower level

of education and gender differences [26], which was not confirmed by the data of our study.

Thus, the average values of the P300 EP amplitudes, as well as their ranges, do not always have a statistically significant dependence on age in elderly individuals. In the study by C.F. Kügler et al. [7], a slight age-related decrease in the P300 EP amplitudes with aging was also indicated. Apparently, a change in the perception of auditory information due to an increasing neurosensory deficit in sound recognition can cause compensatory activation of various cortical areas to maintain the process of recognizing sensory information, which can contribute to the expansion of the normal range of the P300 EP amplitude, characteristic of healthy aging. It can be stated that in our study, the P300 EP amplitude is represented by a wide range of values – both towards low and towards fairly high amplitudes, especially at the upper percentiles (P75–P95 – up to 18–22 µV).

The prolongation of the P300 EP latency in individuals with intact cognitive functions according to neuropsychological testing data can be considered
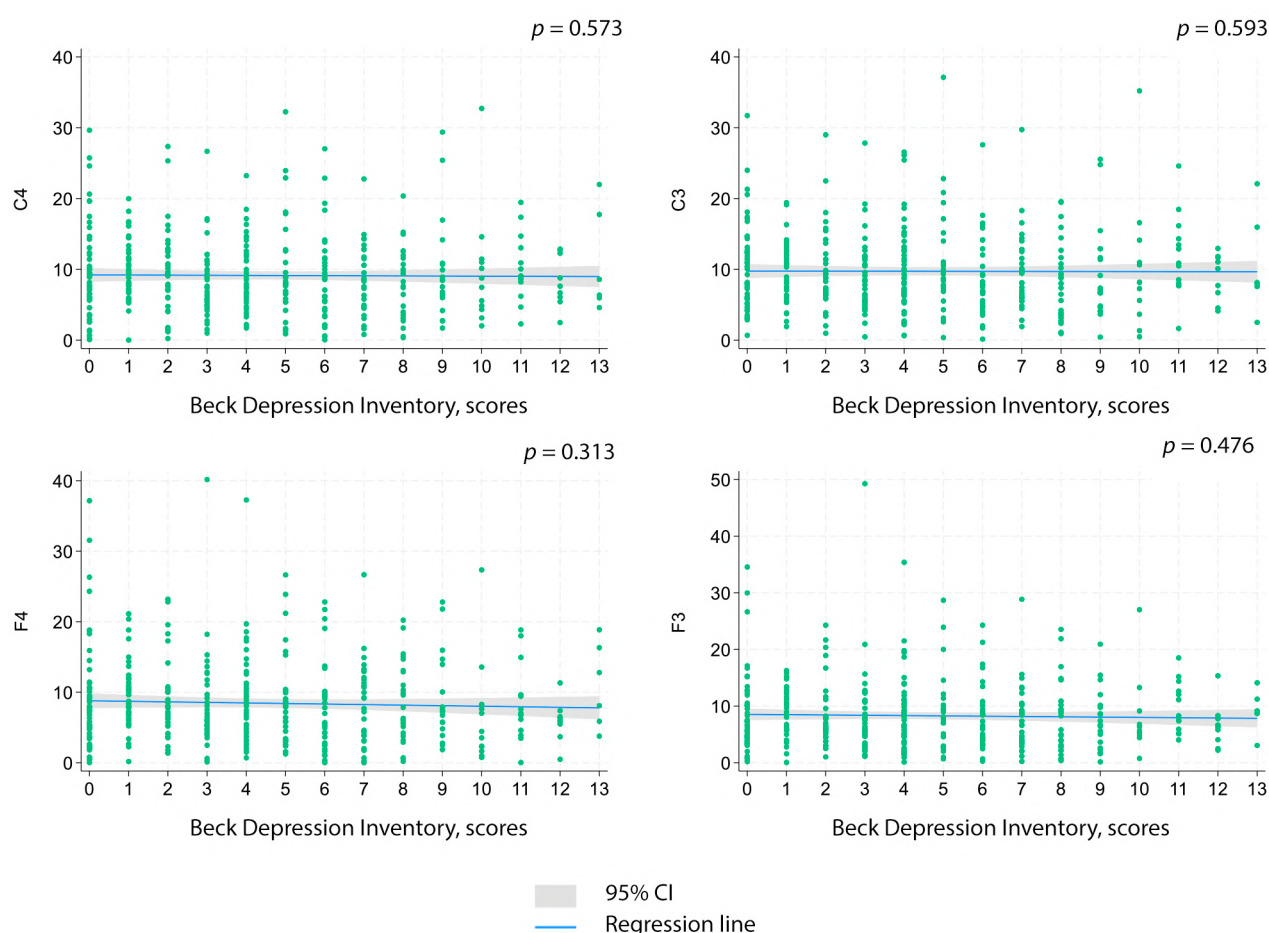
FIG. 3.
Results of multiple regression analysis showing the relationship between P300 evoked potential amplitude and Beck Depression Inventory scores ranging from 0 to 13 points in individuals with normative values of P300 evoked potential parameters: regression lines and relationships between variables are defined with correction for gender and age

from the standpoint of a decrease in cognitive reserve. The concept of cognitive reserve includes the ability of the brain to optimize or maximize its performance due to a differentiated set of neural connections that allows finding alternative cognitive strategies when making a decision [27, 28]. Therefore, the optimal time for making a decision when recognizing a significant sensory stimulus, reflected in the auditory P300 EP latency, may reflect the process of effective adjustment of the brain neural network in the decision-making process.

Based on the experience of previous researchers and taking into account our own results, in individuals aged 60–69 years, the P300 EP latency values higher than P75 (in individuals aged 60–69 years – more than 400 ms, in individuals aged 70–74 years – more than 443 ms) can be considered from the position of a decrease in cognitive reserve and a prognostically unfavorable risk criterion for the cognitive impairment development in elderly people living in a certain climatic and geographic region (Arkhangelsk). For subsequent analysis of the reasons for the significant representation

of the extended P300 EP latency (in percentiles, P75 and above), dynamic observations are necessary, as well as a more in-depth study of cognitive functions, neuroimaging data on morphofunctional changes in the brain, in order to differentiate groups with "normal" aging and "pathological" aging with the risk of developing various pathophysiological variants of dementia (vascular, neurodegenerative nature) [29].

It is also important to further study the role of endocrine-metabolic factors that directly or indirectly determine changes in the rate of brain neuronal activity during decision-making, for example, the state of the thyroid system, metabolic parameters (carbohydrate, fat, protein). These endocrine-metabolic factors can affect both the formation of the normal ranges of the P300 EP parameters and the effectiveness of cognitive functions in residents of the Arctic zone of the Russian Federation, primarily memory functions [30].

Based on the fact that with age the values of the conditional norm of the P300 EP latency increase, the preservation of the P300 EP latency within the age

norm or even at the level of the previous age decade can be considered as an electroneurophysiological reflection of the cognitive reserve preservation for an elderly person, the basis of his cognitive longevity.

The P300 EP amplitude below the P25 value can also be considered in the context of a decrease in cognitive reserve. However, its minimal changes in the age aspect give reason to believe that during healthy aging, the P300 EP amplitude may not undergo significant changes. A pronounced decrease in the P300 EP amplitude in this case will be more associated not with physiological, but with pathological vascular, metabolic changes in brain functions, primarily associated with the risk of developing neurodegeneration [13].

The limitation of the presented study may be associated with the insufficient analysis of possible gender differences, age-related changes in the studied parameters taking into account cognitive impairment according to neuropsychological testing, and the technical complexity of assessing morphofunctional changes in the brain in all participants of the population study using neuroimaging methods. Such an analysis would be more correct in a comparative analysis with the inclusion of younger age groups (up to 60 years), which is planned for the next stage of the study. Thus, the subsequent development of the research topic is planned in the context of the analysis of the role of socio-demographic, behavioral factors, cognitive decline (according to the expanded neuropsychological study) and the severity of depression, which have the greatest impact on the age ranges of the P300 EP parameter values in the elderly, as well as in comparison with individuals of the previous age group (average age).

Another possible limitation of the study may be the inclusion in the analyzed group of 84 (21 %) participants with probable preasthenia and 5 (1.3 %) participants with probable frailty, who got 3–4 and 5–7 scores, respectively, on the Age Is No Barrier test. According to the questionnaire requirements, it was necessary to check the cognitive functions of individuals with 3 points or more using the Mini-Cog questionnaire [14, 15], which was not done. However, the results obtained on the MoCA scale, which is more informative than the Mini-Cog screening test [16, 17], demonstrated normal values according to the MoCA scale, which served as the basis for considering probable preasthenia and asthenia in these individuals to be due to a decrease in physical functions, and not the presence of cognitive decline.

CONCLUSION

For the first time, the normative values of the parameters of cognitive auditory evoked potentials P300 in residents of the European North of Russia aged 60–74 years in the range from 5-95 percentile are presented. In the group of 60–69 years, the range of P300 EP latencies at the level of the "average" norm (P25–P75)

was 343–401 ms, and in the group of 70–74 years – 359–443 ms. Age differences in the P300 EP amplitudes were minimal, the range on average in the total sample was 4–13 µV (P25–P75). Latency above 400 ms (60–65 years) or above 443 ms (70–74 years) in individuals with preserved working capacity and/or social functions and normal indicators on the MoCA scale and the absence of depression (according to the Beck Depression Inventory) is proposed to be considered from the position of a decrease in cognitive reserve and a prognostically unfavorable criterion for the risk of developing cognitive impairment in elderly people living in the European North of Russia.

Conflicts of interest

No potential conflict of interest relevant to this article reported.

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