Potential Neurophysiological Markers of Combat-Related Post-Traumatic Stress Disorder: A Cross-Sectional Diagnostic Study

Потенциальные нейрофизиологические маркеры посттравматического стрессового расстройства у участников боевых действий: кросс-секционное диагностическое исследование

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Original research

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ABSTRACT

BACKGROUND: Studies suggest that the components of brain-evoked potentials (EPs) may serve as biomarkers of the post-traumatic stress disorder (PTSD) caused by participation in combat operations; however, to date, research remains fragmented, with no studies that have attempted to combine different paradigms. In addition, the mismatch negativity component has not been studied in a Russian sample of veterans with PTSD.

AIM: To identify objective neurophysiological markers of combat-related PTSD using the method of auditory-evoked potentials in active and passive listening paradigms.

METHODS: The study included a recording of auditory EPs in an oddball paradigm in three settings: 1) directed attention to auditory stimuli, 2) passive listening while viewing a neutral video sequence, and 3) viewing a video sequence associated with a traumatic event. Combatants diagnosed with PTSD (18 people) were compared with mentally healthy civilian volunteers (22 people).

RESULTS: An increase in the latency period of the early components of auditory EP (N100 and P200), an increase in the amplitude of the P200 component to a deviant stimulus, and a decrease to a standard one in the active listening

paradigm were established in the PTSD group. There were no significant differences in the parameters of the P300 component. The characteristics of mismatch negativity in the passive paradigm were revealed: an increase in the phenomenon amplitude, both when shown a video sequence associated with a traumatic event and when shown a neutral video sequence. A binary logistic regression model constructed using the selected parameters showed that the identified characteristics can potentially be considered as diagnostic markers of PTSD in combatants, as the classification accuracy stood at 87% (sensitivity — 81%, specificity — 91%).

CONCLUSION: Potential neurophysiological markers of PTSD are the following: the amplitude and latency of early components of auditory EPs in the paradigm of directed attention to stimuli and the amplitude of mismatch negativity during passive attention.

АННОТАЦИЯ

ВВЕДЕНИЕ: Исследования показывают, что компоненты вызванных потенциалов головного мозга (ВП) могут являться биомаркерами посттравматического стрессового расстройства (ПТСР) вследствие участия в боевых действиях, однако на сегодняшний день исследования фрагментарны, не представлены исследования, сочетающие различные парадигмы. На русской выборке ветеранов с ПТСР не изучался компонент негативности рассогласования.

ЦЕЛЬ: Выявление объективных нейрофизиологических маркеров ПТСР вследствие участия в боевых действиях методом слуховых вызванных потенциалов в парадигмах активного и пассивного слушания.

МЕТОДЫ: Исследование включало регистрацию слуховых ВП в парадигме вероятностного предъявления (oddball) в трех состояниях: 1) направленное внимание на слуховые стимулы; 2) пассивное слушание при просмотре нейтрального видеоряда; 3) при просмотре видеоряда, связанного с травматическим событием. Обследованы комбатанты с диагнозом ПТСР (18 человек) в сравнении с психически здоровыми гражданскими добровольцами (22 человека).

РЕЗУЛЬТАТЫ: В группе лиц с ПТСР обнаружено увеличение латентного периода ранних компонентов слухового ВП (N100 и P200), увеличение амплитуды компонента P200 на девиантный стимул и снижение на стандартный в парадигме активного слушания. Не выявлено значимых различий в показателях компонента P300. Выявлены особенности негативности рассогласования в пассивной парадигме: увеличение амплитуды феномена как при предъявлении видеоряда, связанного с травматическим событием, так и при предъявлении нейтрального видеоряда. Построенная с использованием выделенных показателей модель бинарной логистической регрессии показала, что выявленные особенности потенциально можно рассматривать как диагностические маркеры ПТСР у комбатантов — точность классификации составила 87% (чувствительность — 81%, специфичность — 91%).

ЗАКЛЮЧЕНИЕ: Потенциальными нейрофизиологическими маркерами ПТСР являются амплитуда и латентный период ранних компонентов слуховых ВП в парадигме направленного внимания на стимулы, а также амплитуда негативности рассогласования при пассивном внимании.

Keywords: *post-traumatic stress disorder; auditory evoked potentials; N100; P200; P300; mismatch negativity; combatants*
Ключевые слова: *посттравматическое стрессовое расстройство; слуховые вызванные потенциалы; N100; P200; P300; негативность рассогласования; комбатанты*

INTRODUCTION

As researchers stress, identifying a specific diagnostic biomarker for post-traumatic stress disorder (PTSD) is a challenging undertaking, because PTSD symptoms overlap with those of generalized anxiety, depressive disorder, and panic disorder (negative affect, anhedonia,

problems with sleep and concentration, irritability, overexcitement) [1]. PTSD encompasses those same psychopathological manifestations, but it is separated by a fairly typical clinical presentation [2]. In combat veterans, PTSD has unique features: the symptoms of PTSD are detected in more than a third of combatants within the first few days after the trauma, and they are accompanied by acute psychotic, affective, anxiety, dissociative, and other disorders [3, 4]. The diagnosis and treatment are further complicated by the fact that, among combatants, symptoms range in a continuum from the psychological to the psychopathological state [5].

The development of PTSD is triggered by changes in the subcortical reactivity to trauma-related memories and emotions, the impairment of inhibitory control and frontal regulation [6, 7], and a deficit in the downregulation of hyperreactivity in the amygdala [8, 9]. All this occurrences culminate in an inability to judiciously apportion attention when responding to threatening and emotional stimuli [10].

Cognitively evoked potentials are a method for recording the electrical potentials of the brain arising in response to the presentation of a significant sensory stimulus (deviant, different) in a series of insignificant (standard) ones [10, 11]. Early components of evoked potentials are associated with attention and the processing of incoming signals [12]. An increase in the amplitude of the early components of the evoked potentials N100 and P200 in response to an auditory stimulus indicates a modulation of the functioning of the amygdala and lateral prefrontal cortex [13], which is associated with hypervigilance in the event of a threat [14]. The amplitude of the N100 component increases both in individuals with PTSD and in individuals exposed to trauma but without PTSD symptoms [15], and it positively correlates with the assessment of hyperarousal [16]. In addition, individuals with PTSD exhibit a significant increase in the amplitude of the N1-P2 complex (the amplitude of the potential from the N100 peak to the P200 peak), which positively correlates with the severity of the symptoms of the disorder [16]. In this case, maladaptive avoidance is associated with a decrease in the amplitude of early components, while obsessive re-experiencing is associated with an increase in the amplitude of the P200 component [17]. An increase in the N100 amplitude was also found in other conditions associated with high levels of anxiety [18, 19].

The P300 component of evoked potentials is used to assess the severity of cognitive impairment, psychomotor functions, and the ability to plan and control goal-directed behavior at the decision-making stage [20]. In individuals with PTSD, there is an increase in the latency of the P300 component [21, 22], as well as a decrease in the amplitude of this component [22, 23], which respectively indicate a longer time for stimulus assessment (neural activity speed) and reduced cognitive processing efficiency [20]. It is also known that the P300 parameters (amplitude and latency) can be used to quantify the post-trauma state dynamics [22] and, in addition, to differentiate PTSD (due to various types of trauma, but not participation in combat) and depressive disorder [24].

The phenomenon of mismatch negativity (MMN) is assessed as the largest amplitude of the difference between the reaction to deviant and standard stimuli in the absence of directed attention [25]. The MMN amplitude reflects the processes of searching for discrepancies in short-term and sensory memory [26, 27], as well as cortical processing of the stimulus at the pre-attention stage, which does not depend on the direction of the attention [27]. In PTSD, a larger MMN amplitude was noted both in comparison with individuals who had no trauma and individuals with a history of traumatic events, but without PTSD [27, 28], which is regarded as a sign of increased sensitivity of these patients to deviant stimuli and reflects their hypervigilance, with a high MMN amplitude being associated with a high level of anxiety [29].

The development and progression of PTSD are complex mechanisms, due to symptoms that can manifest long after the trauma (within six months) and the lack of a correlation between acute reactions and long-term mental states [2, 30]. The similarity of PTSD symptoms with those of depressive, anxiety, and panic disorders [1], adaptation disorders, social and specific phobias further complicates its clinical diagnosis. The challenge is exacerbated by the wide range of symptom clusters, a low diagnostic threshold, and high comorbidity.[1] Therefore, objective diagnostic tools are crucial. Methods such as magnetic resonance imaging, positron emission tomography, computed tomography, and magnetic resonance spectroscopy are

[1] Russian Society of Psychiatris; Ministry of Health of the Russian Federation. Post-traumatic stress disorder. Clinical guidance; 2023–2024–2025. Available from: https://cr.minzdrav.gov.ru/schema/753_1. Russian.

used to diagnose PTSD, but they are expensive and labor-intensive [31]. Diagnostic models are being developed based on language characteristics (area under the curve 0.72) [32]. An attempt was made to create a diagnostic model based on physiological parameters; however, of all the parameters studied (heart rate, heart rate variability, respiratory recursion, galvanic skin response), differences at $p \leq 0.05$ were found only in the amplitude of the systolic wave in terms of stimulation options [33]. Electroencephalography (EEG) is an inexpensive, accessible and fairly flexible tool that can serve as an auxiliary method to improve the accuracy of PTSD diagnosis. However, a model using background EEG parameters (more than 25,000 characteristics, including spectral power, temporal and functional connectivity, frequency of microstate changes) showed an accuracy of 62.9%, indicating the limited efficiency of using background EEG parameters, with the recording process being labor-intensive [34]. The use of EPs can expand EEG diagnostic capabilities. To date, no comprehensive neurophysiological model of auditory-evoked potential testing has been proposed for combatants with PTSD. Studies of the MMN phenomenon have not previously been conducted in a Russian sample of PTSD patients. The combination of different paradigms (active and passive listening, with neutral and trauma-related videos) in one diagnostic model can significantly improve the quality of the neurophysiological diagnosis of the disorder.

The aim of this study was to search for quantitative neurophysiological markers of PTSD in combat participants.

METHODS

Study design

A cross-sectional diagnostic study was carried out.

Study conditions

The main group included persons who had undergone examination and treatment in general psychiatric department No. 11 of Mental-health clinic No. 1 named after N.A. Alexeev (Moscow), in the period from October to November 2023. The control group was selected among volunteers.

Participants

The main group included male combatants with PTSD. The diagnosis was made by the attending physician, in accordance with the ICD-10 diagnostic criteria. Individuals with a history of acute psychotic symptoms, other mental illness, traumatic brain injuries, or a neuroinfection (according to self-report data) were not enrolled. Enrollment was conducted within 2 weeks from the moment of hospitalization.

The control group included individuals without a history of mental illness, traumatic brain injuries or a neuroinfection (based on self-reported data), who did not participate in combat operations, and who did not report traumatic events in their past, from among colleagues and acquaintances of the investigators.

Both groups included only right-handed men.

All participants were assessed for functional interhemispheric asymmetry, having to do with the influence of the dominant hand on cognitive EP parameters [20]. The profile of the lateral organization was assessed based on the results of a questionnaire (with which hand the patient writes, draws, holds a toothbrush when brushing their teeth, uses scissors, a hammer, holds a match when lighting a fire, a spoon when stirring liquids) and motor tests on the dominant hand (applause, intertwined fingers).

Determination of the dominant hand was done immediately before the neurophysiological examination.

Variables

Evoked potentials for standard (100–120 realizations after artifact removal) and deviant stimuli (20–30 realizations after artifact removal) were averaged, and the averaged potentials were filtered in the frequency band of 0.3–20 Hz [31].

Data sources/measurement

EEG recording was performed in a separate darkened room, in the morning hours (09:00–13:00), and in a state of quiet wakefulness in a sitting position (in a chair). The Neuro-KM encephalograph (Statokin, Russia) was used, with the Brainsys analysis software package (developed by A.A. Mitrofanov, Russia) from 19 leads located according to the international 10–20 scheme, with reference electrodes on the earlobes. The sampling frequency of the EEG signal was 1000 Hz, and the bandwidth of the frequency filters when recording the signal was 0.3–70 Hz (the choice was determined by the characteristics of the amplifier).

Neurophysiological testing included 3 series of auditory stimulation with an oddball paradigm presentation: a standard stimulus of 1000 Hz with an 80% probability of presentation (120 stimuli), and a deviant stimulus of

2000 Hz with a 20% probability of presentation (30 stimuli). The duration of the sound stimuli was 10 ms, the intensity was 85 dB, and the interstimulus interval was 1 second [31]. Stimuli were presented binaurally through headphones randomly. The generation of stimuli and their presentation order were managed using the Brainsys software. In the first session, the subject sits with his eyes closed and receives instructions to press a button at the moment the deviant stimulus sounds. In the second and third sessions, the subject received instructions not to pay attention to sounds and to look at the laptop screen (diagonal 17.3 inches or 43.94 cm, resolution 1920x1080 pixels), located at a distance of 60 cm from the subject's eyes. The screen displayed a sequence of nature images (30 landscape images of bodies of water, mountains, steppes, forests, hereinafter referred to as "neutral video sequence"), then a video sequence with images associated with the traumatic event (25 photographs of military operations, destroyed buildings, military equipment, hereinafter referred to as "negative video sequence"). All the photographs were obtained from open sources. The images were presented at a frequency of 1 frame every 2 seconds, and the video sequences were looped and repeated until the total video length was 3 minutes. There were 1- to 2-minute breaks between each EEG recording session.

Visual analysis of all native EEG recordings involved the removal of artifacts and noisy channels. Data from the 9 channels (F3, F4, Fz, C3, C4, Cz, P3, P4, Pz) least susceptible to oculogram and myogram artifacts but characterized by sufficient information content regarding lateralization were selected for analysis [32].

EEG was recorded by a research assistant and a senior researcher at Mental-health clinic No. 1 named after N.A. Alexeev, in a specially equipped separate room. The EEG was analyzed by an employee of the laboratory of clinical neurophysiology of the V. Serbsky National Medical Research Centre of Psychiatry and Narcology of the Ministry of Health of the Russian Federation, with technical support from the software developer. All the researchers were aware of the diagnosis of the subjects.

Quantitative variables

In the first session (active listening — pressing a button at the moment the sound of a deviant stimulus is heard), the components of the auditory-evoked potential for standard and deviant stimuli (N100, P200, P300) were isolated and the amplitude and latent period of the components were analyzed. In sessions with visual stimulation (passive listening), the averaged EP files for the standard stimulus were subtracted from the potentials for the deviant stimulus to obtain the values of the MMN component and the amplitude and latent period of the negativity peak in the interval 150–250 ms were also analyzed.

Statistical methods

The study results were analyzed using the statistical software package SPSS, version 11.5 (SPSS Inc., USA) — distribution analysis, data description, comparison of the means, and binary logistic regression. The distribution of the values of quantitative characteristics was checked using the Shapiro-Wilk test. In all cases, the distribution deviated from normal. In this regard, quantitative parameters were described with the indication of the median, first and third quartiles (Q1; Q3), and the assessment of the differences was done using the Mann-Whitney test. Repeated measures analysis of variance (rmANOVA) with the Greenhouse–Geisser correction (accounting for the inequality of variances) with an inter-subject factor of "group" (nominal variable, n=2: control and PTSD) was used to assess the influence of the factors of stimulus frequency, stimulation content, laterality, and location, intra-subject factors of "stimulus" (n=2, quantitative parameters of evoked potentials to standard and deviant stimuli — for the analysis of the components of evoked potentials); "content of video sequence" (n=2, quantitative parameters of evoked potentials upon presentation of "neutral" and "negative" video sequences — for the analysis of the MMN phenomenon); "distribution" (n=3, quantitative parameters of evoked potentials by electrodes): frontal (F), central (C), and parietal (P); "lateralization" (n=3, quantitative parameters of evoked potentials on the electrodes of the left [F3, C3, P3], right hemisphere [F4, C4, P4], and central electrodes [Fz, Cz, Pz]).

Binary logistic regression models were used to identify independent predictors of PTSD from the evoked potentials and to determine the potential diagnostic value of auditory-evoked potentials for PTSD. Variables were selected using the method of direct, step-by-step inclusion into the equation of predictors with the greatest impact on the dependent variable (Forward: Wald), 8 steps were completed, and the step-by-step procedure was discontinued if there was no change in the previously fitted model when the variables were included.

Ethical approval

The study protocol was approved by the local ethics committee at Mental-health clinic No. 1 named after N.A. Alexeev (Meeting minutes No. 6 of August 11, 2023). A mandatory condition for inclusion in the study was signing the informed voluntary consent to participate in the study and the processing of personal data. Information included explaining to potential participants the purpose, methods, and protocol of the study, with the opportunity to ask clarifying questions.

RESULTS

Participants

During the study period, a diagnosis of PTSD was established for 20 patients and they were asked to participate in the study; 18 agreed and underwent neurophysiological examination. The main group included 18 people with experience of military combat diagnosed with PTSD. They were examined. The control group included 22 people.

Descriptive data

The median age of the PTSD patients and participants in the control group was 34.5 years (29; 41) and 27.5 years (25; 39), respectively (p=0.195). The median duration of the stay in combat conditions for the PTSD patients was 210 (130; 270) days, and the duration from the end of participation in military operations to the time of examination was 50 (38; 120) days.

Main results

Repeated measures analysis of variance was performed to assess the differences in evoked-potential components between the groups. The inter-subject factor of "group" (n=2: control and PTSD), the intra-subject factors of "stimulus" (n=2: standard and deviant), "distribution" (n=3: frontal, central, parietal), and "lateralization" (n=3: left hemisphere, right, central location) were selected.

Amplitude analysis of the N100 component revealed intergroup differences under the influence of the factors of "distribution" (F=14.45, p <0.001), "lateralization" (F=3.20, p=0.048), as well as the interaction of the factors of "stimulus–distribution" (F=9.48, p=0.002) and "distribution–lateralization" (F=10.83, p <0.001). When analyzing the latent period of the N100 component, a significant influence of the "lateralization" factor (F=5.64, p=0.006) and interaction of the "distribution" and "lateralization" factors (F=2.82, p=0.028) was revealed. For the amplitude of the P200 component, differences were revealed under the influence of the interaction of the "stimulus" and "group" factors (F=8.14, p=0.011), the factor "lateralization" (F=10.22, p=0.005), for latency — the influence of the "stimulus" factor (F=9.15, p=0.007), and interaction between the "stimulus" and "group" factors (F=4.92, p=0.040).

For the amplitude of the P300 component, intergroup differences were revealed under the influence of the factors of "stimulus" (F=82.23, p=0.0001), "lateralization" (F=11.97, p=0.0001), interaction of the "stimulus" and "lateralization" factors (F=6.78, p=0.002), and for latency, also the influence of the factors of "stimulus" (F=21.69, p=0.0001), "distribution" (F=3.72, p=0.031), interaction of the "stimulus" and "lateralization" factors (F=8.45, p=0.001). Comparison of the groups using the Mann-Whitney test revealed statistically significant differences in the early components of the evoked potentials, mainly for the deviant stimulus (Tables 1 and 2). The N100 component in individuals with PTSD is characterized by a long latency period to a deviant stimulus in the parietal-central regions, the P200 component has an increased amplitude and an increased latent period to a deviant stimulus in the frontal and central leads, and a reduced amplitude to a standard stimulus in the frontal leads. There were no significant differences between the compared groups *vis-a-vis* the parameters of the P300 component.

In the experimental design using video sequences, repeated measures analysis of the variance was also performed. Significant differences were found under the influence of the "zone" factor (F=18.77, p=0.0001), the "location" factor (F=6.25, p=0.005), and the combination of the "location" and "group" factors (F=3.43, p=0.043). The visual stimulation content factor did not have a significant effect on the MMN scores (F=0.143, p=0.709).

Further comparison of the mean values using the Mann-Whitney test revealed that in individuals with PTSD, the MMN latency period when presented with a negative video sequence, and the MMN amplitude when presented with a neutral video sequence, was higher than in participants in the control group (Table 3).

From among the studied EEG parameters, eight variables, independent predictors of PTSD, were selected: the latent period of the N100 component, the amplitude and latent period of the P200 component to a deviant stimulus, and the amplitude and latent period of the MMN upon presentation of a neutral and negative video sequence in different leads (Table 4).

Table 1. Parameters of evoked potentials to a deviant stimulus in individuals with PTSD compared with values in the control group [median (lower quartile; upper quartile) (number of people)]

Component	Lead	PTSD	Control	Z	*p*
Latent period (ms)					
N100	P3	134 (112; 138) (*n*=17)	108 (102; 116) (*n*=22)	2.549	0.011
	P4	124 (112; 137) (*n*=16)	108 (100; 116) (*n*=22)	2.453	0.014
	Pz	127 (104; 158) (*n*=16)	109 (98; 118) (*n*=22)	1.774	0.076
	C3	132 (117; 140) (*n*=17)	112 (110; 118) (*n*=21)	2.361	0.018
	C4	125 (116; 132) (*n*=16)	112 (106; 122) (*n*=22)	2.407	0.016
	Cz	128 (118; 136) (*n*=17)	110 (104; 116) (*n*=21)	2.143	0.032
	F3	132 (116; 142) (*n*=17)	116 (112; 124) (*n*=22)	1.644	0.100
	F4	130 (118; 134) (*n*=17)	113 (108; 126) (*n*=22)	1.784	0.074
	Fz	131 (115; 140) (*n*=18)	116 (110; 126) (*n*=22)	1.463	0.143
P200	P3	184 (162; 202) (*n*=17)	163 (152; 184) (*n*=22)	1.246	0.213
	P4	184 (152; 189) (*n*=16)	162 (152; 176) (*n*=22)	1.012	0.312
	Pz	187 (163; 197) (*n*=16)	163 (148; 180) (*n*=22)	1.567	0.117
	C3	193 (173; 202) (*n*=17)	166 (156; 184) (*n*=21)	2.883	0.004
	C4	183 (171; 189) (*n*=16)	166 (158; 180) (*n*=22)	1.839	0.066
	Cz	178 (167; 189) (*n*=17)	156 (148; 172) (*n*=21)	2.820	0.005
	F3	190 (176; 200) (*n*=17)	176 (160; 190) (*n*=22)	1.673	0.094
	F4	182 (172; 200) (*n*=17)	177 (160; 200) (*n*=22)	0.821	0.411
	Fz	193 (178; 204) (*n*=18)	172 (156; 188) (*n*=22)	2.484	0.013
P300	P3	334 (310; 366) (*n*=17)	340 (320; 354) (*n*=22)	-0.088	0.930
	P4	348 (313; 363) (*n*=16)	334 (326; 376) (*n*=22)	0.169	0.866
	Pz	340 (311; 362) (*n*=16)	330 (322; 346) (*n*=22)	0.981	0.327
	C3	332 (310; 360) (*n*=17)	334 (316; 342) (*n*=21)	0.107	0.915
	C4	336 (320; 359) (*n*=16)	330 (312; 354) (*n*=22)	0.322	0.748
	Cz	338 (320; 362) (*n*=17)	330 (308; 342) (*n*=21)	0.881	0.378
	F3	330 (320; 354) (*n*=17)	336 (322; 350) (*n*=22)	0.147	0.883
	F4	338 (320; 356) (*n*=17)	330 (314; 344) (*n*=22)	0.935	0.350
	Fz	349 (322; 361) (*n*=18)	335 (318; 342) (*n*=22)	1.390	0.165
Amplitude (μV)					
N100	P3	5.04 (3.61; 6.82) (*n*=17)	3.60 (1.59; 6.26) (*n*=22)	1.742	0.082
	P4	5.12 (2.08; 6.18) (*n*=16)	4.54 (2.50; 5.93) (*n*=22)	0.169	0.866
	Pz	5.12 (2.58; 6.16) (*n*=16)	2.87 (1.30; 5.30) (*n*=22)	1.478	0.139
	C3	4.73 (2.81; 6.82) (*n*=17)	5.50 (3.26; 6.93) (*n*=21)	-0.628	0.530
	C4	6.15 (2.43; 7.74) (*n*=16)	5.93 (3.27; 7.47) (*n*=22)	-0.337	0.736
	Cz	6.99 (2.60; 9.12) (*n*=17)	6.16 (4.45; 7.60) (*n*=21)	0.123	0.902
	F3	3.70 (2.89; 6.99) (*n*=17)	5.22 (3.79; 6.46) (*n*=22)	-0.587	0.557
	F4	5.00 (3.21; 7.79) (*n*=17)	6.42 (3.89; 7.79) (*n*=22)	-0.666	0.506
	Fz	5.15 (3.40; 7.09) (*n*=18)	5.54 (2.87; 8.230(*n*=22)	-0.414	0.679
P200	P3	2.73 (2.20; 3.44) (*n*=17)	1.63 (0.87; 3.56) (*n*=22)	1.303	0.193
	P4	2.49 (0.84; 3.22) (*n*=16)	1.89 (0.67; 2.70) (*n*=22)	0.567	0.571
	Pz	2.44 (1.45; 3.51) (*n*=16)	1.82 (0.84; 3.36) (*n*=22)	0.902	0.367
	C3	2.38 (1.59; 4.29) (*n*=17)	1.70 (0.40; 2.90) (*n*=21)	1.390	0.165
	C4	3.20 (1.68; 4.21) (*n*=16)	1.48 (0.91; 2.60) (*n*=22)	2.728	0.006
	Cz	3.24 (2.19; 5.89) (*n*=17)	2.57 (1.65; 3.68) (*n*=21)	1.502	0.133
	F3	2.66 (1.84; 4.61) (*n*=17)	1.53 (0.66; 3.93) (*n*=22)	1.894	0.058
	F4	3.72 (2.02; 4.73) (*n*=17)	2.13 (0.87; 3.27) (*n*=22)	1.898	0.058
	Fz	4.14 (2.88; 5.17) (*n*=18)	1.63 (0.65; 3.92) (*n*=22)	2.927	0.003
P300	P3	7.21 (5.88; 8.87) (*n*=17)	7.98 (4.99; 10.07) (*n*=22)	-0.878	0.380
	P4	6.82 (4.88; 8.76) (*n*=16)	7.40 (5.53; 11.46) (*n*=22)	-0.674	0.500
	Pz	7.41 (5.98; 9.41) (*n*=16)	8.40 (5.81; 11.82) (*n*=22)	-0.887	0.375
	C3	7.55 (5.03; 9.20) (*n*=17)	6.31 (4.78; 10.35) (*n*=21)	-0.207	0.836
	C4	7.15 (4.80; 9.51) (*n*=16)	7.01 (5.06; 9.34) (*n*=22)	-0.092	0.927
	Cz	8.39 (6.33; 11.14) (*n*=17)	7.43 (5.22; 10.84) (*n*=21)	0.602	0.547
	F3	6.34 (4.52; 8.44) (*n*=17)	6.09 (4.69; 8.89) (*n*=22)	-0.198	0.843
	F4	6.57 (3.87; 8.50) (*n*=17)	6.90 (4.54; 8.880) (*n*=22)	-0.227	0.821
	Fz	8.46 (5.86; 9.87) (*n*=18)	7.94 (6.18; 10.83) (*n*=22)	-0.237	0.813

Note: The description is made with the indication of the median (Q1; Q3). P, C, F — parietal, central and frontal location of electrodes; (F3, C3, P3) — quantitative parameters of evoked potentials on the electrodes of the left hemisphere; (F4, C4, P4) — on the right hemisphere; (Fz, Cz, Pz) — on the central electrodes.

Table 2. Parameters of evoked potentials to standard stimulus in individuals with PTSD versus the values in the control group

Component	Lead	PTSD	Control	Z	*p*
Latent period (ms)					
N100	P3	120 (108; 128) (*n*=17)	116 (110; 122) (*n*=22)	0.609	0.543
	P4	120 (102; 124) (*n*=16)	114 (102; 120) (*n*=22)	0.939	0.347
	Pz	122 (103; 127) (*n*=16)	115 (108; 122) (*n*=22)	0.828	0.408
	C3	119 (111; 129) (*n*=17)	116 (112; 124) (*n*=21)	0.429	0.668
	C4	120 (112; 124) (*n*=16)	116 (110; 120) (*n*=22)	0.828	0.408
	Cz	122 (112; 126) (*n*=17)	116 (110; 120) (*n*=21)	1.218	0.223
	F3	120 (112; 128) (*n*=17)	116 (112; 122) (*n*=22)	0.680	0.497
	F4	118 (114; 124) (*n*=17)	116 (108; 124) (*n*=22)	0.722	0.470
	Fz	122 (114; 126) (*n*=18)	118 (114; 124) (*n*=22)	0.665	0.506
P200	P3	188 (182; 206) (*n*=17)	192 (180; 204) (*n*=22)	-0.949	0.343
	P4	186 (172; 192) (*n*=16)	182 (168; 216) (*n*=22)	-0.381	0.703
	Pz	186 (181; 204) (*n*=16)	192 (180; 222) (*n*=21)	-0.889	0.374
	C3	185 (178; 194) (*n*=17)	187 (180; 204) (*n*=21)	-0.695	0.487
	C4	187 (171; 199) (*n*=16)	183 (176; 194) (*n*=22)	-0.191	0.849
	Cz	186 (176; 198) (*n*=17)	184 (176; 194) (*n*=21)	-0.042	0.966
	F3	184 (176; 192) (*n*=17)	182 (174; 204) (*n*=22)	-0.269	0.788
	F4	174 (168; 198) (*n*=17)	174 (170; 192) (*n*=22)	-0.368	0.713
	Fz	180 (172; 192) (*n*=18)	177 (170; 196) (*n*=22)	0.429	0.668
P300	P3	282 (270; 296) (*n*=17)	277 (264; 294) (*n*=22)	0.326	0.745
	P4	282 (264; 288) (*n*=16)	280 (262; 300) (*n*=22)	-0.558	0.577
	Pz	284 (267; 298) (*n*=16)	284 (264; 308) (*n*=22)	-0.177	0.859
	C3	285 (269; 303) (*n*=17)	287 (270; 310) (*n*=21)	0.015	0.988
	C4	286 (270; 299) (*n*=16)	278 (266; 294) (*n*=22)	0.506	0.613
	Cz	290 (274; 304) (*n*=17)	277 (268; 294) (*n*=21)	0.552	0.581
	F3	298 (280; 326) (*n*=17)	282 (274; 308) (*n*=22)	0.763	0.445
	F4	292 (268; 310) (*n*=17)	286 (270; 320) (*n*=22)	-0.227	0.821
	Fz	298 (285; 327) (*n*=18)	288 (272; 314) (*n*=22)	0.990	0.322
Amplitude (μV)					
N100	P3	3.85 (2.42; 4.72) (*n*=17)	4.34(3.10; 5.49) (*n*=22)	-1.147	0.251
	P4	3.40 (1.95; 4.71) (*n*=16)	3.97(3.02; 4.90) (*n*=22)	-1.453	0.146
	Pz	3.41 (1.73; 6.10) (*n*=16)	4.40(3.24; 5.30) (*n*=22)	-1.123	0.261
	C3	4.08 (2.72; 6.37) (*n*=17)	5.14(4.46; 7.73) (*n*=21)	-1.360	0.174
	C4	4.26 (3.08; 6.98) (*n*=16)	5.49(4.35; 6.82) (*n*=22)	-1.410	0.158
	Cz	5.29 (3.36; 7.55) (*n*=17)	5.51(4.04; 7.44) (*n*=21)	-0.765	0.444
	F3	3.65 (2.34; 5.51) (*n*=17)	5.13 (4.10; 7.17) (*n*=22)	-1.855	0.064
	F4	3.60 (2.32; 8.35) (*n*=17)	5.93 (4.11; 7.42) (*n*=22)	-1.301	0.193
	Fz	3.85 (2.42; 4.72) (*n*=18)	4.34 (3.10; 5.49) (*n*=22)	-1.147	0.251
P200	P3	1.26 (0.77; 1.99) (*n*=17)	1.99 (0.93; 3.15) (*n*=22)	-1.473	0.141
	P4	1.68 (0.86; 2.28) (*n*=16)	1.52 (0.62; 2.66) (*n*=22)	-0.061	0.951
	Pz	1.55 (0.91; 2.26) (*n*=16)	2.01 (0.96; 3.06) (*n*=22)	-0.659	0.510
	C3	1.17 (0.50; 1.94) (*n*=17)	1.90 (0.49; 3.41) (*n*=21)	-1.138	0.255
	C4	1.28 (0.77; 2.05) (*n*=16)	2.00 (1.10; 2.98) (*n*=22)	-1.544	0.123
	Cz	1.65 (1.00; 2.73) (*n*=17)	2.42 (0.65; 3.86) (*n*=21)	-0.991	0.322
	F3	1.30 (0.64; 2.10) (*n*=17)	1.55 (0.96; 3.31) (*n*=22)	-1.416	0.157
	F4	1.21 (0.88; 1.91) (*n*=17)	2.09 (1.34; 2.85) (*n*=22)	-2.068	0.039
	Fz	1.27 (0.61; 2.34) (*n*=18)	2.22 (0.99; 3.24) (*n*=22)	-1.744	0.081
P300	P3	3.02 (1.54; 3.56) (*n*=17)	2.63 (1.90; 4.34) (*n*=22)	-0.156	0.876
	P4	2.72 (1.80; 3.60) (*n*=16)	2.50 (1.83; 3.25) (*n*=22)	0.382	0.703
	Pz	2.77 (1.95; 4.22) (*n*=16)	2.69 (1.94; 4.83) (*n*=22)	-0.325	0.745
	C3	2.67 (1.74; 3.94) (*n*=17)	2.93 (1.91; 4.43) (*n*=21)	-0.443	0.657
	C4	2.38 (1.58; 3.90) (*n*=16)	3.07 (2.00; 3.81) (*n*=22)	-0.353	0.724
	Cz	2.27 (1.50; 4.78) (*n*=17)	3.09 (2.05; 4.04) (*n*=21)	-0.496	0.620
	F3	2.04 (1.57; 3.25) (*n*=17)	2.76 (1.87; 4.08) (*n*=22)	-0.705	0.481
	F4	1.94 (1.31; 2.76) (*n*=17)	2.62 (1.59; 3.53) (*n*=22)	-0.595	0.552
	Fz	2.02 (1.61; 3.56) (*n*=18)	2.99 (1.76; 4.57) (*n*=22)	-1.404	0.160

Note: The description is made with the indication of the median (Q1; Q3). P, C, F — parietal, central and frontal location of electrodes; (F3, C3, P3) — quantitative parameters of evoked potentials on the electrodes of the left hemisphere; (F4, C4, P4) — on the right hemisphere; (Fz, Cz, Pz) — on the central electrodes.

Table 3. Parameters of mismatch negativity in individuals with PTSD versus the values in the control group

Component	Lead	PTSD	Control	Z	*p*
Latent period (ms)					
Neutral video sequence	P3	189 (157; 220) (*n*=16)	169 (158; 211) (*n*=20)	0.446	0.656
	P4	189 (171; 209) (*n*=16)	174 (158; 212) (*n*=21)	0.644	0.520
	Pz	187 (165; 215) (*n*=16)	173 (160; 230) (*n*=20)	0.350	0.726
	C3	178 (160; 212) (*n*=16)	176 (162; 248) (*n*=19)	-0.116	0.908
	C4	181 (162; 199) (*n*=16)	168 (150; 178) (*n*=22)	1.176	0.240
	Cz	186 (169; 192) (*n*=16)	172 (160; 238) (*n*=20)	0.927	0.354
	F3	204 (171; 227) (*n*=16)	163 (158; 184) (*n*=20)	1.719	0.086
	F4	192 (165; 226) (*n*=16)	169 (157; 212) (*n*=22)	0.939	0.348
	Fz	176 (155; 229) (*n*=16)	174 (160; 244) (*n*=19)	-0.497	0.619
Negative video sequence	P3	188 (174; 236) (*n*=15)	170 (154; 183) (*n*=20)	2.136	0.033
	P4	184 (174; 240) (*n*=15)	169 (154; 201) (*n*=21)	1.718	0.086
	Pz	178 (160; 186) (*n*=15)	174 (158; 186) (*n*=22)	0.274	0.784
	C3	178 (158; 220) (*n*=15)	171 (159; 180) (*n*=19)	1.212	0.225
	C4	178 (162; 186) (*n*=16)	164 (154; 181) (*n*=22)	1.140	0.254
	Cz	178 (168; 184) (*n*=16)	168 (159; 183) (*n*=21)	1.126	0.260
	F3	178 (162; 182) (*n*=15)	172 (163; 180) (*n*=22)	0.505	0.613
	F4	176 (162; 182) (*n*=15)	168 (157; 176) (*n*=22)	0.852	0.394
	Fz	176 (164; 182) (*n*=16)	169 (162; 185) (*n*=20)	0.548	0.583
Amplitude (μV)					
Neutral video sequence	P3	2.64 (1.47; 5.36) (*n*=16)	2.64 (1.10; 3.54) (*n*=20)	0.891	0.373
	P4	3.32 (2.17; 4.63) (*n*=16)	2.13 (1.61; 2.64) (*n*=21)	1.931	0.053
	Pz	3.48 (2.17; 5.17) (*n*=16)	2.61 (0.70; 3.40) (*n*=20)	1.608	0.108
	C3	4.30 (2.55; 5.72) (*n*=16)	2.35 (0.91; 4.69) (*n*=19)	1.490	0.136
	C4	3.63 (2.36; 4.83) (*n*=16)	2.99 (1.60; 4.39) (*n*=22)	1.043	0.297
	Cz	3.75 (2.18; 5.15) (*n*=16)	4.13 (2.25; 5.21) (*n*=20)	0.099	0.921
	F3	4.69 (3.45; 6.50) (*n*=16)	3.56 (1.23; 5.05) (*n*=20)	2.006	0.045
	F4	3.74 (2.38; 6.22) (*n*=16)	3.40 (1.60; 4.82) (*n*=22)	1.114	0.265
	Fz	5.86 (3.92; 7.99) (*n*=16)	3.26 (1.31; 5.43) (*n*=19)	2.980	0.003
Negative video sequence	P3	1.38 (0.60; 3.15) (*n*=15)	2.07 (0.58; 3.33) (*n*=20)	-0.202	0.840
	P4	2.12 (1.10; 3.45) (*n*=15)	1.97 (0.78; 2.74) (*n*=21)	0.058	0.954
	Pz	2.84 (1.72; 4.35) (*n*=15)	2.21 (1.27; 3.20) (*n*=22)	1.472	0.141
	C3	3.05 (1.92; 6.10) (*n*=15)	2.53 (1.24; 3.81) (*n*=19)	1.184	0.237
	C4	2.85 (0.54; 4.16) (*n*=16)	1.59 (0.82; 3.21) (*n*=22)	0.606	0.544
	Cz	2.38 (1.72; 4.70) (*n*=16)	2.42 (1.13; 4.38) (*n*=21)	0.419	0.676
	F3	4.10 (1.54; 7.02) (*n*=15)	2.56 (1.85; 4.77) (*n*=22)	1.328	0.184
	F4	2.93 (1.88; 4.80) (*n*=15)	2.72 (1.49; 4.80) (*n*=22)	0.318	0.751
	Fz	4.57 (1.80; 5.63) (*n*=16)	3.29 (1.86; 5.02) (*n*=20)	0.346	0.729

Note: The description is made with the indication of the median (Q1; Q3). P, C, F — parietal, central, and frontal location of the electrodes; (F3, C3, P3) — quantitative parameters of evoked potentials on the electrodes of the left hemisphere; (F4, C4, P4) — on the right hemisphere; and (Fz, Cz, Pz) — on the central electrodes. Neutral video sequence — images of nature, negative video sequence — photographs of military operations.

Table 4. Independent PTSD predictors: binary logistic regression model

Parameter	Lead	B	Standard error	Wald test	*p*
Latent period N100	P3	0.027	0.036	0.569	0.451
Latent period N100	P4	-0.033	0.073	0.203	0.653
Latent period P200	P3	-0.037	0.025	2.126	0.145
Latent period N100	C3	0.058	0.074	0.625	0.429
Amplitude P200	P4	-0.185	0.318	0.340	0.560
Amplitude P200	Fz	0.492	0.306	2.586	0.108
Latent period MMN, negative video sequence	C4	0.175	0.140	1.555	0.212
Amplitude MMN, neutral video sequence	Fz	-0.081	0.100	0.663	0.415
Constant	-	-12.348	5.561	4.930	0.026

Note: Statistical characteristics of the model: log likelihood value of the regression model 32.580, Nagelkerke R2— 72.5%.

Predicted conditions were classified using a multifactorial model on the data of 16 people in the PTSD group and 21 in the control group, for whom the data of all independent predictors included in the model were known (data for some parameters were missing for 2 people in the PTSD group and 1 in the control group due to the removal of artifact channels). The classification accuracy was 86% (32 conditions out of 37 observations were correctly classified). The classification results are shown in Table 5.

The high percentage of correct matches proves that the chosen study design allows one to identify the information processing characteristics in individuals with PTSD. This experimental design with the specified predictors can be used as the basis for a diagnostic model.

Table 5. Classification table of the binary logistic regression model for the diagnosis of PTSD

Observed condition	Predicted condition		Correct classification, %
	Control	PTSD	
Control, abs.	19	2	91
PTSD, abs.	3	13	81

Note: Statistical characteristics of the discriminant model: chi-square 18.036, p=0.021.

DISCUSSION

Key results

The study that included different paradigms for recording auditory-evoked potentials revealed the characteristics of individuals with PTSD in the active paradigm: the most pronounced changes were found in the parameters of the N100 component; i.e., in PTSD patients, the amplitude was reduced and the latent period for the deviant stimulus was shortened versus the standard one. The P200 component in PTSD patients is characterized by an increased amplitude and latency period for a deviant stimulus, and a reduced amplitude for the standard stimulus. There were no significant differences in the parameters of the P300 component. In the passive paradigm, it was found that in the PTSD group, the latent period of MMN when presented with a negative video sequence, and the amplitude when presented with a neutral video sequence, was higher than in the control group

Limitations

A key limitation of the study is its small sample size. In this regard, it can be noted that the lack of statistically significant differences between the compared groups in certain parameters, particularly the P300 component, is indicative of a low information content. In addition, it is known that in small samples random factors have a greater influence on the identification of differences/associations than in studies with larger sample sizes. The use of mentally healthy individuals as controls is also an important limitation of the study, but this type of study constitutes a significant portion of the research on combat-related PTSD [1, 9, 35].

Another important limitation of the present study is the lack of comparison groups (persons with depression, generalized anxiety disorder), which could help assess the sensitivity of the proposed experimental design. Moreover, it seems relevant to test the diagnostic model on individuals who participated in combat but do not exhibit clinical symptoms of PTSD.

Validation of the model in such groups is a prerequisite for its clinical application.

The use of ANOVA for EEG data analysis assumes a normal distribution of the parameters, given the nature of the signal. However, applying parametric statistical methods to data with a skewed distribution is a limitation, as the discriminant function in this case reflects the properties of a specific sample rather than the general population [36].

Interpretation of the main study results

Differences have been identified that indicate impairment of the early components of auditory-evoked potentials in individuals with PTSD. The extended latency of the N100 component in response to a deviant stimulus is linked to the severity of the cognitive impairment in PTSD patients [37; 38; 39], the risk of psychotic symptoms [35], and the number of subconcussive impacts on the brain [40], potentially resulting from combat participation. The increased amplitude of the P200 component observed in PTSD patients is similar to that seen in attention deficit hyperactivity disorder and reflects insufficient inhibitory mechanisms [41], and the extended latent period of P200 suggests impaired stimulus recognition [42]. However, no differences were found in the P300 component parameters, which relate to attention efficiency, psychomotor functions, and the ability to plan and control goal-directed behavior [24]. The absence of differences in the P300 component may be associated with disease progression: PTSD symptoms may worsen after the end of combat participation, with reduced amplitude and increased latency correlating with symptom deterioration, and vice versa [22]. The study group had an average of 50 days from the end of combat participation, and changes in the later stages of evoked potentials may occur over a longer period. When developing a diagnostic model based on these parameters, it is necessary to consider the length of time after the trauma.

The limited number of significant differences in the parameters when presenting trauma-related videos is noteworthy. A recent meta-analysis comparing studies using affective and neutral paradigms showed that individuals with PTSD allocate more resources when faced with threatening stimuli (evidenced by an increased amplitude of early components), but they exhibit impairments in working memory updating (shown by extended latency and a decreased P300 amplitude) when exposed to non-affective information. However, this review included various types of PTSD while the affective stimuli in most studies were images (such as facial emotions) not specifically associated with trauma [35]. This limited number of differences may necessitate adjustments in the study design.

The differences in the components of auditory-evoked potentials identified in the pilot study when used as predictors in the classification model show high accuracy (87%: sensitivity — 81%, specificity — 91%). The use of the parameters obtained in three different stimulus presentation paradigms (active, passive with the presentation of video sequences: with content related to the traumatic event and not related) allows one to expand the diagnostic capabilities of the auditory-evoked potential method.

Generalizability

The evoked-potential performance is highly influenced by the amplifier characteristics, software, and examination settings. To use EP parameters as biomarkers, it is necessary to recruit a control group using the same amplifier, the same conditions, and identical settings and stimulus characteristics.

This pilot study identified potential targets for the diagnostic model, but it does not have sufficient bandwidth to be used as an off-the-shelf diagnostic tool due to these limitations.

CONCLUSION

Potential neurophysiological markers of combat-related PTSD within up to 120 days after the end of combat participation are the amplitude and latency of the early components of auditory-evoked potentials (N100 and P200) and the amplitude of the MMN phenomenon. A diagnostic model using a set of parameters in various stimulus presentation paradigms can be instrumental in diagnosing PTSD.

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