

Auditory Steady-State Evoked Potentials in Post Traumatic Stress Disorder: Introduction of a Potential Biomarker

Gila Pirzad Jahromi¹, Hossein Gharaati Sotoudeh^{2,3}, Romina Mostafaie^{3,4}, Ali Khaleghi^{5,6*}

Abstract

Objective: The lack of steady-state evoked potential (SSEP) studies on post-traumatic stress disorder (PTSD) has led to undiscovered useful information about the pathophysiology of the disorder. Thus, we explored SSEP patterns in PTSD patients during a stop-signal task to disclose possible impairments in these informative brain potentials.

Method: 25 adult patients with PTSD and 25 healthy adults participated in this research. Subjects were assessed with electroencephalography while the tone signal stimuli at 40 Hz were used to evoke SSEPs and subjects performed a stop-signal task. The amplitude and phase of SSEPs were then computed in different brain regions. The subjects were also evaluated using the Mississippi PTSD questionnaire. Appropriate statistical methods such as repeated measure ANOVA were used to compare the two groups, and the correlation between SSEPs and clinical symptoms was assessed using Pearson correlation analysis.

Results: Patients showed considerably poorer performance in the cognitive task ($P < 0.01$), accompanied by raised SSEP phase and amplitude in the anterior and midline regions compared to healthy controls ($P < 0.05$). The Mississippi total score was positively correlated with the SSEP amplitude in the midline region ($r = 0.62$, $P < 0.05$). Furthermore, based on ROC analysis, the SSEP amplitude in the midline region provided an excellent AUC value ($AUC = 0.850$) for distinguishing patients with PTSD from normal subjects.

Conclusion: Current findings suggest that abnormalities in the anterior and midline cortical neural networks are involved in the pathophysiology of PTSD. Importantly, midline abnormalities may provide a clinically-relevant measure for researchers wishing to assess the use of biomarkers for early diagnosis of PTSD as well as to evaluate new therapeutic and management approaches in the treatment of PTSD.

Key words: Biomarker; Electroencephalography; Pathophysiology; Post-Traumatic Stress Disorder

1. Neuroscience Research Centre, Baqiyatallah University of Medical Sciences, Tehran, Iran.
2. Roozbeh Hospital, Tehran University of Medical Sciences, Tehran, Iran.
3. Department of Psychology, Faculty of Psychology, Central Tehran Branch, Islamic Azad University, Tehran, Iran.
4. Aknoon Institute of Psychology, Tehran, Iran.
5. Psychiatry and Psychology Research Center, Tehran University of Medical Sciences, Tehran, Iran.
6. Department of Psychology, University of Religions and Denominations, Qom, Iran.

*Corresponding Author:

Address: Roozbeh Hospital, Psychiatry and Psychology Research Center, Tehran, Iran., Postal Code: 1333715914.
Tel: 9821 55422002, Fax: 9821 55421959, Email: alikhaleghi_bme84@yahoo.com

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Dangerous traumatic happenings such as combat and natural disasters may cause serious mental health problems. Evidence indicates that more than 21% of veterans who have experienced war, as well as survivors of natural disasters such as floods and earthquakes, are suffering from post-traumatic stress disorder (PTSD) (1, 2). Patients with PTSD experience reliving trauma, hyperarousal and hypervigilance, and behavioral and cognitive avoidance symptoms (3). However, many patients with PTSD are not identified immediately after exposure to trauma but become apparent a few months later, indicating postponed-onset stress reactions (4). The postponed-onset emphasizes the need for highly accurate approaches to early diagnosis of PTSD. Meanwhile, early signs of change in mental health status can help identify people at risk and evaluate the treatment process (5).

Currently, the diagnosis and assessment of PTSD is based on psychiatric interviews and self-reported instruments. Although these measures are largely reliable and standardized, their accuracy depends upon the correctness of patient reports, due to the subjective nature of such assessments. Furthermore, vulnerable individuals such as military staff are likely to understate their psychological symptoms because of concerns about job status, self-image, etc. (6). In such circumstances, developing physiological and biological tools to objectively detect alterations in mental health would be an important approach for early diagnosis and better management of PTSD (7). Previous studies have shown that various brain regions (such as the prefrontal cortex, amygdala, and limbic system) and neurotransmitters (such as catecholamines) are affected by PTSD (8-10). In the meantime, some studies have linked brain disorders in PTSD with cognitive processing deficits and have suggested neurophysiological-based biomarkers for the diagnosis and monitoring of this disorder (1, 5, 11, 12). However, previous research has relied more on anatomical rather than functional information.

The brain is the main organ of stress reactions, and electrophysiological tools that directly measure brain activity (e.g., electroencephalography (EEG) and evoked potentials) achieve valuable information about the neural mechanisms involved in neuropathology and psychopathology (13-20). Although the ongoing EEG contains useful information about brain activity, the findings of previous resting-state electrophysiological studies of PTSD have been either inconsistent or lacking sufficient reliability to qualify as a biomarker (21). Thus, EEG studies of PTSD have mostly focused on event-related potentials (ERPs), especially the P300. The P300 has been shown to be a reliable index for the diagnosis and monitoring of PTSD, providing important insight into the working memory and attentional processes that are impaired in this disorder (22, 23). However, it should be noted that ERP components have a small amplitude compared to background EEG, and the general strategy

for extracting these components is to average a large number of signals recorded during consecutive trials. This not only requires time and special recording equipment (for synchronizing the recorded signal), but also can introduce confounding variables (such as subject fatigue and the appearance of functional differences between the recorded trials) into the experiment (24). On the other hand, steady-state evoked potentials (SSEPs) are highly resistant to artifacts and have a large signal to noise ratio. SSEPs are induced in the background EEG through alternating stimulations with a frequency higher than 10 Hz, and due to their relatively large amplitude, there is no need to use averaging methods to extract them; they can be used directly. This can shorten the experiment time and thus reduce the probability of error. In addition, this characteristic makes SSEPs robust against blinking, eye movements, and myogram-induced interference (25, 26). SSEPs have been investigated in major psychiatric disorders such as depression (27), bipolar disorder (28), schizophrenia (29), and attention deficit/hyperactivity disorder (30) and have yielded interesting findings about the brain function in these patients. However, to the best of our knowledge, despite the evidence of brain dysfunction and cognitive deficits in PTSD, these valuable potentials have not yet been used to investigate and evaluate the brain function of PTSD patients. Therefore, in this study, we designed an experiment to investigate auditory steady-state responses during a stop-signal task in adult patients with PTSD. Our hypothesis is that these brain responses can not only provide new information regarding the underlying neuropathology of PTSD, but may introduce a new biomarker with high reliability for the diagnosis and management of this disorder.

Materials and Methods

Participants

Subjects included 25 patients with PTSD (20 men, 5 women; mean age of 42.13 ± 16.11 years) and 25 healthy controls (22 men, 3 women; mean age of 40.25 ± 13.64 years). Patients were selected from two private psychiatric clinics in Tehran. All patients were unmedicated patients diagnosed with PTSD by an experienced psychiatrist via clinical interviews based on the DSM-5 criteria (31). In addition, healthy subjects were recruited through notification from available people in the local community. They were evaluated through clinical interviews. Exclusion criteria were defined as the presence of any major neurological or mental illness, severe head damage, drug or alcohol abuse, mental retardation, hearing or learning disabilities. All individuals were right-handed, as identified through the Edinburgh Handedness Inventory. After becoming familiar with the research process, all the subjects gave their informed written consent for participating in the study. This research was confirmed

by the Ethics Committee of Baqiyatallah University of Medical Sciences.

Clinical Evaluation

The Mississippi PTSD questionnaire was used to evaluate PTSD symptoms in the patient group. It is a 35-item self-report scale to assess the severity of PTSD symptoms. Participants were instructed to rate their feeling about every question through five-point Likert categories. The Cronbach's alpha coefficient of this test is reported in the range of 0.86 to 0.94. This scale has also been validated in Iranian populations, with good to excellent test-retest reliability ($r = 0.91$) and internal consistency (Cronbach's alpha = 0.93) (32).

SSEPs Recording and Analysis

Participants were seated in a chair in a quiet environment during EEG recording. A custom program was designed in the MATLAB environment to present the stimulus and synchronize the data with the EEG. Auditory steady-state paradigm was utilized as a

stimulation pattern. This stimulation consisted of a sine wave at 40 Hz modulated by another sine wave at 1000 Hz. Auditory stimulations with a duration of 1.5 seconds and an inter-stimulus of 1 second were applied via headphones in a binaural manner. In fact, the auditory stimuli were stereo. Subjects were presented with a stop-signal task (picture of a car facing left or right) during EEG recording and receiving auditory stimulation. They have to press the right/left button depending on the direction of the front of the car. The picture of the car was fixed on the LED display for one second, followed by a one-second rest, after which the next trial began. The stop-signal was defined as a red bar next to the image of the car. Figure 1 depicts the schematic of the experimental procedure. A quarter of all trials were stop signals, and subjects had to press no button on these trials. Depending on the subjects' cooperation, at least 40 trials were recorded for each subject.

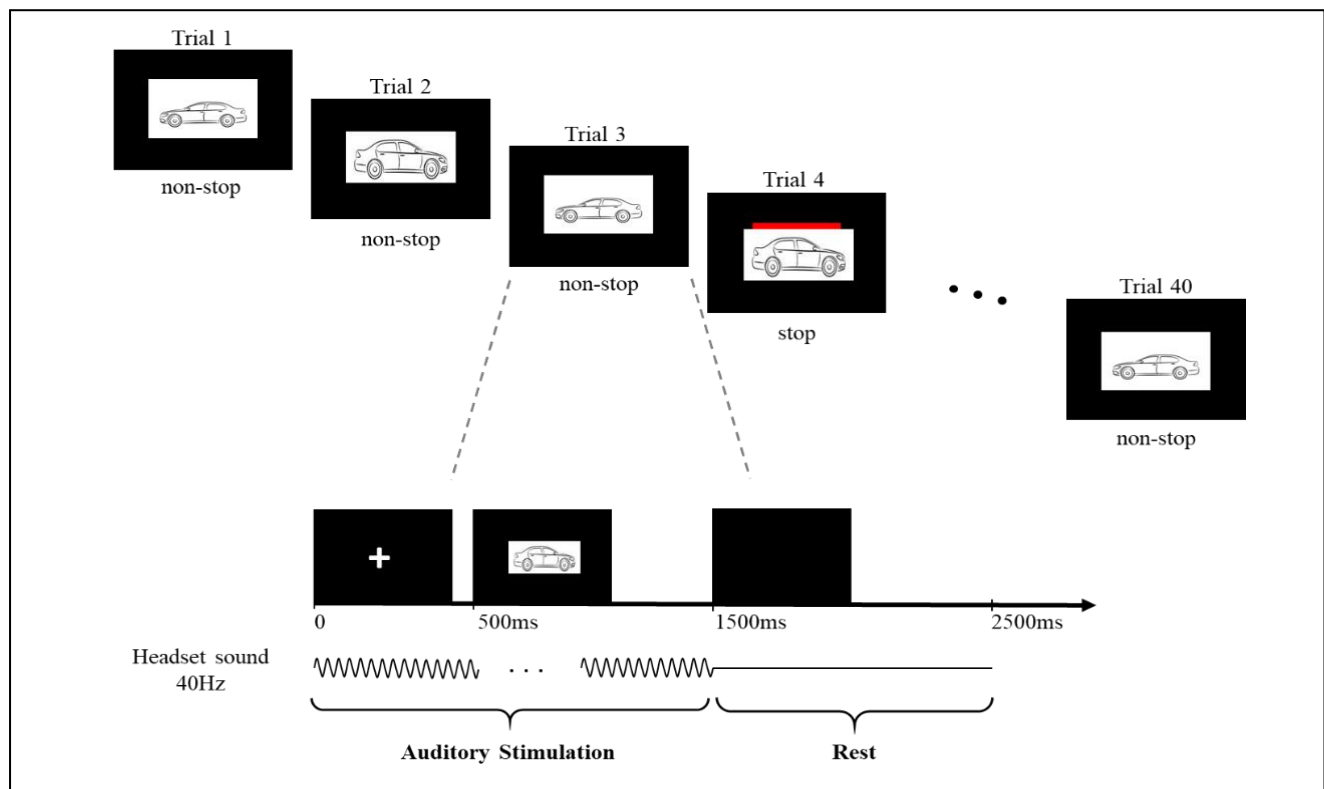


Figure 1. The Sequence of Stop-Signal Task with Auditory Stimulation and Visual Stop Signal. In Each Trial, a Car with Random Direction Was Shown after a Plus Sign. Then Subjects Were Asked to Press Left or Right Keys According to the Car Direction. In Quarter of all Trials, a Bold Red Line Was Presented Simultaneously with the Car Picture so that Subjects Should Avoid Pressing any Keys. In Each Trial, 40 Hz Tone Sound Was Used as Auditory Stimulation, Starting at the Beginning of the Trial and Lasting for 1500 ms until the Beginning of the Rest Time.

EEG signals were captured through a g.USBamp amplifier (Gtec Corp., Austria) with Ag/AgCl electrodes mounted on Fp1, Fp2, F3, Fz, F4, C3, Cz, C4, T3, T4,

P3, Pz, P4, O1, Oz, and O2 locations according to the 10-20 placement protocol. Reference electrode A1 was connected to the left earlobe. The impedances of the

electrodes were less than 10 kΩ. The EEG signal was recorded through a bandpass filter of 0.1 to 60 Hz with a sampling rate of 512 Hz.

Various steps were taken to extract the SSEPs, as described here. First, the data were divided by a rectangular window (length of 125 ms). The window with a step size of 25 ms was shifted on the signal for one-second trials. Then, we performed time averaging on these segments. In order not to reduce the amplitude of the potentials and not to lose their phase information, it was important that the time segments were synchronized in the averaging process. Therefore, we used an interpolation technique to up-sample the data by a factor of four to avoid the error of non-integer rates. Eventually, we applied Fast Fourier Transform (FFT) to compute the phase and amplitude of the SSEPs. Readers can refer to (28, 30, 33) for more information about the method of extracting SSEPs and calculating their amplitude and phase.

Statistical Analysis

Differences between groups in demographic and neuropsychological data were evaluated through independent t-test and Chi-squared test. Differences between groups in SSEP amplitude and phase were examined through repeated-measures analysis of variance (ANOVA) with brain regions (left hemisphere, right hemisphere, midline, anterior and posterior) as the within-subject factor (Table 1), and groups as the between-subject factor. Greenhouse–Geisser’s modification was conducted when necessary and adjusted P-values were presented. Pearson’s correlation coefficient was estimated for associations between SSEP amplitudes at electrode sites and clinical assessments in

the PTSD group. The significance of correlation coefficients was evaluated through Fisher’s transformation with t-statistics. P-values less than 0.5 were considered significant.

Table 1. Brain Regions Included in the Statistical Analysis of EEG Channels.

Brain Region	EEG Channels
Left hemisphere	Fp1, F3, C3, T3, P3, O1
Right hemisphere	Fp2, F4, C4, T4, P4, O2
Midline	Fz, Cz, Pz, Oz
Anterior	Fp1, Fp2, F3, Fz, F4
Posterior	P3, Pz, P4, O1, O2, Oz

Results

The basic information of the participants is presented in Table 2. As indicated, no significant difference was found between the age and gender of the two groups ($P > 0.05$). Moreover, the neuropsychological functions of the PTSD and control groups can be observed in Table 2. On average, throughout the stop-signal task with auditory stimuli, patients with PTSD exhibited a significantly higher reaction time, commission errors, and omission errors compared to normal subjects ($P < 0.01$). Also, normal individuals exhibited more correct responses than patients ($P = 0.014$).

Table 2. Basic and Neuropsychological Data and Comparison of Subjects with Post-Traumatic Stress Disorder (PTSD) with Healthy Individuals.

Variables	Groups		Group comparison	
	PTSD (n = 25) Mean ± SD	Healthy Control (n = 25) Mean ± SD		
Age (years)	42.13 ± 16.11	40.25 ± 13.64	t = 0.445	P = 0.658
Gender	20 men 5 women	22 men 3 wpmen	$\chi^2 = 0.59$	P = 0.440
Mississippi score	123.64 ± 21.76	52.12 ± 10.31	t = 14.85	P < 0.001
Reaction time (ms)	486.12 ± 94.76	412.36 ± 73.53	t = 3.075	P = 0.003
Correct responses (%)	36.67 ± 3.65	38.81 ± 2.14	t = 2.529	P = 0.014
Omission error (%)	3.44 ± 1.89	1.10 ± 0.62	t = 5.882	P < 0.001
Commission error (%)	1.37 ± 1.29	0.48 ± 0.51	t = 2.675	P = 0.002

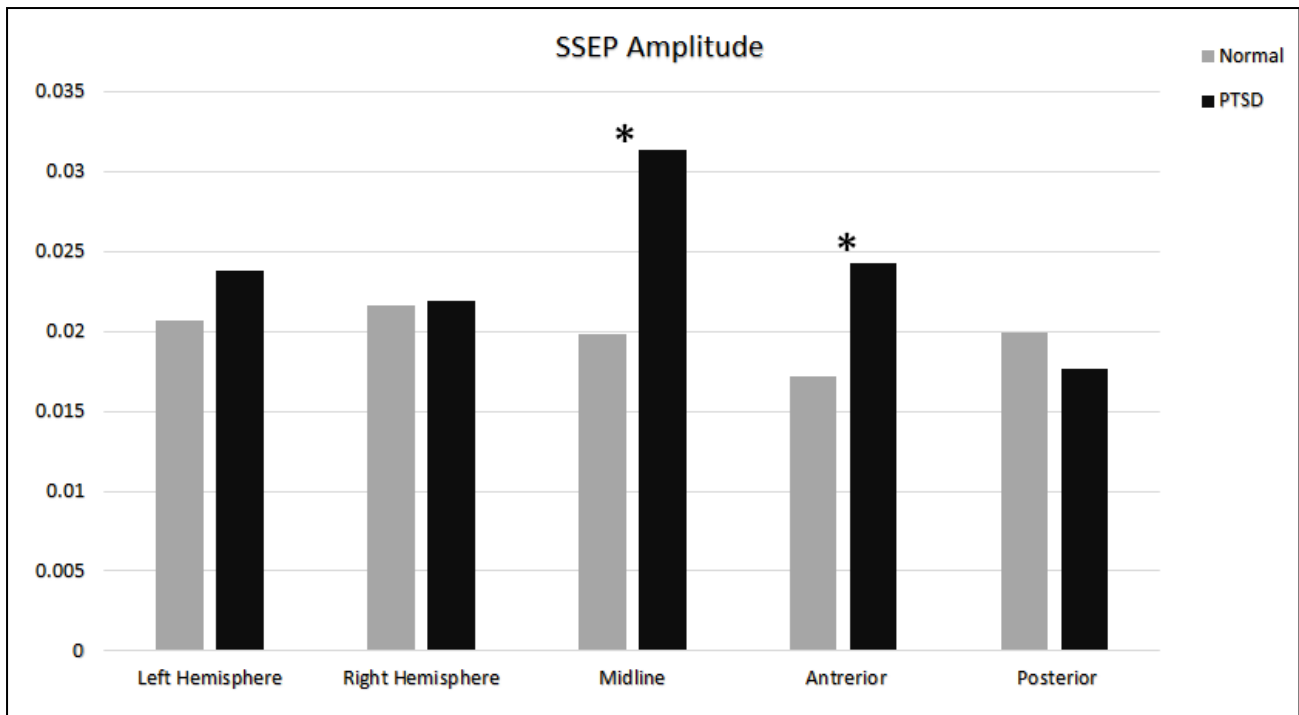


Figure 2. Comparison of the Amplitude of Steady-State Evoked Potential (SSEP) between Patients with Post-Traumatic Stress Disorder (PTSD) and Healthy Individuals.

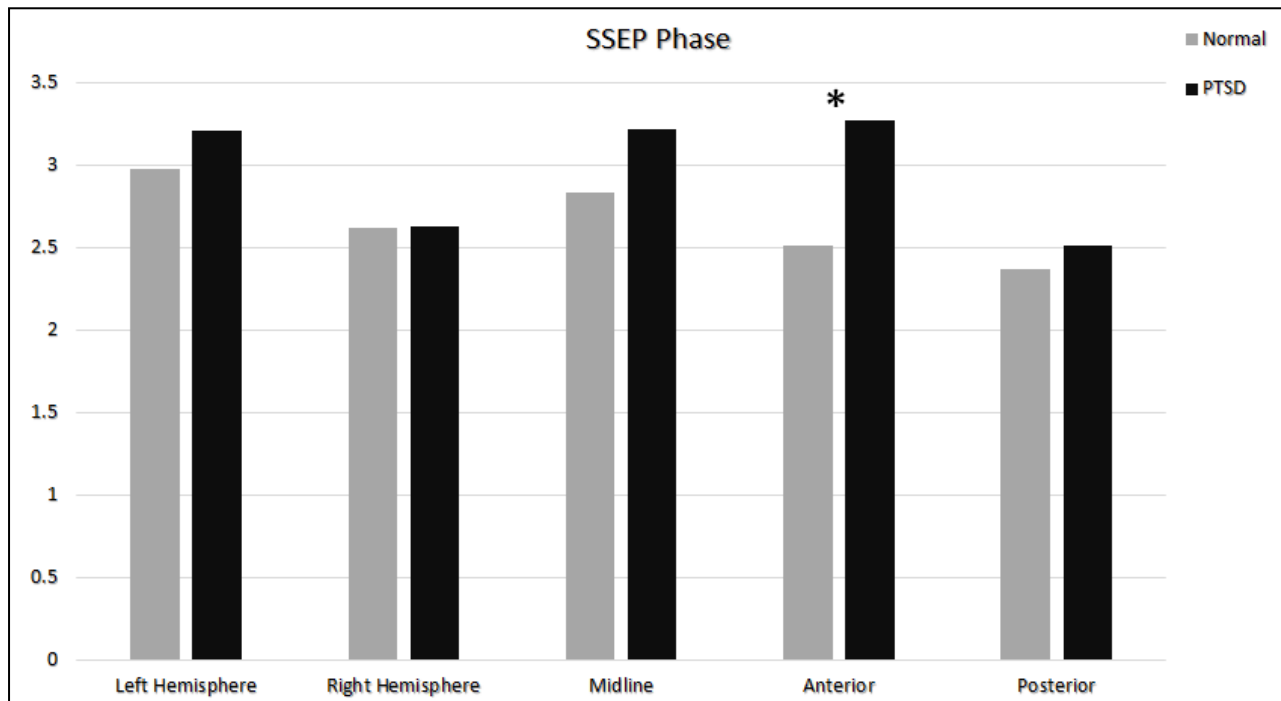


Figure 3. Comparison of the Phase of Steady-State Evoked Potential (SSEP) between Patients with Post-Traumatic Stress Disorder (PTSD) and Healthy Individuals.

Repeated measures ANOVA of SSEP amplitude of the brain as a whole indicated no difference between the groups [$F(1,48) = 1.642, P > 0.05$]. However, there was a significant difference between brain areas [$F(1,48) = 5.110, P < 0.01$]. Moreover, the interaction between the brain areas and the groups was significant [$F(1,48) = 4.232, P < 0.01$]. Post-hoc analysis indicated that the SSEP amplitude significantly increased in the patient group compared to the healthy control group in the middle and anterior brain regions ($P < 0.05$) (Figure 2). Furthermore, repeated measures ANOVA of SSEP phase of the brain as a whole indicated no difference between the groups [$F(1,48) = 1.436, P > 0.05$]. However, there was a significant difference between the brain areas [$F(1,48) = 3.911, P < 0.01$]. Post-hoc analysis indicated that the SSEP phase significantly increased in the patient

group compared to the healthy control group in the anterior brain region ($P < 0.05$) (Figure 3). Furthermore, ROC curves and AUC values of significant variables were computed and are displayed in Figure 4. As shown, the SSEP amplitude in the midline region provided an excellent AUC value ($AUC = 0.850$) for distinguishing patients with PTSD from normal subjects. According to the results of the ROC curve, the SSEP amplitude in the midline area had a sensitivity of 82.50% and a specificity of 81.8% for distinguishing patients with PTSD from normal individuals. In addition, a significant positive correlation was found between the SSEP amplitude in the midline region and the Mississippi total score for the PTSD group ($r = 0.62, P < 0.05$).

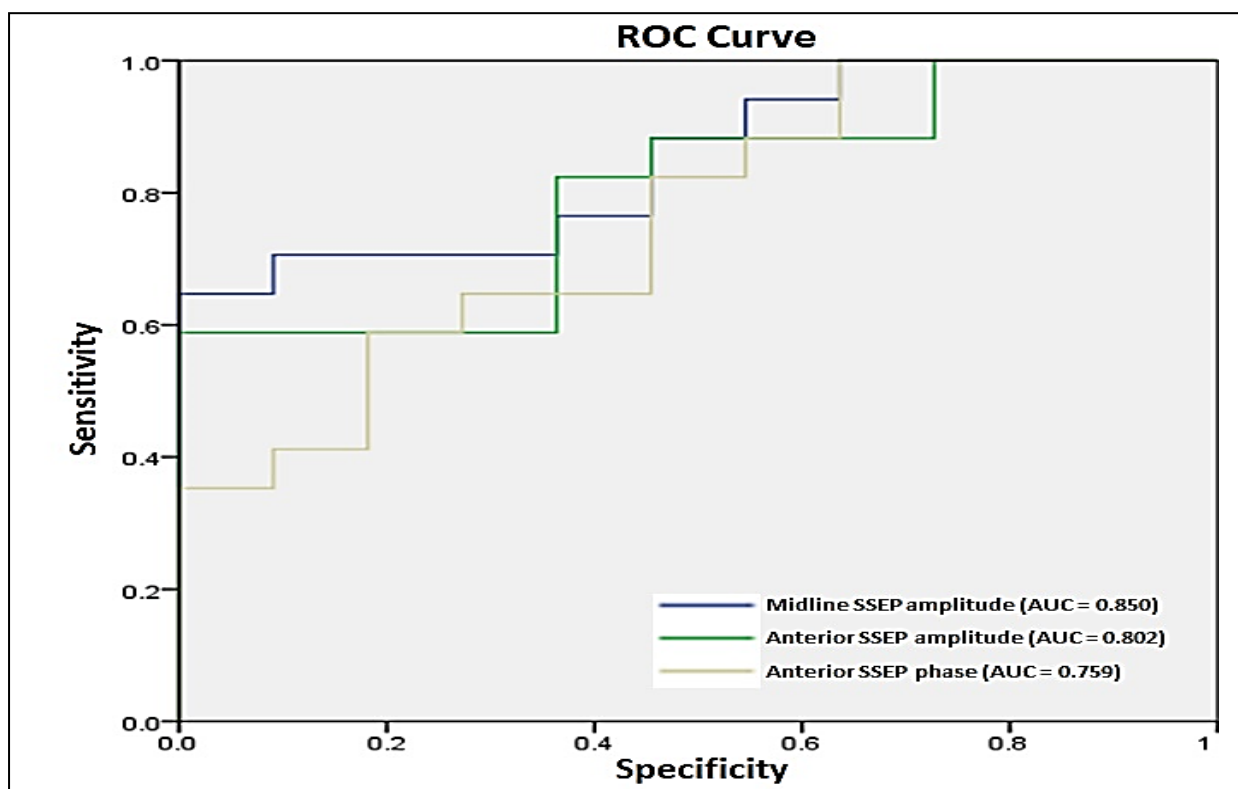


Figure 4. Receiver Operating Characteristic (ROC) Curves of Significant Variables for Discriminating Patients with PTSD from Normal Subjects.

Discussion

The current research evaluated the steady-state evoked potential in adult patients with PTSD compared to normal adults during a cognitive task. This stop-signal task was utilized to investigate motor response inhibition in the subjects. According to the results, the patient group showed poorer performance (i.e., more errors and less correct answers) than the control group. In general, more errors of omission and commission and slower reaction times may indicate inattention in patients with PTSD.

Electrophysiological examinations indicated some abnormalities in the midline and anterior cortices in PTSD patients. Indeed, the patient group tended to show higher amplitude and phase of SSEPs in response to 40 Hz stimulation than the healthy control group. A common theory about SSEPs suggests that SSEP amplitude and SSEP phase reflect cortical activity and information processing speed, respectively. According to this theory, there is an inverse relationship between the SSEP amplitude and the amount of cortical activity, as well as between the SSEP phase and the speed of information processing in synaptic processes (34-36).

Therefore, the increase of the SSEP amplitude in the patient group in the midline and anterior areas shows a lower cerebral cortex activity in these areas compared to the normal group. Additionally, the higher SSEP phase in the anterior region in the patient group suggests that the frontal region of PTSD patients may be disrupted and lead to impaired information processing functions compared to healthy individuals. This impairment and dysfunction in cortical activation and processing capacity during auditory stimulation in PTSD patients may be associated with the inability of the neural circuits in the frontal cortex to properly coordinate with periodic external stimulations when performing cognitive tasks. In addition, reduced activation of the anterior area, which plays an important role in various executive tasks including inhibitory control behaviors, may lead to performance deterioration in cognitive function. The findings observed from the stop signal task designed in this study support this view. Previous electrophysiological and neuropsychological research have also indicated a variety of impairments in neurocognitive functions in PTSD, such as deficits in attention, memory, learning abilities and executive functions (37, 38). In addition, reviewing neuroimaging findings in PTSD shows that the frontal lobe dysfunction is involved in cognitive and behavioral impairments of these patients (39).

40 Hz SSEP represents the neurons' propensity for the oscillation at gamma frequency resulted from periodical external stimulations (28, 30). The current observation of SSEP abnormalities may be related to N-methyl-D-aspartate receptor (NMDAR) and glutamatergic deficits in PTSD. NMDARs are critical for the neuroplasticity underlying memory and learning, and glutamatergic neurotransmission through NMDARs has been implicated in the pathophysiology of PTSD (40). Indeed, the loss of synaptic spines due to dysregulated levels of glutamate in PTSD may cause improper functioning of the cortical neural networks (41). With this in mind, dysregulated activity of NMDARs can result in irregular gamma oscillations, leading to SSEP deficits and, eventually, illness-dependent cognitive and behavioral malfunction in PTSD.

The main finding of most ERP studies regarding PTSD has been impaired midline electrophysiological activity (1, 42-44). A finding supported the use of SSEPs in this study. Therefore, it seems that the midline regions of the cerebral cortex play an important role in the pathophysiology of PTSD. Interestingly, the present study showed that this midline dysfunction is associated with PTSD symptoms. In fact, some symptoms of PTSD may be linked to a specific pattern of deficits and impairments in midline areas known to be involved in attention (45). Furthermore, according to the ROC analysis, abnormalities in this region can be used as a good potential biomarker for the diagnosis of patients with PTSD. Indeed, SSEPs abnormalities in the midline region may provide an appropriate objective measure for

the early detection of PTSD. However, such a finding is preliminary and needs to be confirmed in clinical settings through large population studies.

Limitation

Evaluating the cognitive capacity of the subjects using a valid and official cognitive test could provide a more comprehensive cognitive profile. However, the trade-off between the duration of the subject's assessment and more accurate evaluation using different tests led to the exclusion of such a task in the present study. In addition, visual stimulation may provide more information about the pathophysiology of this disorder, which was not used in this study. Furthermore, it is important to replicate the current research with larger preclinical and clinical populations. Indeed, this is a preliminary investigation to use steady-state evoked potentials to study PTSD patients, and more detailed analysis with a larger population may be necessary to introduce efficient diagnostic tools.

Conclusion

The present study is the first research to explore steady-state evoked potentials in PTSD. Current findings suggest that abnormalities in the anterior and midline cortical neural networks are involved in the pathophysiology of PTSD. Importantly, midline abnormalities may provide a clinically-relevant measure for researchers wishing to assess the use of biomarkers for early diagnosis of PTSD as well as to assess new therapeutic and management approaches in the treatment of PTSD. In addition, our findings may confirm the hypothesis of glutamatergic and NMDAR disturbances in PTSD.

Conflict of Interest

None.

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