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Original Research

Auditory Cognitive Impairment Reflects Source Localization of the P300 ERP Component in MBI Patients: The sLORETA Investigation

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Abstract

Objectives: This study aimed to investigate the differences between the source localization of the P300 event-related potential (ERP) component among the healthy and mild brain injury (MBI) patient population using standardized low-resolution electromagnetic tomography (sLORETA). **Methods**: Thirty-eight participants were divided into control (n = 19) and MBI (n = 19) groups. Control participants were normal, healthy people, and participants with MBI were assigned into two groups: MBI 1st Test (7 days after a road traffic accident (RTA)) and MBI 2nd Test (2–6 months after RTA with the same participants of the 1st Test group). The 128-ERP nets were used on the heads of the participants during the experiments. Under the auditory oddball paradigm, all participants silently counted the target tones, while ignoring the standard tones. This study used the sLORETA tool in the Net Station software for the source localization of the P300 ERP component. The Mann-Whitney U test was used to compare intensities between groups, while the Wilcoxon Signed-Rank test was applied for paired observations within groups. **Results**: Standard stimuli evoked P300 sources in the superior frontal gyrus (BA11) of the right frontal lobe in the control group, the superior temporal gyrus (BA38) of the right temporal lobe in the MBI 1st Test group, and the inferior frontal gyrus (BA47) of the left frontal lobe in the MBI 2nd Test group. Meanwhile, target stimuli evoked P300 sources at BA11 for all groups but in different gyrus: the superior frontal gyrus, orbital gyrus, and rectal gyrus in the control, MBI 1st Test, and MBI 2nd Test groups, respectively. In addition, there were significant differences in dipole intensities between and within groups among control and MBI patients in both standard and target stimuli. **Conclusion**: P300 source localization was shifted presumably due to the auditory cognitive impairment, and the dipole intensities were significantly higher in the MBI group than in the control group, indicating that the MBI group compensated for both standard and target tone stimuli, reflected in the sLORETA investigation.

Keywords: source localization; mild brain injury; cognitive processing; event-related potentials; neural compensation

1. Introduction

Mild brain injury (MBI) and mild traumatic brain injury (mTBI) are neurological disorders that significantly affect cognitive function [1]. Patients with MBI have a deficiency in attention, working memory, and processing speed [2,3]. A previous study revealed that MBI can reduce auditory processing [4]. Patients with MBI cannot follow proper conversation and sound localization without auditory attention [5,6]. This situation can decrease the quality of life. Therefore, it is necessary to understand the source localization of auditory attention with an objective assessment to improve quality of life using therapeutic approaches.

Event-related potential (ERP) is a useful tool for objective assessment [7,8]. Among other ERP components, the P300 ERP component is a well-established biomarker that expresses neurological mechanisms related to auditory stimulation. The P300 component is a positive waveform that appears approximately 300 ms after the stimulus. This component reflects the source allocation of auditory attention [9] in the auditory oddball paradigm [10]. The amplitude and latency of the P300 ERP component can be affected by different factors, such as stimulus type, complexity of the task, and cognitive condition of the person [11]. Additionally, deviant or target stimuli are part of the oddball paradigm. During the deviant auditory attention process, people can identify and react to unexpected or unusual audio events that help them adapt to changing environments to maintain proper behavioral responses. Therefore, this study used the auditory oddball paradigm to identify auditory impairment in the group of MBI patients using the source localization of the P300 ERP component.

Source localization is a procedure used to identify the cerebral origins of electrical activity documented on the scalp using electroencephalography (EEG). Source localization can be found in different brain lobes of patients with MBIs. Standardized low-resolution electromagnetic tomography (sLORETA) is a widely used technique that can identify the exact brain regions involved in generating the P300 ERP component and provides an understanding of the efficient integrity and possible damage to specific areas of the brain in patients with MBI [12]. P300 source localization can guide us in identifying MBI, observing recovery, and evaluating the success of therapeutic measures [9], such as cognitive rehabilitation efforts, by focusing on the affected brain areas [13]. Patients with MBI have less activity in the frontal and parietal lobes [2,14], with delayed P300 latencies and altered source localization patterns, indicating that patients with MBI have poor neuronal processing and connection [15], which can lead to impaired attention and cognitive processing [9,16]. Therefore, this study used the P300 source localization procedure, which can provide important information about neurological impairment in patients with MBI using the sLORETA technique.

Cognitive impairment can affect ERP source localization due to changes in brain activity in different diseases, such as Alzheimer's disease, Parkinson's disease, and traumatic brain injury (TBI). This neuronal alteration can change ERP component amplitudes, latencies, and distributions, making source localization difficult [9]. Brain trauma affects the neural networks that control cognitive function and hidden source localization [17]. ERP source localization can be blocked by reducing the signal-to-noise ratio during ERP recording which is particularly problematic in the cognitive process [18].

Therefore, this study investigated P300 ERP source localization using the sLORETA technique in the auditory oddball paradigm in patients with MBI to identify reflected cognitive impairment.

2. Methodology

2.1 Study Design

This is a prospective observational study. All subjects in both groups were randomly chosen.

2.2 Inclusion and exclusion criteria

The inclusion criteria were as follows: age 20–50 years old (for both groups), no previous history of injury for the control group and prior history of injury for the MBI group, and no treatment for any other diseases, such as heart, lung, or kidney diseases. The exclusion criteria for both groups were as follows: participants were excluded if they were outside the age range of 20 to 50 years, had any major diseases like heart, lung, kidney, etc., were undergoing treatment for conditions such as heart, lung, or kidney disease, or had any psychiatric illness. Control participants were additionally excluded if they had any previous or recent history of brain injury.

2.3 Sample Size Calculation

The sample size for this study was calculated using Power and Sample Size (PS) software v3.1.6 (Vanderbilt University, Nashville, TN, USA). This study included the control and MBI groups. The tests for the MBI group were further divided into two: 7 days after the road traffic accident (RTA) (1st test) and 2–6 months after the RTA (2nd test). The ratio of controls to MBI participants was 1:1 (m). The true difference between the control and MBI means was 0.51 (α), standard deviation (σ) was set at 0.55 [19]. Therefore, we need 19 participants in each group (control = 19, MBI = 19) to reject the null hypothesis that the population means in each group are equal with a probability (power β) of 0.8. The Type 1 error probability (α) was set at 0.05. A 10% dropout rate was added to the sample size. Therefore, the final sample size was 21 (19 + 2) in each group.

2.4 Recruitment of Participants

Control participants were chosen from the local community and institutions through notice board advertisements and personal communication. Participants with MBI were selected from the Neurosurgery Outdoor Clinic at the Hospital Universiti Sains Malaysia (HUSM). All participants were matched according to age, education, and corrected vision, and written informed consent was obtained before the experiments. This study was carried out in the MEG/ERP laboratory at HUSM, Malaysia.

2.5 Experimental Paradigm

The auditory oddball paradigm comprised standard and target tones/stimuli. The standard tones had a sound pressure level (SPL) of 60 dB, a high frequency of repetition (80%), and a low pitch (1 KHz). In contrast, the target tones were 60 dB SPL, low frequency of repetition (20%), and high pitch (2 KHz). Both tones/stimuli lasted 100 ms with a randomized inter-stimulus interval (ISI) of 500–1500 ms (Fig. 1). The stimuli were administered binaurally through headphones.

2.6 Experimental Procedure

The E-Prime software (version 2.0; Psychology Software Tools, Inc., Sharpsburg, PA, USA) was used to present the auditory oddball paradigm. All participants used a 128-ERP net on their heads while sitting in a sound-treated room, 80 cm from the 22-inch liquid crystal display (LCD) monitor that displayed the stimuli. Participants silently counted the target tones, ignoring the standard tones. After completing the experiment, the examiners wanted to know the count of the target stimuli to ensure that they remained attentive to the experiment. There were two blocks. Each block consisted of 160 standard tones and 40 target tones.

3. Data Analysis

3.1 ERP Data Acquisition and Analysis

Data acquisition and pre-processing were performed using Net Station software from EGI (Electrical Geodesics, Inc., Eugene, OR, USA). The electrode impedance was kept below 50 KΩ. The high-pass filter (HPF) was 0.03 Hz, and the low-pass filter (LPF) was 30 Hz with a 250 Hz sampling rate. Data were segmented from –100 to 600 ms. Artifact detection tools were used to correct and eliminate eye blinks, eye motions, and body movement artifacts. The baseline was set at –100 ms. As a final procedure, the grand average data from both groups were entered into the

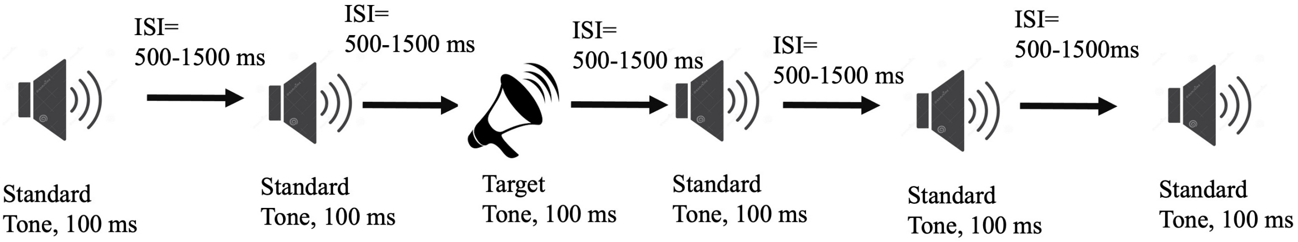

Fig. 1. Experimental procedure of the auditory oddball paradigm. Standard and target stimuli were presented for 100 ms with 500 to 1500 random ISI. ISI, inter-stimulus interval.

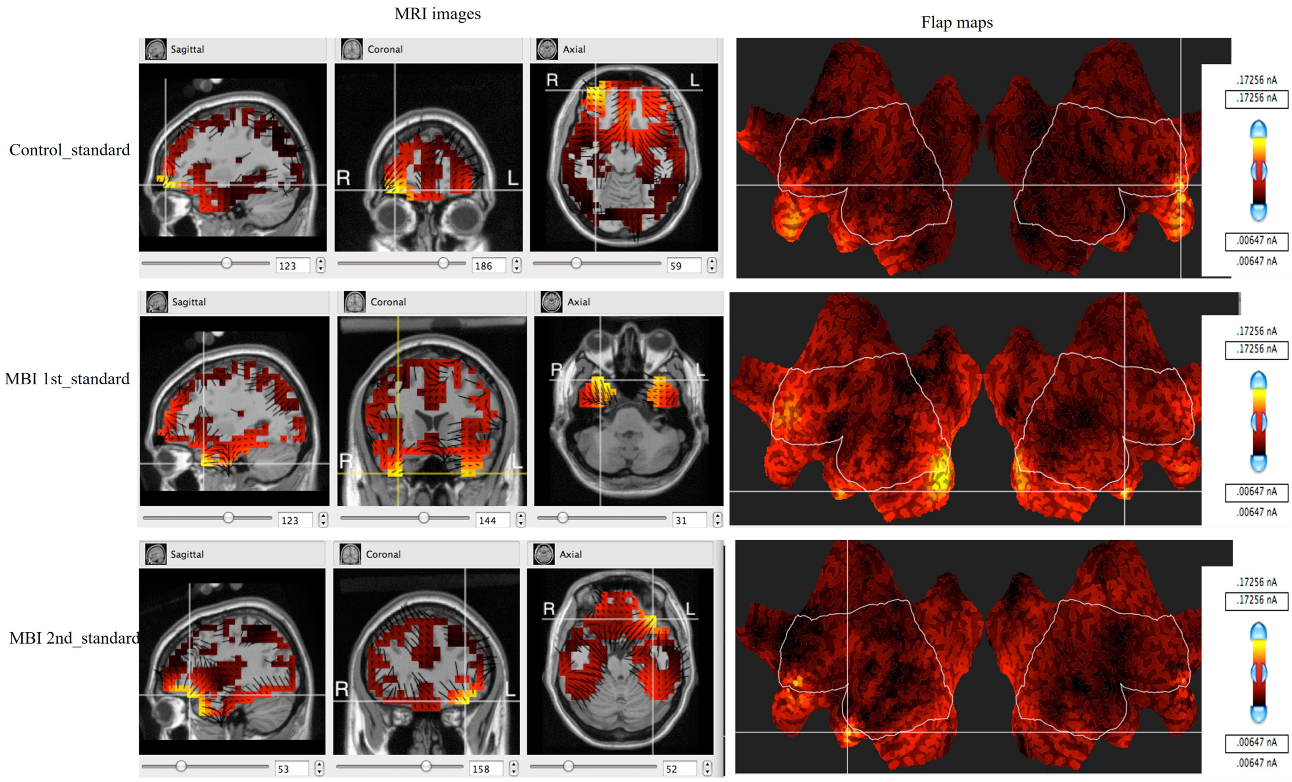

Fig. 2. MRI images and its corresponding flap map for P300 ERP component source localization during standard stimuli in the control, MBI 1st test, and MBI 2nd test groups (from upper to lower panels) over 400 ms using sLORETA. The brighter yellow color indicates an activated source area. Note: 'L' indicated 'Left' and 'R' indicated 'Right'. MRI, magnetic resonance imaging; MBI, mild brain injury; ERP, event-related potential; sLORETA, standardized low-resolution electromagnetic tomography.

EGI Geosource program to detect brain source localization using sLORETA in Net Station software v5.2 (Electrical Geodesics, Inc., Eugene, OR, USA).

3.2 P300 ERP Source Localization Procedure

A realistic head model was created using an magnetic resonance imaging (MRI) template from the Montreal Neurological Institute (MNI) in GeoSource, an electrical source imaging software from EGI of the Net Station software. This study used sLORETA, a multiple source beamformer (MSBF), and minimum norm estimates (MNE) to estimate the neuronal sources of the P300 ERP component using this head model. The MSBF is a spatial filtering method that can identify sources by maximizing the signal from a specific area and minimizing interference from other areas [20]. The MNE deals with a distributed solution by determining the minimum overall source strength for the observed data [21]. In the sLORETA technique, the source of the P300 ERP component was selected 400 ms after the stimuli, which was within the timeframe of the P300 component. sLORETA source-imaging specifications with a dense dipole set consisting of 2447 dipoles and forward and inverse head models were selected. The P300 sources were localized in the superimposed 3D MRI (MNI template) slices. The activation zones of the P300 source localization were mapped onto a 3D brain model with a yellow/bright yellow color (Figs. 2,3).

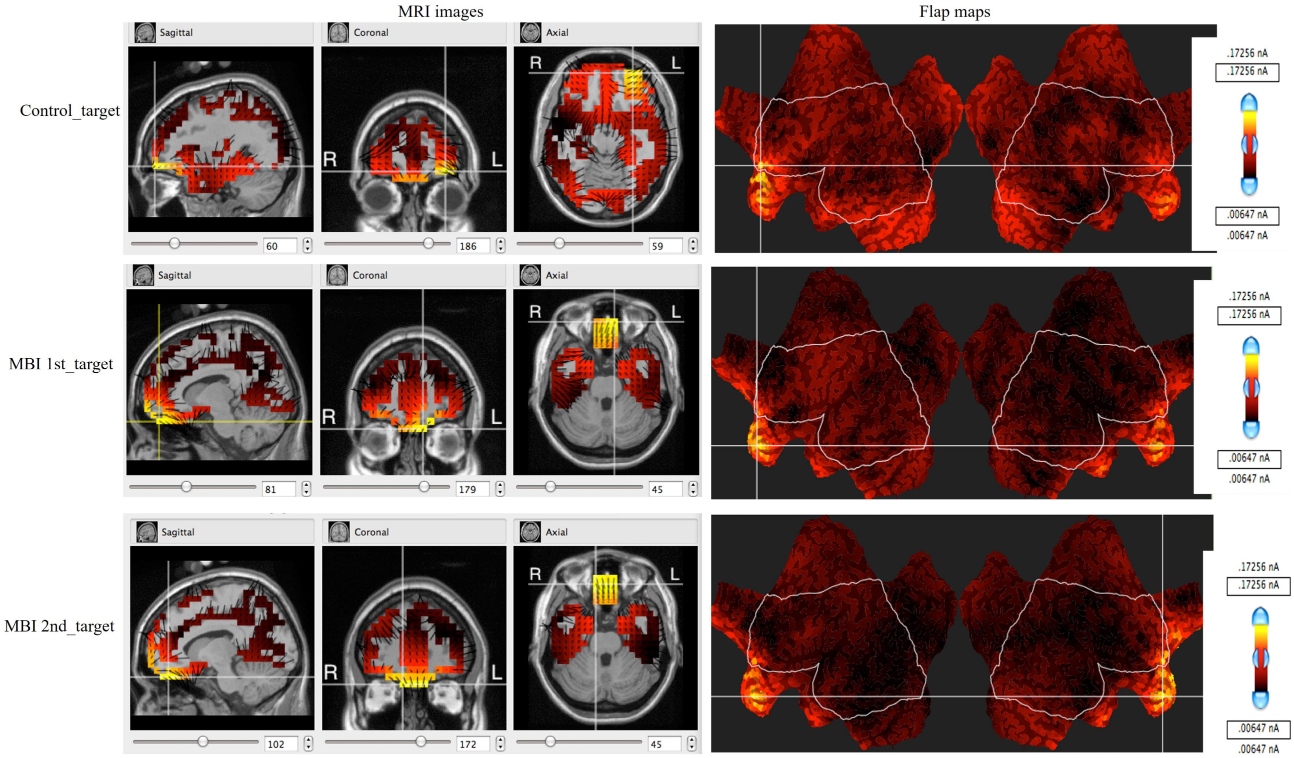

Fig. 3. MRI images and its corresponding flap map for P300 ERP component source localization during target stimuli in the control, MBI 1st test, and MBI 2nd test groups (from upper to lower panels) over 400 ms using sLORETA. The brighter yellow color indicates an activated source area. Note: 'L' indicated 'Left' and 'R' indicated 'Right'.

3.3 Statistical Analysis

This study collected dipole intensity values for all participants across groups. The Statistical Package for the Social Sciences (SPSS v28, IBM Corp., Chicago, IL, USA) was used to assess the normality of the data and determine significance levels between and within groups, with the *p*-value set at 0.05.

The categorical variables included gender and handedness. In the control group, 11 (57.9%) participants are male and 8 (42.1%) are female. In the MBI group, 16 (15.8%) are female and 3 (84.2%) are male. Regarding handedness (Dominance), 3 (15.8%) of the control group are left-handed and 16 (84.2%) are right-handed. In the MBI group, 1 (5.3%) and 18 (94.7%) are left-handed and right-handed, respectively. We performed the Shapiro-Wilk Test to assess normality for the continuous variables—intensity values, age, and years of education. The normality test indicated that the maximum numbers of the continuous variables were not normally distributed except for dipole intensities of the target stimuli. Hence, we used the non-parametric Mann-Whitney U test to assess significance in intensity values between and within groups for standard and target stimuli, as well as age and years of education between the control and MBI groups. For the categorical variables, normality tests were unnecessary; however, we performed the Chi-Square test to assess the effect of gender and handedness differences between the control and MBI groups. We employed the Wilcoxon Signed-Rank test for between-group comparison for standard and target stimuli in MBI 1st and 2nd test groups (paired observation). Additionally, within-group comparisons were done for standard and target stimulus intensities (paired observation) in the control, MBI 1st, and MBI 2nd test groups.

4. Results

4.1 Demographic Information

The median (IQR—Interquartile Range) for the ages of the control and MBI groups were 29.1 (26.2–36) years and 24.1 (22.5–37.9) years, respectively. Meanwhile, the median (IQR) for the educational level of the control group was 11.0 (11.0–13.0) years and the MBI group was 11.0 (11.0–11.0) years. There were no significant differences in age (U = 144.500, p = 0.293) and educational experiences (U = 167.500, p = 0.624) in the control and MBI groups. The control group consisted of 11 males and eight females. The MBI group consisted of 16 males and three females. The Chi-Square test of independence revealed no significant difference in handedness (χ^2 (1, n = 19) = 0.279, p = 0.597), or gender (χ^2 (1, n = 19) = 3.199, p = 0.074) between the control and MBI groups (Table 1).

Table 1. Demographic information and test results between the control (n = 19) and MBI groups (n = 19).

	Mann-Whitney U test		Chi-Square (df) test	
Groups	Age (years), median (IQR) U = 144.500, p = 0.293	Education (years), median (IQR) U = 167.500, p = 0.624	Gender (χ^2 (1) = 3.199, p = 0.074).	Dominance (χ^2 (1) = 0.279, p = 0.597).
Control	29.1 (26.2–36)	11.0 (11.0–13.0)	11 males, 8 females	3 left-handed, 16 right-handed
MBI	24.1 (22.5–37.9)	11.0 (11.0–11.0)	16 males, 3 females	1 left-handed, 18 right-handed

MBI, mild brain injury; IQR, Interquartile Range.

Table 2. This table describes the source locations of the P300 ERP component with intensities among groups (n = 19 for each), during standard and target auditory oddball stimuli based on sLORETA MRI images and flap map.

Groups	Intensity (nA) median (IQR)	Brodmann area (BA)	Gyrii	Lobe	Hemisphere
Standard stimuli					
Control	0.05 (0.03–0.06)	11	Superior frontal gyrus	Frontal lobe	Right
MBI 1st test	0.08 (0.07–0.08)	38	Superior temporal gyrus	Temporal lobe	Right
MBI 2nd test	0.09 (0.09–0.1)	47	Inferior frontal gyrus	Frontal lobe	Left
Target stimuli					
Control	0.106 (0.053–0.135)	11	Superior frontal gyrus	Frontal lobe	Left
MBI 1st test	0.166 (0.16–0.171)	11	Orbital gyrus	Frontal lobe	Middle - left
MBI 2nd test	0.202 (0.19–0.211)	11	Rectal gyrus	Frontal lobe	Middle- right

4.2 sLORETA Results

Standard stimuli evoked a P300 source at the superior frontal gyrus (BA11) of the right frontal lobe with a median intensity of 0.05 (IQR 0.03–0.06) nA in the control group. Standard stimuli induced the P300 ERP source at the superior temporal gyrus (BA38) of the right temporal lobe with an intensity of 0.08 (IQR 0.07–0.08) nA in the MBI 1st test group and at the inferior frontal gyrus (BA47) of the left frontal lobe with an intensity of 0.09 (IQR 0.09–0.1) nA in the MBI 2nd test group (Fig. 2, Table 2).

The P300 source localization for the target tone was discovered at BA11 for all groups, but in different gyri of the frontal lobe, such as the superior frontal gyrus, orbital gyrus, and rectal gyrus, in the control, MBI 1st, and MBI 2nd test groups, respectively. The median values of source intensities for the control, MBI 1st, and MBI 2nd test groups were 0.106 (IQR 0.053–0.135), 0.166 (IQR 0.16–0.171), and 0.202 (IQR 0.19–0.211) nA, respectively (Fig. 3 and Table 2).

The Mann-Whitney U test indicated higher dipole intensities in both the MBI 1st and 2nd test groups compared to the control group for standard (control *Vs* MBI 1st test group: U = 7.500, $p < 0.001$; control *Vs* MBI 2nd test group: U = 0.000, $p < 0.001$) and target stimuli (control *Vs* MBI 1st test group: U = 37.500, $p < 0.001$; control *Vs* MBI 2nd test group: U = 5.500, $p < 0.001$). Additionally, both control and MBI groups demonstrated higher intensities during target stimuli compared to standard auditory stimuli. The Wilcoxon Signed-Rank test showed that the MBI 2nd test group had significantly higher dipole intensities during standard (Z = –3.794, $p < 0.001$) and target stimuli (Z = –3.824, $p < 0.001$) (between-group) (Table 3). A within-group paired observation of standard and target stimuli showed that the dipole intensity for target stimuli was significantly higher than for standard stimuli in the control (Z = 2.777, $p = 0.005$), MBI 1st test group (Z = –3.825, $p < 0.001$), and MBI 2nd test group (Z = –3.824, $p < 0.001$) groups (Table 3).

5. Discussion

This study investigated the source localization of the P300 ERP component that reflects cognitive impairment in MBI groups using the sLORETA technique in the auditory oddball paradigm. We found that standard stimuli evoked P300 source localization in various lobes, but the target stimuli induced source localization in the same brain lobe in all groups. There were significant differences in dipole intensities between and within groups among control and MBI patients in both standard and target stimuli.

5.1 Shifted P300 Source Localization

P300 ERP source localization using sLORETA was infrequent. The activated source depends on the type of stimulus that causes the ERP response. No previous studies have investigated P300 source localization using sLORETA

Table 3. Test results of the dipole intensities (median value) between and within groups during standard and target stimuli.

Between-groups		
Standard stimuli	Mann-Whitney U Test	Wilcoxon Signed-Rank Test
Control (0.05) *Vs* MBI 1st test (0.08)	U = 7.500, $p < 0.001$	
Control (0.05) *Vs* MBI 2nd test (0.09)	U = 0.000, $p < 0.001$	
MBI 1st test (0.08) *Vs* MBI 2nd test (0.09)		Z = –3.794, $p < 0.001$
Target stimuli		
Control (0.106) *Vs* MBI 1st test (0.166)	U = 37.500, $p < 0.001$	
Control (0.106) *Vs* MBI 2nd test (0.202)	U = 5.500, $p < 0.001$	
MBI 1st test (0.166) *Vs* MBI 2nd test (0.202)		Z = –3.824, $p < 0.001$
Within-groups		
Control (standard (0.05) *Vs* target stimuli (0.106))		Z = 2.777, $p < 0.005$
MBI 1st test (standard (0.08) *Vs* target stimuli (0.166))		Z = –3.825, $p < 0.001$
MBI 2nd test (standard (0.09) *Vs* target stimuli (0.202))		Z = –3.824, $p < 0.001$

in the auditory oddball paradigm in patients with MBI. Tsolaki *et al*. (2017) [22] provided evidence using an auditory oddball paradigm in which the P300 source location in control subjects was at BA38 in the temporal lobe; however, this location was shifted to BA11 in the frontal lobe of cognitively impaired patients. In particular, the P300 source location can be found in the frontal, parietal limbic cingulate, and temporal-occipital areas [23]. In the present study, the control group showed an auditory P300 source location in the BA11 of the right frontal lobe, which shifted to the BA38 in the MBI 1st test group and the BA47 in the MBI 2nd test group. Our results are consistent with those of Tsolaki *et al*. (2017) [22] and Anderer *et al*. (1998) [23] in that the auditory P300 source location might shift during cognitive impairment with standard stimuli in patients with MBI.

Moreover, the P300 source location of the target stimuli was found in the BA11, but different gyri were found in the control, MBI 1st, and MBI 2nd test groups. The constant involvement of BA11 highlights its significant role in the processing of target stimuli, which usually requires excessive cognitive effort and attentional resources [24,25]. Consistently, we assume that the constant activation of BA11 during target stimuli between the groups in our study indicates that all groups require extra auditory attention to recognize the target stimuli. Furthermore, the shifting of the P300 source location among patients with MBI compared to controls within the BA11 area proved that patients with MBI have an auditory cognitive impairment, and to compensate for this impairment, the P300 source location was shifted.

We assume that the shifted P300 source locations reflect auditory cognitive impairment in our groups of patients with MBI during both standard and target auditory stimuli.

5.2 Intensity Difference of the P300 Source Location

According to between-group statistical analysis, the control group had the significantly lowest intensity during both standard and target stimuli, and the MBI 2nd test group had the significantly highest intensity. The relatively lower intensity observed in the control group was consistent with the engagement of this area in routine cognitive processing without additional demands of novelty or complexity. However, the significantly higher intensity during target stimuli in the control group demonstrates the increased focus required for target stimuli [24,26]. Therefore, taking this note, we correspond the result of significantly higher intensity in patients in the MBI 1st and 2nd test groups that the MBI 1st test group needs extra effort for neuronal processing during standard and target stimuli 7 days after RTA due to neuronal injury (significant higher intensity compared to the control group) and to compensate this injury, the MBI 2nd test group needs additional effort (significant highest intensity between the groups) compared to the MBI 1st test group due to neuronal compensation or altered neuronal pathway for auditory standard and target stimuli processing.

The shifting of the P300 source localization and the significantly higher intensity compared to the control group indicate a substantial reorganization of neuronal resources in response to MBI, possibly as a compensatory adaptation to maintain cognitive performance.

No significant differences in age, years of education, handedness, and gender prove that this study's results were not affected by the participants' demographic information of both groups. The limitation of this study is a small sample size. A larger sample size might bring reliable and stable results. We recommended a longitudinal study for the future to get a robust finding.

6. Conclusion

Using the sLORETA technique in the auditory oddball paradigm, we investigated the altered source localization of the P300 ERP component reflecting cognitive impairment in patients with MBI. The gradual increase of higher intensity of the source dipole may indicate cognitive impairment in patients pointing to compensatory mechanisms during the task. These results reveal adaptive alterations in neural processing and highlight notable differences in the brain's response to auditory cognitive activity after mild brain injury. More studies in large homogeneous brain injury patients with behavioral data are needed to confirm these findings.

Availability of Data and Materials

All datasets reported in this study are available upon request.

Author Contributions

MFR designed the research study. TB performed the data acquisition. MFR and TB analyzed the data. TB drafted the first manuscript. TB and MFR prepared the final version of the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study gained human ethical permission from Universiti Sains Malaysia's (USM) ethical committee (USMKK/PPP/JEPeM/232.3[9]) and was done under the principles of the Declaration of Helsinki. Each subject provided written informed consent before being included in the study. Participants' confidentiality was scrupulously safeguarded during the investigation.

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Conflict of Interest

The authors declare no conflict of interest.

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