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ORIGINAL ARTICLE

The use of event-related potential (P300) and neuropsychological testing to evaluate cognitive impairment in mild traumatic brain injury patients

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ABSTRACT

Background: The aim of the study is to compare the amplitude and latency of the P300 event-related potential (ERP) component between a control group and patients after mild traumatic brain injury (mTBI) during 1–7 days (short duration) and 2–3 months (long duration), and to compare the outcome of neuropsychological tests between the long duration postinjury and control study groups.

Materials and Methods: We studied responses to auditory stimulation in two main and one subgroups, namely the control healthy group (19 patients, both ERP and neuropsychology test done), the mTBI 1 group (17 patients, only ERP done within 7 days after injury), and the mTBI 2 subgroup (the 17 mTBI 1 patients in whom a repeated ERP together with neuropsychological testing was done at 2–3 months postinjury). Auditory evoked responses were studied with two different stimuli (standard and target stimuli), where the P300 amplitude and latency were recorded from three midline sites and results were compared between the groups, as were the neuropsychological test results.

Results: There was a significant prolongation of the target P300 latency values shown by the MBI 1 group measured at the central electrode when compared to the control group, which was also seen when the mTBI 1 and mTBI 2 groups were compared. The results of the P300 amplitude values measured at the frontal electrode showed the control group to have higher readings during the presentation of standard tones when compared to the mTBI 1 group. The mTBI 2 group performed better on some neuropsychological tests.

Conclusion: The latency of P300 was significantly prolonged in early mTBI patients who improved over time, and the neuropsychological testing on mTBI 2 patients showed them to be comparable to the control group. The study indicates that ERP should be used as an additional modality of investigation in mTBI patients.

Key words: Cognition, event-related potential, mild traumatic brain injury, neuropsychology, P300

Introduction

Millions of closed head injuries occur each year. The average incidence in the United States is estimated at 200 patients per 100,000 population.[1] In Malaysia, the incidence of road traffic accidents is one of the highest in the world, with about 22 deaths from this cause per 100,000 population.[2] There are three types of head injury: Mild, moderate, and severe. Deficits after closed head injury differ in type and severity, mild head injury patients presenting with a variety of physical, cognitive, and emotional impairments. The criteria used for

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clinical identification of mild traumatic brain injury (mTBI) in this study include:

i. One or more of the following: Disorientation or confusion, loss of consciousness for ≤30 min, posttraumatic amnesia for <24 h, and/or other transient neurological abnormalities such as seizure, focal signs, and intracranial lesion not requiring surgery
ii. Glasgow coma scale score of 13–15 upon presentation to health care center after 30 min postinjury. These manifestations of mTBI must not be due to alcohol, drugs, or medications, or caused by other injuries or treatment for other injuries.

Individuals who have sustained mTBI have been known to demonstrate a change in cognition, with slower information processing, impaired focused attention, and memory impairment.[3,4] Electrophysiological measures of the brain provide researchers and clinicians with a noninvasive and relatively inexpensive method of investigating the functional integrity of neuronal activity, an example being the long latency event-related potentials (ERPs) such as P300. Electroencephalograph (EEG) waves are the recordings of electrical activity obtained from the scalp using a 128-electrode sensor net. ERP is the averaged EEG responses that are related to the more complex processing of stimuli. The use of the P300, which is an important component of ERP, is seen as a possible diagnostic test for cognitive dysfunction, especially when it is combined with other tests such as neuropsychological testing, as ERP assesses functional brain activity and is able to reveal subtle changes in information processing resulting from diffuse axonal injury.[5] This modality may aid in revealing subtle cognitive impairments in patients with mild head injury who are unable to return to work as a consequence without being accused of being malingerers and cheats.

Auditory ERPs have a defined set of major components ranging from about 100 to 600 ms following presentation of a stimulus. The P300 component of the ERP is the positive peak identified between 250 and 500 ms after the onset of the stimulus, and is associated with the evaluation of a stimulus as being salient in the task, usually because it is a target that requires a response.[6] Using ERP along with neuropsychological testing, we tried to evaluate the cognitive changes seen in patients with mTBI.

Materials and Methods

This study was performed in a single institution and was a prospective cohort study performed initially on 20 mild brain injury patients and 22 controls before 3 patients from each group dropped out. They were all aged between 20 and 50 years. The study subjects were selected based on the defined inclusion and exclusion criteria and were divided into two groups. Group 1 consisted of patients with mild brain injury within 1-week of injury (mTBI 1) and the same patients in whom a repeated ERP and neuropsychological testing was done at 2–3 months postinjury (mTBI 2). Group 2 was a control group.

The study subjects underwent ERP testing in which the EEG waves were recorded from the scalp using a 128-electrode sensor net. EEG is the recording of electrical activity along the scalp. EEG measures voltage fluctuations' resulting from ionic current flows within the neurons of the brain, meaning, it refers to the recording of the brain's spontaneous electrical activity over a period of time. ERP refers to averaged EEG responses that are related to the more complex processing of stimuli.

This 128-scalp sensor net was connected to a 128-channel head box. The net is elastic in nature, allowing for the stable placement of the electrodes. A small plastic pedestal encases each silver/silver chloride electrode and a sponge that is in contact with the scalp. Before placement of the net on the head of the subjects, the net was soaked in an electrolytic mixture of potassium chloride solution and shampoo for approximately 10 min. Each subject was then given a pair of headphones to be placed over both ears and the subjects were comfortably seated in a dimly lit room, which was sound proofed and electrically shielded. The P300 ERP latencies and amplitudes of all subjects were measured using the "oddball task." In this task, the subjects were presented binaurally with two target tones at 60 dB sound pressure level, the first being tones of low frequency (20%) and high pitch (2000 Hz) and the second being tones of high frequency (80%) and low pitch (1000 Hz). The duration of tone delivery was 100 ms with a rise/fall time of 10 ms. The patient was instructed to count the number of high-pitched tones silently. Amplifiers had a band pass of 0.1–50 Hz and the stimulus rate was 0.5 Hz. Linked electrodes on earlobes were used as references and the forehead as ground. All electrode impedances were 10–50 kOhm and the subjects were reminded to fix their gaze on a circled point on the screen in front of them so as to minimize ocular movement and to avoid electrooculogram contamination from eye movements. ERP components were analyzed for abnormalities in amplitude and latencies in relation to the duration of head injury and neuropsychological factors. The control and mTBI 2 groups were then subjected to a battery of neuropsychological tests.

Data obtained from the neuropsychological and ERP testing were entered for analysis into the IBM Statistical Package for Social Sciences (SPSS) version 18.0, Chicago, Illinois, U.S.A. Analysis for age was done using independent *t*-test and Pearson's Chi-square for gender and dominancy. Independent *t*-test and Mann–Whitney U-test were used to compare the results between the control and head-injured groups after checking the assumptions of normality using Shapiro–Wilk and histogram. Paired *t*-test and Wilcoxon signed-rank test were used for additional comparisons of the head-injured group earlier (mTBI 1) and 2–3 months after injury (mTBI 2) after checking the assumptions, as above, using Shapiro–

Wilk and histogram. Owing to the current small sample size, some of the data were not normally and equally distributed. The significance level was set at 0.05. The comparisons that were made between the groups were P300 latencies, P300 amplitude, and neuropsychological test results. The results of the neuropsychological test were compared for the control group and the mild head injury at long duration group (mTBI 2).

Results

Nineteen controls and 17 TBI patients were finally used, showing similar characteristics in demographic variables such as age and education level. The mean (standard deviation [SD]) age for the mTBI subjects was 29.84 (9.33) years, while the mean (SD) age for the control group was 34.75 (10.58) years, the difference being statistically insignificant. There were 14 males and 3 females in the mTBI group, while the control group consisted of 8 males and 11 females. Males made up 82.4% of the mBTI group, a significant difference ($P < 0.05$). Most of the subjects in the control and patients group were right-handed. The demographics are summarized in Table 1.

The results in Table 2 reveal a significant finding from measurement of the P300 amplitude values at the frontal electrode (Fz) during the introduction of standard tones of high frequency (80%) and low pitch (1000 Hz). The analysis was done using independent *t*-test and Mann–Whitney U-test, which showed $P = 0.045$ at Fz, which was significantly higher in the control group than in the patient group. The study did not show any significant difference in amplitude values after analysis using Mann–Whitney U-test for standard tones and independent *t*-test for target tones between the mTBI 2 and control groups.

However, there was a significant prolongation of the target P300 latency values shown by the mTBI 1 group measured at the central electrode (Cz) when compared to the control group during the introduction of target tones. The analysis was done using independent *t*-test and Mann–Whitney U-test. Results at Cz using independent *t*-test showed $P = 0.046$, while analysis using Mann–Whitney U-test and independent *t*-test did not show any significant difference in latency values for both standard and target tones between the mTBI 2 and control groups.

Table 1: Description of the study subjects

Characteristics	mTBI group (*n*=17)	Control group (*n*=19)	Total (*n*=36)
Age (years)			
Mean (SD)	29.84 (9.33)	34.75 (10.58)	32.43 (10.17)
Gender *n* (%)			
Male	14 (82.4) *	8 (42.1)	22 (61.1)
Female	3 (17.6)	11 (57.9)	14 (38.9)
Dominancy *n* (%)			
Right	16 (94.1)	16 (84.2)	32 (88.9)
Left	1 (5.9)		

*Significant at *P*<0.05; SD – Standard deviation; *n* – Number of subjects; mTBI – Mild traumatic brain injury

There was also no significant difference in amplitude values between the mTBI 1 and mTBI 2 groups after analysis using paired *t*-test and Wilcoxon signed-rank test for both standard and target tones [Table 3]. There was a significant prolongation of the target P300 latency values shown by the mTBI 1 group compared to the mTBI 2 group, measured at the Cz electrode. The analysis was done using Wilcoxon signed-rank test, which showed $P = 0.028$ [Table 3].

Neuropsychological testing showed that there were significant differences between the study groups ($P < 0.05$) in mean Wechsler memory scale–verbal memory immediate recall (WMSVM1), Rey auditory verbal learning test–delayed recall (RAVLTDR), Rey auditory verbal learning–immediate recall (RAVLTIM), or Wechsler memory scale–face recognition (WMSFACR) scores. The analysis was done using independent *t*-test and Mann–Whitney U-test. The mean scores of WMSVM1, RAVLTDR, and RAVLTIM were higher in the mTBI 2 group, while the mean scores of WMSFACR were higher in the control group.

Discussion

Every year, tens of thousands of people worldwide suffer TBI, causing deficits and disability in cognitive, emotional, and social functioning.[7] The present study examined the differences in the latency and amplitude of the P300 components between a group of individuals with mild brain injury and a matched noninjured group. The mTBI group was tested within 1-week and again 2–3 months after the injury, and the results were compared. The study also compared the results of neuropsychological testing between the groups.

mTBI is most common due to motor vehicle accidents, especially trivial injury incurred while riding a motorcycle without a helmet, followed by falls, being struck by an object (assault), and collisions, after which patients usually present with more severe injury.

Analysis of the electrophysiological tests showed interesting results in relation to the P300 latency and amplitude. The P300 latency refers to the time between stimulus onset and the peak amplitude. It is thought to reflect stimulus evaluation and categorization independently from movement and response selection factors.[8] Our data indicate that there was a significant prolongation of the target P300 latency values during a short time after the injury among the mTBI 1 group as compared to the control group, with a mean of 418.00 ms and 339.37 ms, respectively ($P = 0.046$), which is similar to the findings of a study conducted by Duncan *et al*.[9] These results were measured at the Cz electrode. A majority of studies have also reported prolonged auditory P300 latencies. Furthermore, there is evidence that more severe damage is associated with greater delays in the latency of auditory P300.[10-12] This has led us to believe that patients with traumatic head injury suffer delays in evaluating and categorizing auditory target

Table 2: Comparison of amplitude and latency values between patients with mTBI and the control group at short (mTBI 1) and long (mTBI 2) duration

Duration	Amplitude (μV)		*P*	Latency (ms)		*P*
	Patient group	Control group		Patient group	Control group	
Short						
Standard						
Fz	−0.334 (1.66)	−0.913 (0.524)	0.045[a,*]	268.00 (248.00)	240.00 (80.00)	0.315[a]
Cz	0.292 (0.746)	0.318 (0.676)	0.912	232.00 (120.00)	244.00 (258.00)	0.452[a]
Pz	0.472 (1.33)	0.035 (0.764)	0.531[a]	412.00 (309.00)	472.00 (242.00)	0.754[a]
Target						
Fz	−2.476 (2.325)	−1.304 (2.040)	0.116	316.00 (124.00)	312.00 (140.00)	0.950[a]
Cz	0.413 (1.706)	0.397 (1.695)	0.633	418.00 (44.93)	339.37 (76.43)	0.046[a,*]
Pz	2.292 (2.711)	1.989 (1.358)	0.397[a]	480.35 (138.47)	476.11 (138.47)	0.915[a]
Long						
Standard						
Fz	−0.593 (1.454)	−0.938 (0.524)	0.257[a]	244.00 (104.00)	240.00 (80.00)	0.688[a]
Cz	0.312 (1.193)	0.457 (0.423)	0.754[a]	220.00 (24.00)	244.00 (258.00)	0.156[a]
Pz	0.472 (1.330)	0.035 (0.764)	0.531[a]	280.00 (318.00)	472.00 (242.00)	0.146[a]
Target						
Fz	−1.177 (2.014)	−1.304 (2.040)	0.852	308.00 (112.00)	312.00 (140.00)	0.778[a]
Cz	0.663 (1.807)	0.397 (1.695)	0.652	320.00 (60.00)	330.00 (72.00)	0.300[a]
Pz	1.779 (1.281)	1.856 (1.011)	0.842	407.88 (109.56)[a]	476.11 (95.50)[a]	0.054

*Significant at $P<0.05$; [a]Comparison between median (IQR) with Mann–Whitney U-test. Fz – Frontal electrode; Cz – Central electrode; Pz – Parietal electrode; mTBI – Mild traumatic brain injury; IQR – Interquartile range

Table 3: Comparison of amplitude and latency values between patients with mTBI at short (mTBI 1) and long (mTBI 2) duration

	Amplitude (μV)		*P*	Latency (ms)		*P*
	Short duration	Long duration		Patient group	Control group	
Standard						
Fz	−0.334 (1.66)[a]	−0.593 (1.454)[a]	0.113[a]	268.00 (248.00)	244.00 (104.00)	0.435
Cz	0.292 (0.746)	0.362 (0.934)	0.776	232.00 (120.00)	220.00 (24.00)	0.209
Pz	0.472 (1.33)[a]	0.472 (1.330)[a]	0.554[a]	412.00 (309.00)	280.00 (318.00)	0.177
Target						
Fz	−2.476 (2.325)	−1.177 (2.014)	0.121	316.00 (124.00)	308.00 (112.00)	0.831
Cz	0.126 (1.670)	0.663 (1.807)	0.402	376.00 (270.00)	320.00 (60.00)	0.028*
Pz	2.292 (2.711)[a]	2.292 (2.711)[a]	0.316[a]	412.00 (309.0)	380.00 (132.00)	0.098

*Significant at $P<0.05$; [a]Comparison between median (IQR) with Mann–Whitney U-test. Fz – Frontal electrode; Cz – Central electrode; Pz – Parietal electrode; mTBI – Mild traumatic brain injury; IQR – Interquartile range

stimuli. Pratap-Chand *et al*. also reported a significant acute prolongation of the P300 component in their mTBI group, a finding that is consistent with the results of this study.[13] There was a significant prolongation of the target P300 latency values shown by the mTBI 1 group compared to the mTBI 2 group, measured at the Cz electrode, the means being 376.00 ms and 320.00 ms, respectively ($P = 0.028$). This shows that the prolonged P300 latency seen early after the head injury had improved 2–3 months posttrauma. Karen and Onofrj reported that recovering head-injury patients showed improving P300 latency results, which also correlated with improvement in performing several cognitive tasks.[11,14] No significant difference was found in latency values for both standard and target tones between the mTBI 2 and control groups. This further shows that there is a definite improvement with time in the P300 latency in mild brain injury patients; the initially prolonged latency has approached values of the control group. Segalowitz *et al*. observed no differences in the latency of the P300 component in a group of self-reported mTBI subjects who were an average of 6 years postinjury relative to a noninjured subject group.[15] In view of the long duration postinjury, it is probable that the P300 latency had improved and approached the values of the noninjured, as was also observed in this study.

The amplitude of the P300 is one of the ERP components commonly studied that shows some significant differences when mild brain injury patients are compared to noninjured subjects. The usual findings are a reduction in the P300 amplitude in mTBI patients compared to normal subjects. In our study, amplitude values between patients with mTBI at

short duration (mTBI 1) and the control group only showed significance for the standard frequent stimuli, rather than of both standard and target, the amplitude for the control group being larger, with $P = 0.045$. A study by Lavoie *et al*. found a significant reduction in amplitude between control and symptomatic groups around the frontal region, as well as when frequent stimuli were presented.[16] There was an overall larger increase in the P300 amplitude at the same electrode when the target tone was presented, but there was no statistical significance between the symptomatic and control groups. This could mean that, even when presented with standard frequent tones, the mild brain injury patients lose focus and attention. The P300 amplitude is said to become larger when more effort is utilized and when more attentional resources are recruited.[17] Our results showed that the rare target stimuli elicited larger P300 amplitude than the frequent nontarget stimuli, indicating that more attentional resources were recruited to detect the target stimuli. Hence, in normal subjects in whom the ability to recruit the attentional resources is intact; the amplitude produced will be larger. However, the decrease in amplitude in mTBI patients usually holds true when the complexity of the oddball task is increased.[18] This may explain why no statistical significance was achieved in relation to the oddball task in our study, which was basic and not complex enough.

The mean difference in amplitude values between patients with mild brain injury at long duration (mTBI 2) and controls did not reach any significance. There was an increase in amplitude in both groups when a target tone was presented compared to the standard tone, which was expected. When comparing the P300 amplitude values of mTBI 1 and mTBI 2 groups, no statistical significance was found that would indicate the need to increase the complexity of the task.

The mTBI 2 subjects and control groups were subjected to a battery of neuropsychological tests. The mTBI 1 group was omitted because, during the acute period, most of the patients were unable to complete the tests for reasons such as headaches, dizziness, confusion, and other associated injuries. When the mTBI 2 and control groups were compared, some interesting findings were noted. There were significant differences in mean WMSVM1, RAVLTDR, RAVLTIM, and WMSFACR scores between the study groups ($P < 0.05$). The mean scores of WMSVM1, RAVLTDR, and RAVLTIM were higher in the mTBI 2 group, while the mean scores of WMSFACR were higher in the control group. These findings were rather surprising, as we expected the noninjured control group to perform better in the neuropsychological tests; the literature does report a reduced performance in the intellectual abilities following brain injury.[19] On the other hand, a study by Hartikainen *et al*. showed significant differences in scores mainly in the domains of executive functioning only.[20] WMSFACR results were higher in the control group, in keeping with the study of Matser *et al*. on soccer players, in whom the degree of concussion was inversely related to the facial recognition task and the subjects obtained poorer results on tests measuring visual and verbal memory.[21]

However, research by Skandsen has found neuropsychological tests to demonstrate low sensitivity to TBI and reported cognitive complaints.[22] A study by Segalowitz *et al*. also showed there was no difference in the results of WAIS testing between control subjects and mild head injury patients, as was also observed in our study.[15] In a study using the Wechsler memory scale (WMS), the results of good effort among mTBI patients did not differ from normal controls, and the patients' effort had a larger effect than injury severity on WMS scores, which may explain the performance noted by the mTBI 2 group, 2–3 months postinjury.[23] Data documenting the predictive value of the RAVLT in discriminating individuals with neurological injury from healthy controls have not consistently been provided, suggesting that results between groups could be comparable and also linked to the education level and occupation of the subjects.[24]

The results obtained in our study could be due to a few factors. It could be that there has been a significant amount of cognitive improvement, evidenced by the improvement in the ERP results; 2–3 months postinjury. Ponsford *et al*. also showed that neuropsychological testing of mTBI patients who were impaired at 1-week postinjury improved to no impairment by 3 months postinjury.[25] A study by Goldstein and Levin done on older mild head injury patients also showed that mTBI patients exhibit cognitive functioning that is comparable to noninjured controls by 1–2 months postinjury.[26] We also noted during our study that the symptoms of the mild head injury patients had improved on the second visit at 2–3 months postinjury. This could be another reason why the mTBI patients performed well and sometimes better than the control group. A study by Dean and Sterr similarly showed that the working memory and information processing speed were only significantly impaired in mTBI participants with persistent and higher postconcussional symptoms (PCS) compared to mTBI participants without PCS and all nonhead-injured participants.[27] A meta-analysis of neuropsychological outcomes by Belanger *et al*. suggests that mild neuropsychological impairments across neuropsychological test domains are found among mTBI subjects within the first 90 days, but with specific and relatively large deficits in fluency and delayed memory recall.[28] However, this impairment is essentially zero by 3 months postinjury.

On the follow-up visit, we managed to interview the patients and noted that some of the mTBI patients who were on sick leave, initially had picked up new hobbies such as reading, designing, handicraft, and solving crossword puzzles. This could have contributed to the unexpected neuropsychological

test results and could suggest that proper rehabilitation and input by the neuropsychologist is of importance. Education status plays an important role in recovery.[29] Dikmen *et al*. predicted a return to work rate of 87% at 2 years postinjury among patients with a Bachelor's degree or higher educational level.[30] This could explain the results obtained for the noninjured group: Hartikainen *et al*. observed that the structured testing environment created to assess distinct functions may not reflect the problems experienced in ordinary situations that affect the patients' daily functioning and quality of life.[20] Hence, a test that represents the familiar daily activities of a mTBI patient may show good results, while presenting tests in unfamiliar settings and circumstances to the noninjured may result in poor performance, making them seem impaired. This shows that it is important to use multiple modalities to assess a patient. Just because a patient does well in a test that reflects familiar things does not mean he or she will not reveal impairments when tested in a different way. In some cases, patients who do not present with objectively measurable difficulties or deficits may be thought of as malingerers, and their applications for further compensation and help may be rejected.

Conclusion

The present study compared a group of mild head injury patients to a group of noninjured subjects. It showed, based on equally matched subjects that the P300 component may be an additional measure that is more sensitive than standard measurements such as neuropsychological tests alone to detect the neural impact of a concussion. It was seen here that the P300 latency was prolonged initially, which improved with time, in keeping with the patient's symptoms and neuropsychological test results. The P300 amplitude for standard tones was also reduced in the mTBI 1 patients when compared to the control group. This also shows that even when the neuropsychological tests appear fairly normal, the P300 components may still be abnormal, indicating neural impairment. The latency of the P300 component was significantly prolonged in the mTBI 1 group compared to both mTBI 2 and control groups. This is an important point, especially when a patient needs to claim aid from relevant agencies.

In conclusion, we noted differences in the P300 components between the groups in our study. A statistically significant prolongation of P300 latency was seen between mTBI 1 patients and the control group when presented with the target tones, a significant prolongation of P300 latency was found between mTBI 1 patients and the mTBI 2 group when presented with the target tones, and finally there was a reduction of the P300 amplitude between the mTBI 1 and control groups when presented with standard tones. There were also significant differences in some of the neuropsychological test results, in which the mTBI 2 group came out better than the control group.

We suggest that there are positive indications that ERP should be used as an additional modality of investigation along with neuropsychological testing and that mTBI patients' cognition can improve with time and from involving themselves actively in their work. However, the complexity and difficulty of the tasks presented to the subjects should be increased to further detect subtle impairment.

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Conflicts of interest

There are no conflicts of interest.

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