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Efficiency of using a neurofeedback device in determining ischaemic early electroencephalography indicators in rabbits with acute brain ischaemia

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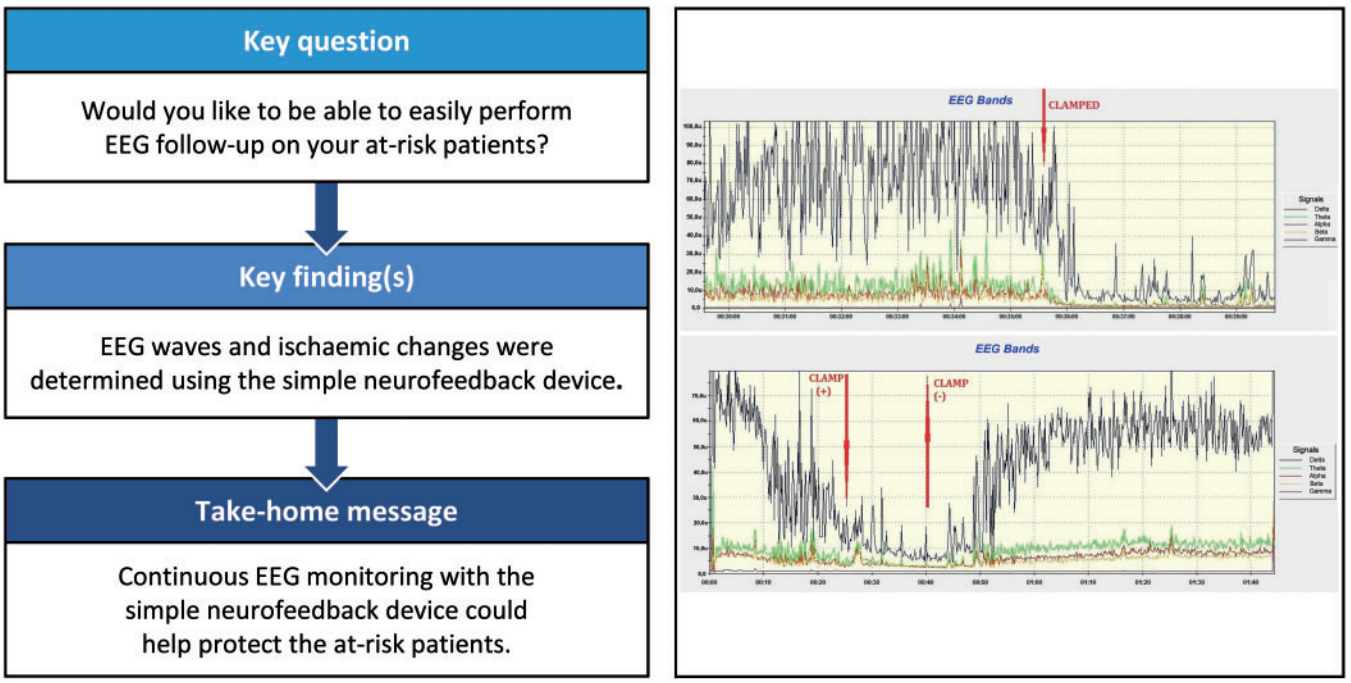

Abstract

OBJECTIVES: Continuous electroencephalography (EEG) monitoring is a useful method in surgical procedures in which brain circulation is at risk. Providing this function using neurofeedback devices reduced to small dimensions may provide ease of use in the early diagnosis of brain ischaemia. The goal of this study was to demonstrate the efficiency of using a neurofeedback device in determining the early EEG indicators of ischaemia in a rabbit model of acute brain ischaemia.

METHODS: Three randomized groups—carotid ischaemia (CI), global ischaemia (GI) and a sham group—each comprising 8 rabbits, were created. In the CI group, the bilateral main carotid artery was clamped; in the GI group, the bilateral subclavian and main carotid arteries were clamped and brain ischaemia was created for 15 min. Brain reperfusion was then achieved for 30 min. In the sham group, the same surgical preparation was performed but no ischaemia occurred. The brain EEG wave activities of all subjects were recorded during the experiment. At the end of the procedure, all brain tissue was removed and apoptotic indexes were determined by histopathological examination. The statistical significance of the histopathological results and the EEG wave activities among the groups was examined.

RESULTS: There was a significant difference between the sham, CI and GI average amplitude ratios, delta (1.02, 0.69, 0.16; $P < 0.001$) and total wave (0.99, 0.78, 0.49; $P < 0.001$), respectively. There was no significant difference between the sham and CI groups in delta (sham, CI, 1.01, 0.87; $P = 0.1$), total wave (sham, CI, 1.22, 0.98; $P = 0.2$) and amplitude standard deviation rates. However, there was a significant difference in the GI group ($P < 0.001$). There was a significant difference between all groups in apoptotic index (sham, 17.88; CI, 40.75; GI, 55.88; $P < 0.001$).

CONCLUSIONS: Significant EEG wave changes resulting from experimental brain ischaemia were analysed with the use of a neurofeedback device. The results indicated that the change in the delta and the total wave standard deviations may be an additional indicator in the formation of permanent brain damage.

Keywords: Brain protection • Electroencephalography • Neurofeedback

ABBREVIATIONS

AAV	Average amplitude value
AI	Apoptotic index
ARs	Alteration rates
CBF	Cerebral blood flow
CI	Carotid ischaemia
EEG	Electroencephalography
GI	Global ischaemia
WSD	Wave standard deviation value

INTRODUCTION

In surgical procedures involving the carotid and the aortic arch, in which brain circulation can be affected, stroke remains a serious problem despite the many protective measures of the brain [1]. Studies have been performed demonstrating the benefits of instant electroencephalography (EEG) follow-up to detect brain ischaemia early during an operation [2].

Brain function is represented on the EEG by oscillations of certain frequencies. Delta (0.5–3 Hz) or theta (4–7 Hz) (slower frequencies) waves are generated by the thalamus and by cells in layers II through VI of the cortex. Faster frequencies such as alpha (8–12 Hz) waves derive from cells in layers IV and V of the cortex [3]. All frequencies are modulated by the reticular activating system, which corresponds to the observation of reactivity on the EEG [4]. Pyramidal neurons found in layers III, V and VI are exquisitely sensitive to conditions of low oxygen, such as ischaemia, thus leading to many of the abnormal changes in the patterns seen on the EEG [5]. EEG changes are closely related to cerebral blood flow (CBF) [6]. When normal CBF declines to ∼25–35 ml/100 g/min, the EEG first loses the faster frequencies. Then, as the CBF decreases to ∼17–18 ml/100 g/min, slower frequencies increase. This pattern represents a crucial ischaemic threshold at which neurons begin to lose their transmembrane gradients, leading to cell death (infarction). When the carotid artery is clamped, CBF that decreases instantaneously to the ischaemic threshold leads to rapid and reversible changes in the EEG (within 20 s) [6]. Infarction may not occur for hours at this degree of flow limitation [7], and some electrical activity (mostly delta frequencies) may be seen. However, as the CBF continues to decrease towards the infarction threshold (≤10–12 ml/100 g/min), the EEG becomes silent and cellular damage becomes irreversible [5–7].

EEG wave changes occurring in ischaemic brain tissue have been investigated in many studies, with findings identifying significant changes [8–12]. These EEG changes occur especially in the form of a decrease in high-frequency brain waves and an increase in low-frequency wave rates [8].

It is known that continuous EEG monitoring benefits the early detection of brain ischaemia [5, 6, 13]. However, the amount of space needed and the connection cables of the EEG devices cause difficulties in the instant follow-up. The need for separate expert staff who follow the brain waves instantly and evaluate the changes also poses a challenge. The quantitative EEG system is a computer-aided system that shows results instantly by processing the obtained EEG waves. Neurofeedback devices based on the principle of instant quantitative EEG wave tracking are used in the treatment of diseases such as hyperactivity adjustment disorders. However, their efficiency in the field of neuroplasty is still under discussion [14]. These devices, which are intended for use with different ailments, have the potential to be suitable for instant detection of brain ischaemia because of their ability to record instant EEG results and to process these data. In addition, they have been minimized to facilitate their use in children. If these devices can be shown to follow the wave changes in brain ischaemia properly, their use in patients at risk will be of great benefit. However, there are not enough studies in the literature regarding the monitoring of acute ischaemic brain wave changes with neurofeedback devices. An animal experiment was designed for this purpose. The goal of the study was to determine whether ischaemic brain wave changes can be monitored with the neurofeedback device by following the brain EEG wave activities of the rabbits in which brain ischaemia was created. In addition, brain tissues removed to confirm the presence of ischaemia were examined histopathologically to determine the apoptotic index (AI).

MATERIALS AND METHODS

This study was approved by the institutional animal use and care committee of Canakkale Onsekiz Mart University and was conducted in accordance with the Helsinki Declaration of the World Medical Association recommendations on animal studies (Protocol date/no: 09-11-2018/1800150180).

Experimental animals

Twenty-four male New Zealand rabbits aged 11–14 months and weighing between 2.1 and 3.3 kg were used for the study. Standard rabbit food, water and maintenance needs were fulfilled throughout the study. Rabbits were kept in special steel cages in which they were separated, at a temperature of 22 ± 2°C in a special room, with humidity of 55–60% and a 12-h dark/light cycle.

Study groups

A total of 24 rabbits were randomized equally into 3 groups. The first group was the carotid ischaemia (CI) group ($n = 8$). Brain ischaemia was created by clamping the bilateral main carotid arteries for 15 min to create conditions similar to those of the brain ischaemia that may occur intraoperatively. The second group was the global ischaemia (GI) group ($n = 8$). Brain ischaemia was created by clamping the bilateral subclavian artery and the bilateral main carotid artery for 15 min to simulate situations in which the total circulation is arrested. In the CI and GI groups, a 30-min reperfusion period was applied after ischaemia [15] and then all brain tissue was quickly removed. The third group was a sham group ($n = 8$) in which the vascular structures were prepared using the same surgical procedure, but all brain tissue was removed without experiencing ischaemia.

Anaesthesia protocol, invasive monitoring and electroencephalographic follow-up

After premedication with xylazine (10 mg/kg), anaesthesia was induced by intramuscular administration of ketamine hydrochloride (40 mg/kg). An isoflurane inhaler FiO2 was given as a 60% mixture for maintenance of anaesthesia. The vital signs of the rabbits were monitored by invasive arterial blood pressure (Mp36r; Biopac, Goleta, CA, USA) via a catheter placed in the femoral artery and by oxygen saturation with the pulse oximeter placed on the ear (Im8; Edan, San Diego, CA, USA). A single EEG sensor was placed under the scalp, corresponding to the vortex region on the rabbit, and the other sensors were fixed to the lower parts of both ear roots (A3 pendant; Pocket Neurobics, Brookvale, Australia) (Fig. 1). Vascular access was provided by a cannula placed in the contralateral femoral vein. Fluid volume support (10 cc/kg) was provided when required with isotonic serum during all procedures, and the arterial mean pressure was maintained above 50 mmHg.

The application of surgical procedures and operations

The necks, ears and legs of the rabbits were shaved and fixed in the supine position. A median skin incision was made from the upper midline sternum to the epiglottic region, the subcutaneous tissues were dissected and the trachea and vascular structures were prepared.

In the CI group, the bilateral carotid artery was prepared and clamped for 15 min to produce ischaemia. In the GI group, the bilateral subclavian artery and bilateral main carotid artery were prepared and clamped for 15 min to create ischaemia. Then, the clamps were removed and brain reperfusion was applied for 30 min. All subjects received unfractionated heparin (100/kg intravenously) 5 min before arterial clamping to prevent thrombus formation. Volume replacement was performed in the subjects when required by closely monitoring the haemodynamics (10 ml/kg). After perfusion of the brain ceased, breathing was supported with manual ambulation by placing an endotracheal tube in the subjects before respiratory depression developed (rate, 80–100/min). Close follow-up of haemodynamics continued; hypotension was prevented; and mean arterial pressure was maintained above 50 mmHg. The same surgical procedure was performed in the sham group, but ischaemia was not created. A craniotomy was then performed, and the brain tissues were removed for histopathological examination after the procedures were completed in all groups.

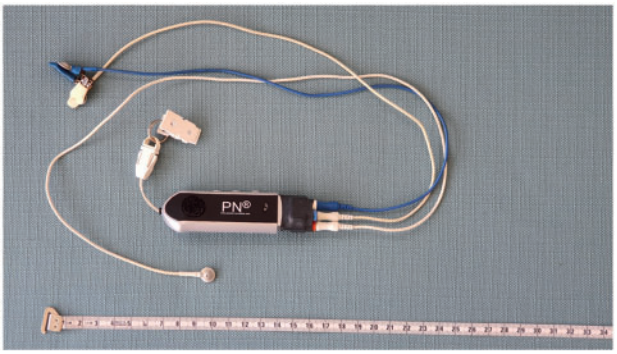

Figure 1: Neurofeedback device.

In all groups, 5 min before beginning the procedure and throughout the procedure, the data were recorded in a computer with instant EEG monitoring and a Wi-Fi connection. Implementation and removal times of clamps were marked in the EEG recordings.

Histopathological evaluation

After the surgical procedure was completed, the brains were fixed in 10% neutral buffered formaldehyde. The samples were prepared from the same anatomical regions, including the hippocampus and parietal lobe cortex, in each subject. To show groups of apoptotic cells, stains were administered after 4-micron-thick sections were cut from paraffin blocks. The ApopTag® Peroxidase In Situ Apoptosis Detection Kit (Merck Millipore, Darmstadt, Germany) was used. Sections of each group were evaluated using a camera attached to a microscope (Cx43; Olympus, Tokyo, Japan) and images were recorded for further analysis. Then, a total of 500 cells were counted under a microscope in 5 randomly selected areas of sections taken from each sample. Cells with nuclei stained blue were considered normal and those stained brown were considered apoptotic. The AI was calculated as a percentage. Histopathological evaluation was performed by an expert histologist who was blinded to the groups from which tissues were obtained.

Processing of electroencephalographic waves

EEG wave activity of all subjects was determined with a neurofeedback device (Fig. 1), transferred to a computer via Wi-Fi and recorded. The recorded brain EEG wave activities were analysed by processing with BioReview, version 1.7 (Cyberevolution; Seattle, WA, USA). Delta, theta, alpha, beta, gamma and total wave (sum of all EEG wave values) EEG activities were determined. Average amplitude values (AAV) indicate the average value of the amplitude levels of an EEG wave, and wave standard deviation values (WSDs) indicate the amplitude distribution in an EEG wave, as the ischaemic EEG indicator [16]. Not all EEG activities were processed in the BioReview programme because the experiment was not designed to compare the EEG wave activities as the ischaemic indicator. Therefore, the most dominant waveform, the delta wave and the total wave data were processed,

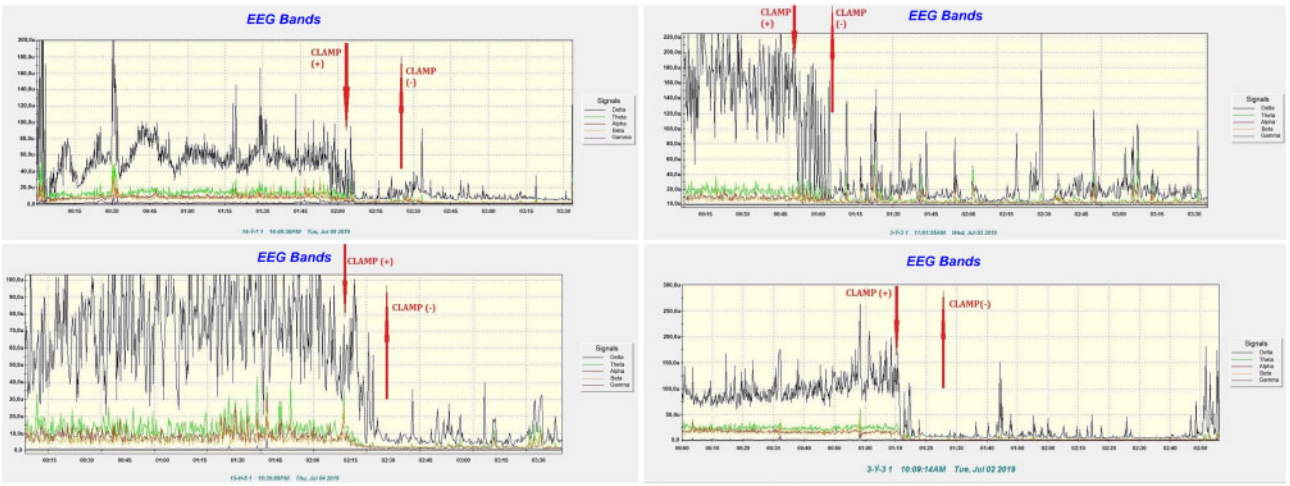

Figure 2: Global ischaemia group delta, theta, alpha, beta and gamma wave amplitude/time (μ volt/h:min) graphs. Clamp (+), the moment of placing the clamps; clamp (-), the moment the clamps are removed.

and the results were obtained. The alteration rates (ARs) were determined by dividing these values into the values obtained after clamping and before clamping because decreases were expected in the wave amplitude and frequency levels when brain ischaemia occurred [5, 7, 8, 16]. Because there was no clamping in the sham group, the same values were obtained by comparing the initial 5 min with the last 5 min of EEG data.

Statistical analyses

Statistical analyses were conducted using SPSS, version 21.0 (IBM, Chicago, IL, USA) software. Continuous variables were defined as the mean and standard deviation. The suitability of variables for normal distribution was examined using histograms and the Shapiro–Wilk test. The differences between the groups were evaluated with the analysis of variance test, and the in-group comparisons were made using the post hoc Tukey test after analysing the homogeneity of the variances with the Levene test. The correlation between variables was examined using the Pearson test. *P*-values <0.05 were considered significant.

RESULTS

Rabbit EEG wave activities with ischaemia marked before and after the clamping are demonstrated in Figs. 2 and 3. The delta and total wave AR values and statistical results of the groups are shown in Table 1. Statistical significance was determined in all values except the sham, CI group delta and total WSD AR values ($P = 0.196$; $P = 0.207$) between the groups. An inverse correlation was determined between the AR values of all waves obtained by histopathological AI (Fig. 4). There was a strong and statistically significant negative correlation between AI (TUNEL: terminal deoxynucleotidyl transferase dUTP nick end labelling) and all EEG data (Table 2).

Figure 2 shows a significant decrease in all EEG wave amplitudes seconds after the clamps were placed in the GI group. A strong statistical significance was determined in all EEG wave ARs ($P < 0.001$). These decreases continued to persist in the GI group after the clamps were removed. This condition may be associated with severe or permanent brain damage. A histopathologically high AI (55.8%; $P < 0.05$) value in the GI group supports this idea (Fig. 4). It is remarkable that the EEG wave amplitude decreases observed after the clamp was placed in the CI group were not prominent and did not show a permanent form (Fig. 3). When the sham and CI groups were compared, there was a significant change in delta AAV AR and total AAV AR values ($P < 0.001$), whereas there was no significant change in delta WSD AR ($P = 0.1$) and total WSD AR ($P = 0.2$) values. The AI value in the CI group (40.7%) was significantly different from that in both the sham (17.8%; $P < 0.001$) and GI (55.8%; $P = 0.001$) groups.

DISCUSSION

The brain is one of the organs most vulnerable to ischaemia. Severe irreversible brain damage can occur as a result of brain ischaemia during surgery or during normal life. Brain perfusion may be at high risk, especially in operations that require the aortic arch, carotid artery or total circulatory arrest, which may affect brain circulation. Brain wave changes begin within seconds with the start of brain ischaemia [17]. Rescue interventions can be performed before permanent brain damage with the help of these waves. The mentioned neurofeedback devices are suitable for EEG monitoring of patients at risk.

It is obvious that a difference exists between human brain waves and rabbit brain waves. However, sudden and significant changes in the current waveforms parallel to the development of ischaemia are also expected.

The results demonstrated that the brain damage in the CI group was significantly higher than that in the sham group and that brain damage in the GI group was significantly higher than damage in the CI group (Table 1). The change in WSD values was not significant in the CI group. However, it showed a significant decrease in the GI group, which may be related to greater brain damage or brain death in the GI group. This difference between the CI and GI groups can be interpreted as follows: Brain circulation in the CI group was achieved by collateral circulation (unclamped subclavian arteries) after a decrease (Fig. 3). In the GI group, there was not enough collateral perfusion to the brain because all arteries were clamped. The permanent decrease in brain wave amplitude forms supports this view (Fig. 2). The fact that

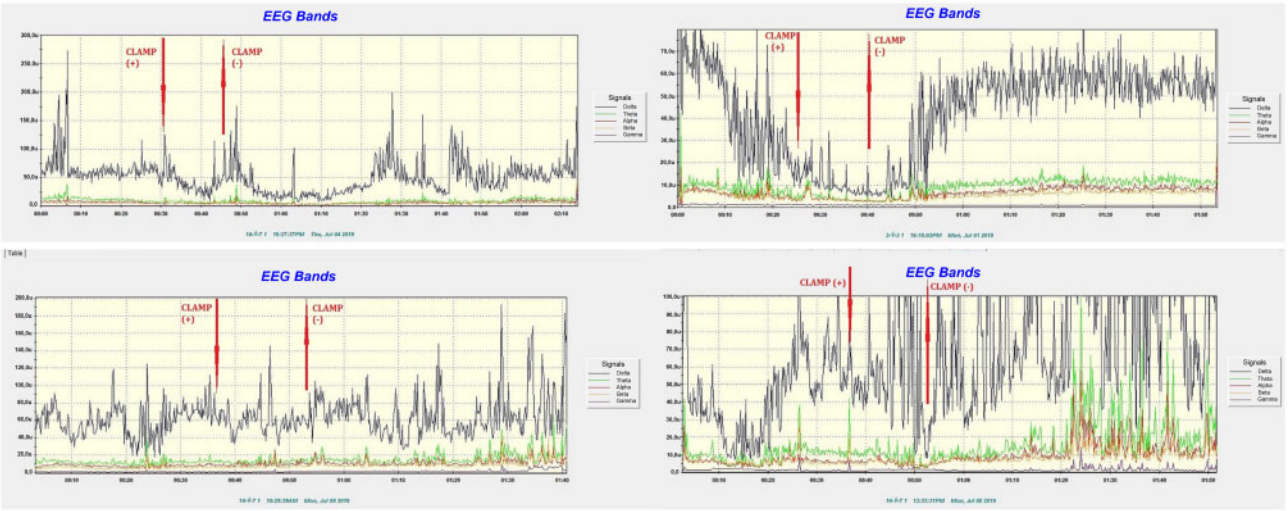

Figure 3: Carotid ischaemia group delta, theta, alpha, beta and gamma wave amplitude/time (μ volt/h:min) graphs. Clamp (+), the moment of placing the clamps; clamp (-), the moment the clamps are removed.

Table 1: Apoptotic index and electroencephalographic wave values in the groups and their statistical significance

	Sham (I)	Carotid ischaemia (II)	Global ischaemia (III)	ANOVA *P*-value	Post hoc Tukey test *P*-value		
	Mean (SD)	Mean (SD)	Mean (SD)		I versus II	I versus III	II versus III
Delta AAV AR	1.02 (0.09)	0.69 (0.21)	0.16 (0.06)	**<0.001**	**0.008**	**<0.001**	**<0.001**
Delta WSD AR	1.01 (0.13)	0.87 (0.18)	0.29 (0.15)	**<0.001**	0.1	**<0.001**	**<0.001**
Total AAV AR	0.99 (0.05)	0.78 (0.04)	0.49 (0.16)	**<0.001**	**<0.001**	**<0.001**	**0.003**
Total WSD AR	1.22 (0.37)	0.98 (0.24)	0.37 (0.19)	**<0.001**	0.2	**<0.001**	**0.001**
TUNEL AI	17.88 (6.20)	40.75 (6.90)	55.88 (7.68)	**<0.001**	**<0.001**	**<0.001**	**0.001**

AAV: average amplitude value; ANOVA: analysis of variance; AI: apoptotic index; AR: alteration ratio; SD: standard deviation; TUNEL: terminal deoxynucleotidyl transferase dUTP nick end labelling; WSD: wave standard deviation.

the waves failed to return to their original form after the clamps were removed in the GI group can be interpreted as an indicator of heavy or permanent brain damage (Fig. 4). The rapid decrease (within seconds) in brain wave amplitudes with a decrease in brain perfusion is an expected response [5, 7, 8]. Also, the same decrease during the time periods occurred in our study of the ischaemia model (mean: 18 ± 4 s). Furthermore, the fact that the significant decrease in WSD did not occur in the CI group but did occur in the GI group may be an indicator of permanent brain damage in the evaluation of ischaemic damage. A strong negative correlation was determined between the AI values and the values of the waves (Table 2). This correlation indicates that, as the wave values decrease, the AI values increase. In other words, the more brain damage that occurs, the more the EEG wave amplitude levels and changes show a decrease. There are many studies on this topic in the literature [10] with similar findings. These values indicate that EEG wave decreases can provide information about both brain ischaemia and brain damage.

Furthermore, the positive aspects of follow-up the patient's alertness and depth of anaesthesia by monitoring EEG waves have been reported in cardiovascular surgical procedures in which the patient is under general anaesthesia [18]. In a study by Friedman *et al.*, the positive benefits of continuous EEG follow-up in intensive care patients at risk were reported, though it was emphasized that these devices can be provided with high costs primarily in large centres. However, it was also emphasized that it would be advantageous to conduct a cost analysis of the benefits these devices would provide [19]. This information indicates that continuous EEG follow-up is a suitable option both for patients in the intensive care risk group and for those receiving perioperative anaesthesia and cerebral circulation follow-up. However, Caricoto *et al.* pointed out that, although its benefits are known, continuous EEG follow-up is not widespread and an experienced neurointensivist is required to follow the device [20]. Similarly, they stated that the application of continuous EEG follow-up was limited because the definitive diagnostic criteria are still not fully developed [21] and the limited number of large centres that can currently perform the application use different criteria [22]. It is noteworthy that, although many publications report the benefits of continuous EEG follow-up, it has not become

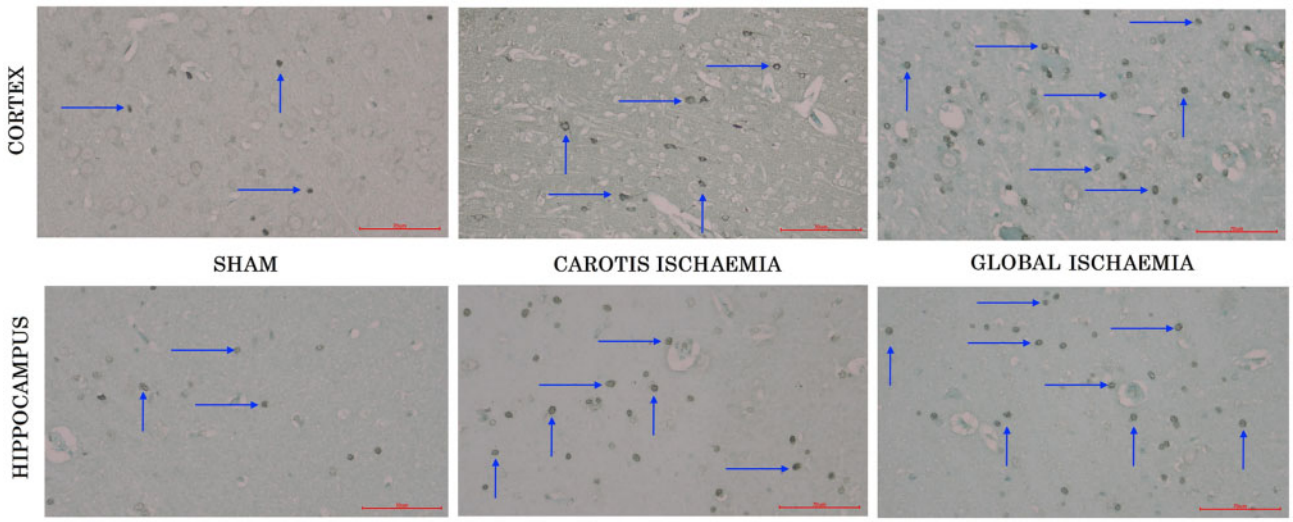

Figure 4: The apoptotic cells in the histopathological study from the hippocampus and cortex regions in the groups, indicated with a blue arrow.

Table 2: Correlation analysis of wave change data with apoptotic index value

		Delta AAV AR	Total AAV AR	Delta WSD AR	Total WSD AR
TUNEL AI	Correlation coefficient	-0.812	-0.874	-0.789	-0.780
	Pearson test	<0.001	<0.001	<0.001	<0.001

AAV: average amplitude value; AI: apoptotic index; AR: alteration ratio; TUNEL: terminal deoxynucleotidyl transferase dUTP nick end labelling; WSD: wave standard deviation.

widespread in current use for the stated reasons [20–22]. The neurofeedback devices that we have mentioned and used in our experiments were reduced to small sizes so they could be easily used in children. They were also wireless, computer-compatible and easy to use and different alarm levels can be created, because they are devices that continuously monitor EEG. These devices have been simplified for parents to use at home and are helpful for continuous EEG follow-up without an expert neurointensivist or neurophysiologist. Additional analyses can be based on different criteria by reprocessing the EEG records in a computer. This situation can facilitate scientific studies and establish new diagnostic criteria. All these factors show that these devices should be considered for making continuous EEG follow-up easy.

CONCLUSION

Significant EEG wave changes resulting from experimental brain ischaemia were analysed with the use of a neurofeedback device. The results indicated that the change in the delta and total wave standard deviations may be additional indicators of the formation of permanent brain damage. It is believed that neurofeedback devices can provide practical useful solutions in perioperative and intensive care applications because they are easy to use, do not require much space, are low cost, can be used with a wireless computer connection and have adjustable warning systems. These results should be supported by clinical studies in which early indicators and warning levels are examined and efficiency evaluations are performed. However, because this new technology is being used in a limited number of experimental subjects, the results need validation with other devices (e.g. near-infrared reflectance spectroscopy) to support future clinical use of the device.

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Author contributions

Sonay Oğuz: Conceptualization; Data curation; Formal analysis; Methodology; Project administration; Software; Visualization; Writing—original draft; Writing—review & editing.

Reviewer information

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