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Identification of hypoglycemic states for patients with T1DM using various parameters derived from EEG signals

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***Abstract*— For patients with Type 1 Diabetes Mellitus (T1DM), hypoglycemia is a very common but dangerous complication which can lead to unconsciousness, coma and even death. The variety of hypoglycemia symptoms is originated from the inadequate supply of glucose to the brain. In this study, we explore the connection between hypoglycemic episodes and the electrical activity of neurons within the brain or electroencephalogram (EEG) signals. By analyzing EEG signals from a clinical study of five children with T1DM, associated with hypoglycemia at night, we find that some EEG parameters change significantly under hypoglycemia condition. Based on these parameters, a method of detecting hypoglycemic episodes using EEG signals with a feed-forward multi-layer neural network is proposed. In our application, the classification results are 72% sensitivity and 55% specificity when the EEG signals are acquired from 2 electrodes C3 and O2. Furthermore, signals from different channels are also analyzed to observe the contributions of each channel to the performance of hypoglycemia classification.**

I. Introduction

According to the Diabetes Control and Complications Trial Research Group [1], intensive insulin therapy is an effective treatment for Type 1 Diabetes Mellitus (T1DM) patients which can significantly delay the appearance as well as reduce the risk of acute diabetic complications like retinopathy, nephropathy and neuropathy. However, it also increases threefold the incidence of hypoglycemia among T1DM patients over conventional therapy. Hypoglycemia, which is the medical term of the state of low blood glucose level (BGL), is the most dangerous complication for individuals with T1DM. It is considered as an important barrier which limits the application of glycemic control therapies for diabetes patients.

Hypoglycemia can produce a variety of symptoms, from mild to severe episodes [2, 3]. Mild hypoglycemia causes sweating, nervousness, heart plumping, confusion, anxiety, etc. It can be fixed by eating or drinking glucose-rich food. If left untreated, hypoglycemia can become severe and lead to seizures, coma, and even death. Hypoglycemia reduces the quality of life for patients as well as carers by causing chronic anxiety about future potential hypoglycemic episodes [4].

One of the most dangerous effects of hypoglycemia is hypoglycemia unawareness. This is caused by frequent episodes of hypoglycemia which can lead to changes in the response of patients' bodies. In unawareness situations, patients' bodies do not release the hormone epinephrine which is the origin of early warning symptoms for patients like sweating, hunger, anxiety [3, 5]. Because of no warning, patients normally cannot realize the occurrence of hypoglycemia until it becomes severe and could lead to fatal damage. Nocturnal hypoglycemia is especially fearful for T1DM patients as sleep can make the symptoms unclear. Because of its severity, a large number of studies have been conducted to develop a system that can detect the onset of hypoglycemia and give an alarm in time for patients with T1DM.

Currently, there are some devices using different techniques to detect hypoglycemia on the market. Some of them require gradually taking patients' blood samples to determine the blood glucose level. This method gives relatively exact information about hypoglycemic status. However, taking blood is uncomfortable for patients and it is very inconvenient for continuous monitoring, especially during night. Obviously, non-invasive technique is a better solution for these disadvantages.

Recently, we developed an effective and sensitive system to monitor hypoglycemia non-invasively using physiological parameters such as heart rate, skin impedance and electrocardiogram (ECG) parameters [6, 7]. However, although hypoglycemia can produce a large number of symptoms, like sweating or increased cardiac output, the principal problems arise from an inadequate supply of glucose, which is the primary metabolic fuel to the brain [5]. Since the electroencephalogram (EEG) signal is directly related to the metabolism of brain cells, hypoglycemia is believed to cause early changes in EEG that can be detected non-invasively.

Previous studies have attempted to find changes in EEG signals due to hypoglycemia [8-10]. Nevertheless, they stopped at using statistical techniques to point out spontaneous EEG changes caused by the onset of hypoglycemic episodes, or permanent EEG changes caused by frequent episodes.

In a recent study, researchers proposed a methodology of using digital signal processing and artificial neural network to detect hypoglycemia from EEG signals [11]. This study

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led to the results of 49.2% accuracy, 76% sensitivity and 32.5% specificity when the neural network was trained and validated with different subject groups. In another study, EEG was used as the physiological parameters to detect hypoglycemia [12]. Although this study has produced a real-time system that can detect hypoglycemia, it uses implanted electrodes to record EEG signals. Recently, we proposed a Bayesian neural network algorithm for the detection of hypoglycemia using EEG signals and surface EEG electrodes [13].

In this paper, we aim to explore the effects of nocturnal hypoglycemia on EEG signals derived from T1DM patients. Using Fast Fourier Transform (FFT), different EEG parameters are extracted and analyzed to find important features that significantly change under hypoglycemia conditions. The EEG signals from different brain positions are used to observe the response of different brain area to hypoglycemia. Finally, a method of classification using neural network will be investigated to classify hypoglycemia from EEG signals. Section II provides an overview of the methodology used in our study. Results of the study will be mentioned in Section III. A conclusion for this study is drawn in Section IV.

II. METHODS

A. Study

Five T1DM adolescents (between the ages of 12 and 18 year old) volunteered for the overnight hypoglycemia study at the Princess Margaret Hospital for Children in Perth, Australia. During the study, EEG signals were continuously recorded and stored using a Compumedics system with the sampling rate of 128 Hz. The EEG electrodes were positioned at O1, O2, C3 and C4 according to the International 10/20 system, referenced to Cz. We also placed 2 electrodes at patients' chins to acquire the electro-myogram (EMG) signals and 2 electrodes near patients' eyes to measure the electro-oculogram (EOG) signals. The actual BGLs were routinely collected to be used as reference using Yellow Spring Instruments with the general sampling period of 5 minutes. Data were collected with the approval of the Women's and Children's Health Service, Department of Health, Government of Western Australia, and with informed consent.

B. Feature extraction

After finalizing the signal acquiring step, signal processing is carried out using EEGLAB [14]. In EEGLAB, EEG signals from patients are filtered using an IIR highpass filter with a cut-off frequency of 2 Hz to get rid of low frequency artifacts and a notch filter at 50Hz to remove power noise. The data after being processed which consist of two phases (normal and hypoglycemia) are segmented into 5-second segments. A visual artifact-rejecting method is used to exclude EEG segments contaminated with artifacts. Segments containing significant artifacts are discarded based on EMG and EOG signals. Finally, the non-artifact signals are transformed into the frequency domain using Fast Fourier Transform (FFT). This transformation results in the power spectral density $P(f)$ which then is subdivided into 3 frequency bands: theta (θ: 3.5-7.5Hz), alpha (α: 8-13 Hz) and beta (β: 13.5-30Hz).

The final extracted feature set includes 6 parameters at each electrode position or channel. The power level within each band at each channel is calculated using a numerical integration technique (the trapezoidal rule). The centroid frequency is defined as the center gravity of each frequency band which subdivides the area under the spectral curve into two identical parts.

The Student's t-test is then applied to every feature to estimate the differences between pre-hypoglycemia and hypoglycemia conditions. Probability values (p-values) less than 0.05 are considered to be significant. The statistically significant features will be used as inputs for the classification. Moreover, in this study, we also explore the differences between electrode positions to find out whether the responses to hypoglycemia of different channels are similar or not.

C. Classification

Artificial neural networks [15, 16] have been employed popularly in biomedical area as a powerful tool of classification and pattern recognition. It has been recognized that neural network is a successful method in classifying complex situations. It can effectively model non-linear relationships between inputs and outputs.

In this study, we develop a neural network with feed-forward multi-layer structure for hypoglycemia classification. This neural network is trained by the Levenberg-Marquardt algorithm which is an effective training algorithm. This network consists of one input layer which includes the features extracted from EEG signals, one hidden layer and one output layer. The output layer has one node which indicates the state of hypoglycemia or non-hypoglycemia. In our study, the BGL threshold for defining hypoglycemia state is set at 3.3mmol/l. 30 data points from each patient are used for comparison and classification, corresponding to the 5-minute duration of each blood glucose sampling point. At each blood sampling point, a 30-second non-artifact fragment of signal is used and divided into six 5-second segments for the feature extraction. The overall data are grouped into a training set, a validation set and a testing set. The optimized neural network is trained from the training set with a stopping procedure determined by the validation set. The testing set is then used to test the generalization of the neural network.

III. RESULTS

The responses of five patients show significant changes during the hypoglycemia state against pre-hypoglycemia state. The actual BGL profiles used in the study are shown in Fig. 1.

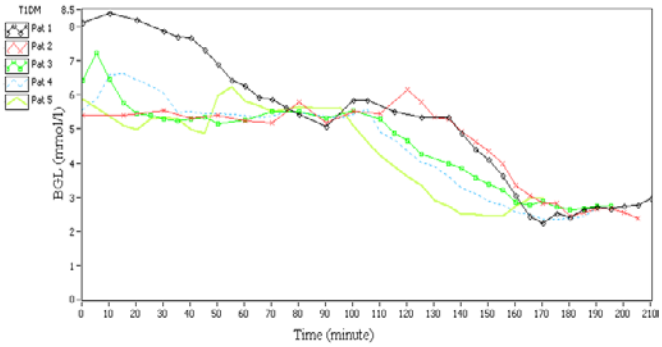

Fig. 1. Actual blood glucose level profiles in 5 T1DM children

Statistical results at each channel are presented in Tables I-IV. Significant features are reported in bold. Because the power levels are very different between patients, an appropriate normalization strategy is used to reduce the variability of these features and to enable group comparison. To do this, we normalize each patient's power levels against their corresponding values at time zero. There are some slight changes in alpha power and theta power at channels O1 and O2. The beta power levels at all channels except C3 do not change significantly between normal and hypoglycemia states. Because these responses are not consistent with all patients, possibly they are caused by the changes in sleep stages of patients during night. The study shows that the centroid alpha frequency is the most significant feature. Under hypoglycemia conditions, the centroid alpha frequency of 5 patients reduces significantly at all four channels ($p \leq 0.0001$). The results also show an increase in centroid theta frequency at all channels (p = 0.026 at O2, 0.007 at C3 and 0.006 at C4). There is no significant change in the centroid beta frequency across all four channels (p = 0.037 at channel C3 and $p > 0.05$ at others). These results demonstrate that during the hypoglycemia onset, possibly there is a power shift to the border area between alpha band and theta band in the power spectra of EEG signals. This is an important finding that should be explored more in future studies to find other features which can enhance the performance of hypoglycemia classification.

Based on these statistical results, the most significant features are selected as inputs of classification. The final set has 8 features including the centroid theta frequency and the centroid alpha frequency at each channel. A neural network is developed using these features as inputs.

TABLE I
CHANGES UNDER HYPOGLYCEMIA CONDITION – CHANNEL C3

Feature	Normal State	Hypoglycemia State	p-value
Power θ	**1.5435 ± 0.7411**	**1.4107 ± 0.6309**	**p = 0.01**
Power α	0.8802 ± 0.3596	0.8510 ± 0.3147	p = 0.242
Power β	**0.7694 ± 0.1965**	**0.8284 ± 0.4013**	**p = 0.011**
CF θ	**5.2347 ± 0.2304**	**5.2800 ± 0.2323**	**p = 0.007**
CF α	**10.2910 ± 0.3107**	**10.1531 ± 0.3415**	**$p \leq 0.0001$**
CF β	**19.8080 ± 0.7664**	**19.9430 ± 0.8253**	**p = 0.037**

TABLE II
CHANGES UNDER HYPOGLYCEMIA CONDITION – CHANNEL C4

Feature	Normal State	Hypoglycemia State	p-value
Power θ	1.3392 ± 0.7256	1.3177 ± 0.7793	p = 0.691
Power α	1.1012 ± 0.4812	1.0982 ± 0.4117	p = 0.928
Power β	0.8907 ± 0.2827	0.9305 ± 0.3601	p = 0.078
CF θ	**5.2318 ± 0.2128**	**5.2757 ± 0.2377**	**p = 0.006**
CF α	**10.2688 ± 0.3136**	**10.1619 ± 0.3221**	**$p \leq 0.0001$**
CF β	20.0541 ± 0.8664	20.1644 ± 0.8197	p=0.074

TABLE III
CHANGES UNDER HYPOGLYCEMIA CONDITION – CHANNEL O1

Feature	Normal State	Hypoglycemia State	p-value
Power θ	**1.6606 ± 0.9692**	**1.5098 ± 0.8384**	**p = 0.025**
Power α	**0.7080 ± 0.4129**	**0.7950 ± 0.5205**	**p = 0.008**
Power β	0.7866 ± 0.3459	0.8348 ± 0.4015	p = 0.069
CF θ	5.2586 ± 0.2260	5.2897± 0.2375	p = 0.095
CF α	**10.2369 ± 0.3046**	**10.0835± 0.3160**	**$p \leq 0.0001$**
CF β	19.8029 ± 0.8032	19.8078± 0.7550	p = 0.932

TABLE IV
CHANGES UNDER HYPOGLYCEMIA CONDITION – CHANNEL O2

Feature	Normal State	Hypoglycemia State	p-value
Power θ	**1.6249± 0.9068**	**1.4449 ± 0.7043**	**p = 0.003**
Power α	**0.7717 ± 0.3769**	**0.8838 ± 0.4971**	**$p \leq 0.001$**
Power β	0.7659 ± 0.3246	0.8081 ± 0.3617	p = 0.084
CF θ	**5.2592 ± 0.2077**	**5.2948 ± 0.2433**	**p = 0.026**
CF α	**10.2110 ± 0.2929**	**10.0883 ± 0.3224**	**$p \leq 0.0001$**
CF β	19.7804 ± 0.7880	19.7957 ± 0.6643	p = 0.779

The overall data are grouped into a training set, a validation set and a testing set, with ratio of 2:1:2 patients. The corresponding Receiver Operating Characteristic (ROC) Curve for the combined training/validation dataset is shown in Fig. 2. With this ROC curve, the most suitable cut-off point is selected as the threshold to distinguish between the hypoglycemia and normal states. To make the comparison between cases easier, we choose the point that gives the result of 70% sensitivity for the training/validation set. After training, the testing set is applied to find the testing sensitivity and specificity. All results are reported in Table V. The best number of hidden node is also given in this table.

Another purpose of our study is to find out how the responses of different channels contribute to the performance of classification. To do this, different neural networks are developed with inputs corresponding to data from only one EEG channel or from two EEG channels separately. For the consideration of the results from two EEG channels, we evaluate the results from various two channels at different sides and different areas of the brain (C3 and O2, C4 and O1).

TABLE V
CLASSIFICATION RESULTS

Inputs	Number of Hidden node	ROC area	Cut-off point	Sensitivity (%)	Specificity (%)
O1,O2,C3,C4	8	0.72	-0.3537	70	55
O1	10	0.64	-0.3370	74	49
O2	7	0.69	-0.3494	70	51
C3	7	0.66	-0.3343	78	37
C4	8	0.61	-0.3422	75	36
O2,C3	9	0.71	-0.3133	72	55
O1,C4	9	0.68	-0.4072	71	47

The classification using data from all four channels results in a sensitivity of 70% and specificity of 55% which indicate a potential ability of detecting hypoglycemia from EEG signals. With these results, it is proved that centroid theta frequency and centroid alpha frequency are two important features in hypoglycemia detection. When using the features of one channel only, the classification results are very similar between O1 and O2 as well as C3 and C4. The results are better at O1 and O2 against those at C3 and C4. Hypoglycemia classification using data from the two EEG channels with electrodes positioned at O2, C3 yields the best results with 72% sensitivity and 55% specificity. These results demonstrate that neural network algorithms can be developed to provide good detection of hypoglycemia episodes using only two EEG channels or even one EEG channel. With the final aim of developing a real-time EEG system to early detect hypoglycemic episodes in patients with T1DM, reducing the number of features as well as electrodes is very important for effective real-time implementation.

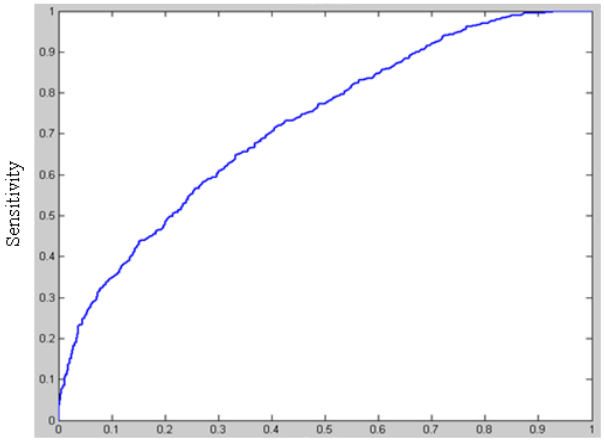

Fig. 2. ROC Plot

IV. CONCLUSION

In this paper, we explore the changes of EEG parameters associated with hypoglycemia in T1DM patients. A neural network algorithm is developed to detect episodes of hypoglycemia from EEG signals. With classification results of 72% sensitivity and 55% specificity derived from two channels C3 and O2, it is shown that hypoglycemia can be detected non-invasively and effectively using EEG signals. However, the overall accuracy including both sensitivity and specificity would be improved. For future research, a post-classification stage which involves some effective trending strategies will be developed. Moreover, advanced computational intelligence technologies will be applied to enhance the performance of hypoglycemia detection.

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