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Hypoglycemia-induced EEG complexity changes in Type 1 diabetes assessed by fractal analysis algorithm

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ABSTRACT

In recent years, hypoglycemia-induced changes in the EEG signal of patients with Type 1 diabetes (T1D) have been quantified and studied mainly by linear approaches. So far, sample entropy (SampEn) is the only nonlinear measure used in the literature. SampEn has the disadvantage of being computationally demanding and, hence, difficult to be used in real-time settings. The present study investigates whether other nonlinear indicators, less computationally demanding than SampEn, can be equally sensitive to changes in the EEG signal induced by hypoglycemia. For such a scope, we considered a database obtained from 19 T1D patients who underwent a hyperinsulinemic-hypoglycemic clamp while continuous EEG was recorded. We analyzed the P3-C3 EEG derivation data using three measures of signal complexity based on an approach originally proposed by Higuchi in the 80s: the original measure of fractal dimension and two new indexes based on the Higuchi's curve. All the three indicators revealed a statistically significant decrease in EEG complexity in the hypo- versus euglycemic state, which is in line with the results previously obtained with SampEn. However, the lower computational cost of the proposed indicators (~O(N) versus ~O(N^2)) makes them potentially more suited for real-time applications such as the use of EEG to trigger hypoglycemia alerts.

1. Introduction

Type 1 diabetes (T1D) is an autoimmune chronic disease, where the insulin-producing beta cells in the pancreas are destroyed. Thus, patients affected by T1D need daily insulin injections. One of the most important complications of insulin treatment is the risk of hypoglycemia (blood glucose, BG < 70 mg/dl), a severe condition that potentially progresses into coma without subject awareness. The brain is dependent upon glucose as a primary source of energy. Indeed, glucose is needed for neuronal and non-neuronal cellular maintenance and for the generation of neurotransmitters [1]. Low blood glucose levels affect the ionic currents within the neurons of the brain and impair brain function. The changes in these ionic currents generate voltage fluctuations, which can be measured by electroencephalogram (EEG).

In the last years, hypoglycemia-associated EEG changes have been investigated in several studies, mostly employing linear indicators like power spectral density and coherence. For instance, it has been shown that EEG power spectral density in the conventional theta ([4–8] Hz) and alpha ([8–13] Hz) bands increases during hypoglycemia with respect to euglycemia [2–4]. A decrease of EEG coherence during the hypoglycemic state was also reported [5]. These results motivated the idea of employing the brain as a biosensor to detect hypoglycemia in real-time, and highlighted the need for a robust panel of EEG indicators to monitor the glycemic state [6].

In the investigation of the relationship between the glycemic state and the EEG signal, the use of nonlinear indexes can yield information complementary to that obtainable by linear methodologies, providing new insights into the effects of hypoglycemia on the brain and possibly improving the methodologies for the

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real-time detection of hypoglycemic events. However, to the best of our knowledge, application of nonlinear indicators to analyze hypoglycemia-associated EEG changes has only been reported by Fabris et al. [7]. They showed that a decrease of EEG complexity (here intended as signal irregularity) was shown to be induced by hypoglycemia by computing the sample entropy (SampEn) index [8] at various scale factors, employing the so-called multiscale entropy algorithm (MSE) [9].

Signal complexity can be assessed using various nonlinear indicators [10]. Among these, entropy-based algorithms are very popular and powerful for analyzing EEG and biomedical signals in general, e.g. [8,11–19], but their high computational cost may render their use difficult, in particular in real-time applications. Other approaches based on signal quantization, such as the Lempel-Ziv method [20], may overlook some information related to changes in the brain function during hypoglycemia.

The aim of this paper is to determine whether other nonlinear complexity indicators, based on fractal analysis, can be used to detect EEG changes related to hypoglycemia. In particular, we considered the Higuchi's measure of fractal dimension [21], already used in EEG analysis [22–24], and two new indexes reflecting both signal amplitude and frequency properties [25]. All the three indexes are characterized by a lower computational cost than SampEn, i.e. ($\sim O(N)$ versus $\sim O(N^2)$) [10]. Although a comprehensive benchmarking of the signal processing methods applicable to investigate EEG changes induced by hypoglycemia is out of the scope of the present study, the comparison of Higuchi's fractal dimension versus SampEn is of practical relevance, because the reduced computational cost of the former can allow the simultaneous computation of multiple features and on grouping their assessments obtained by temporally consecutive epochs.

2. Database

In order to investigate our hypothesis we consider the same data set used by Fabris et al. [7], obtained from 19 T1D patients who underwent a hyperinsulinemic-hypoglycemic clamp procedure while continuous EEG was recorded and blood glucose (BG) was frequently sampled.

2.1. Experimental protocol

The study we set-up has already been published and described in detail in [5,7,26]. Briefly, patients were recruited from the diabetes outpatient clinics at Nordsjællands Hospital, Hillerød and Steno Diabetes Center, Denmark. Inclusion criteria were type 1 diabetes for>5 years, age>18 years and being either hypoglycemia aware or unaware [27]. Exclusion criteria included: pregnancy, breastfeeding, any brain disorder, use of antiepileptic drugs, blocking drugs, or neuroleptic drugs, use of benzodiazepines within the last month, cardiovascular disease, and alcohol or drug abuse. For this study, 19 participants with T1D (58% males, mean age 55 ± 2.4 (SEM) years, diabetes duration 28.5 ± 2.6 years, HbA1c 8.0 ± 0.2%, 6 aware, 13 unaware) were considered. They were instructed to fast and not to take their morning insulin on the day of the study. Since they have no insulin production of their own blood, at the beginning of the study their insulin levels were low and glucose levels increased. The subjects underwent a hyperinsulinemic-hypoglycemic clamp with three steps. Participants were clamped at a euglycemic level, then during hypoglycemia with a target of 36–45 mg/dl, and, finally, during euglycemia following hypoglycemia. Hypoglycemia was induced by an intravenous infusion of fast-acting recombinant human insulin administered at an infusion rate of 1 mU/kg/min. Target BG was obtained by a variable infusion of glucose (200 mg/mL). BG was measured every 5–10 min. with

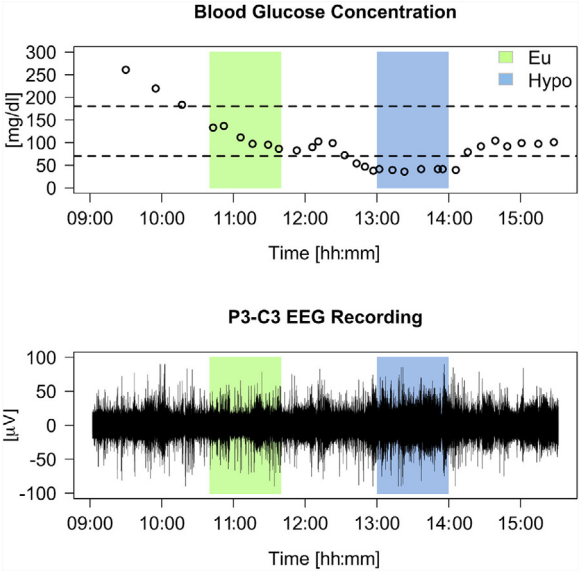

Fig. 1. Data from a representative subject, during the hyperinsulinemic-hypoglycemic clamp: (upper panel) blood glucose concentration (open circles denote YSI samples) during the daytime and simultaneous (lower panel) P3-C3 electroencephalography (EEG) recordings during the daytime. Green and blue areas refer to 1-h eu- and hypoglycemic intervals, respectively. (Color graphics are available online). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the use of a laboratory analyzer (model YSI 2300; Yellow Springs Instrument Co., Yellow Springs, OH). Participants were sitting in an armchair, not allowed to sleep, and under constant observation by a physician evaluating signs of neuroglycopenia. The local ethical committee approved the protocol and all patients gave their informed content.

During the (about) 8-h experiment, the EEG was acquired continuously from 19 channels with a digital EEG recorder (model Easy II; Cadwell Laboratories, Kennewick, WA) using standard cap electrodes, placed on the scalp according to the 10/20 international system. The EEG scan was analogically low-pass-filtered at 70 Hz and then digitally acquired and sampled at 200 Hz. The dynamic range of the EEG was ±4620 μV with an amplitude resolution of 0.14 μV. Internal noise level in the analog data acquisition system was estimated to be 1.3 μV root mean square. Fig. 1 shows the BG data, as well as the P3-C3 EEG recording collected in parallel in a representative subject, randomly taken from the database, during the daytime (the trend of the BG samples is similar in all the subjects).

2.2. Pre-processing

For each subject, two 1-h intervals, corresponding to eu- and hypoglycemia, were identified from the BG time-series by visual inspection as 70 < BG < 180 mg/dl and BG < 70 mg/dl, respectively (Fig. 1) [7]. For data analysis, the P3-C3 EEG derivation was chosen since the EEG signal from this scalp position is known to be highly affected by hypoglycemic events [3,6]. The P3-C3 EEG signal in the eu- and hypoglycemia intervals was split into epochs of 4 s in length, with 2 s overlap. Epoch length and overlap were chosen as a trade-off between the number of samples required to calculate the features for each epoch and the readiness required for a prompt identification of physiological changes.

EEG data can be affected by several sources of noise, such as body movements and propagation of bioelectrical muscles potentials, which are likely to add up into the electroencephalographic signal generated by the brain. As a consequence, recorded EEG signals