12

Using the Brain as a Biosensor to Detect Hypoglycaemia

Rasmus Elsborg, Line Sofie Remvig,
Henning Beck-Nielsen and Claus Bogh Juhl
Hypo-Safe A/S, Odense University Hospital, Sydvestjysk Sygehus Esbjerg
Denmark

1. Introduction

1.1 Definition of hypoglycaemia and its clinical importance

Hypoglycaemia can be defined as an abnormally low blood glucose concentration. This rather open definition implies that a strict biochemical definition may be easy and convenient but insufficient. In biochemical terms, blood glucose lower than 3.5 mmol/l will often be considered low in diabetes patients treated with insulin or oral hypoglycaemia agents. Both in diabetes patients and in healthy persons, however, spontaneous blood glucose values lower than this threshold may frequently be measured. Blood glucose values down to 2.7 mmol/l or even lower with limited or no symptoms can be measured following long term fasting in healthy humans (Hojlund et al., 2001). Diabetes patients with tight glucose control and recurrent episodes of hypoglycaemia may lack symptoms of hypoglycaemia even at very low glucose levels down to 1 mmol/l. Consequently, many different definitions of biochemical hypoglycaemia can be found in the literature regarding hypoglycaemia in diabetes.

In clinical terms, hypoglycaemia can be differentiated into mild, moderate or severe events. Mild hypoglycaemia is present when a diabetes patient experiences symptoms of hypoglycaemia such as sweating, shivering or palpitations. The patient is able to react appropriately by eating or drinking and thereby re-establish a normal blood glucose level, avoiding progression into severe hypoglycaemia. Moderate hypoglycaemia is present when the patient may or may not experience hypoglycaemia symptoms but may require help to take action. This could entail simply guiding the patient to eat or drink or a more active approach of giving the patient the food or drink. Severe hypoglycaemia is present when the patient loses consciousness and an active medical approach is needed such as glucose infusion or glucagon injection. The correlation between biochemical and clinical hypoglycaemia is very poor in type 1 diabetes patients (Pramming et al., 1990).

Events of mild hypoglycaemia are not dangerous per se. Diabetes patients often expect this to be a consequence of a strict insulin treatment regime. The problem, however, is that frequent events of mild hypoglycaemia reduce the patient's awareness of hypoglycaemia, initiating a vicious cycle of recurrent events and thereby increasing the risk of severe hypoglycaemic events. Episodes of severe hypoglycaemia are associated with both risk and fear of recurrent episodes, which may result in the patient striving for a higher glucose

target, and thereby, increased risk of late diabetes complications. In addition, hypoglycaemia related visits to the emergency room and hospitalization constitute a heavy economic burden (Hammer et al., 2009; Lammert et al., 2009). Clearly, there are several reasons to consider alternative methods of reducing this risk of hypoglycaemia events.

1.2 Sympato-adrenal warning symptoms and hormonal counter regulation

Healthy humans have two major supplementary mechanisms to avoid severe hypoglycaemia. The first line of defence is the hormonal counterregulation. When blood glucose falls below 3.5 mmol/l, insulin release will be suppressed and the pancreatic alpha cells will release glucagon. This results in an increased glucose release from the hepatic store. Also adrenalin, cortisol and human growth hormone are released as a consequence of hypoglycaemia and contribute to re-establish euglycaemia. The second line of defence arises from an activation of the sympathetic nervous system resulting in the hypoglycaemic symptoms described above. Awareness of these symptoms alerts the patient and enables an appropriate reaction.

1.3 Hypoglycaemia unawareness

In newly diagnosed diabetes, hormonal counterregulation resembles that of a healthy person despite the fact, of course, that insulin release cannot be suppressed since this is externally delivered. With increased duration of diabetes, hormonal counterregulation may fail. Within five years of diabetes onset, most patients have lost their ability to release glucagon upon hypoglycaemia. Although the release of human growth hormone and cortisol may persist, these hormones are less effective and slower acting and do not prevent the development of severe hypoglycaemia.

With increased diabetes duration the sympato-adrenal activation may likewise fail resulting in impaired awareness of hypoglycaemia and ultimately, hypoglycaemia unawareness (Howorka et al., 2000). This is defined by a severe cognitive impairment occurring without subjective symptoms of hypoglycaemia.

A number of factors contribute to deterioration of the hypoglycaemic defences: Recent hypoglycaemic events, tight glycaemic control, sleep, a supine position and alcohol consumption all tend to reduce the hypoglycaemic defences due to the mechanisms described above, thereby increasing the risk of severe hypoglycaemia (Amiel et al., 1991; Geddes et al., 2008; Howorka et al., 2000). Approximately 25% of all type 1 diabetes patients suffer from hypoglycaemia unawareness and most events of severe hypoglycaemia take place within this group of patients (Pedersen-Bjergaard et al., 2004). The risk of severe hypoglycaemia is estimated to be five to ten times higher in patients suffering from hypoglycaemia unawareness (Geddes et al., 2008; Gold et al., 1994; Pedersen-Bjergaard et al., 2004). The term hypoglycaemia associated autonomic failure (HAAF) has been proposed for the concomitant lack of counterregulatory hormonal release and the lack of sympatoadrenal symptoms (Cryer, 2005).

1.4 How to reduce the risk of severe hypoglycaemia

Assuming that the risk and fear of hypoglycaemia is a major hindrance in achieving an optimal glucose control, all possible efforts should be done to reduce them. The first priority must be to optimize the insulin regime. Often a thorough interview with the patient including a review of blood glucose measurements can uncover risk factors for severe

hypoglycaemic events in the individual patient. Adjustment of the insulin dose and timing may consequently reduce the risk. Switching from one insulin type to another may ensure a better convergence between insulin concentration and insulin need. The long acting insulin analogues insulin glargine and insulin detemir reduce the risk of hypoglycaemia particularly at night-time (Monami et al., 2009). Use of continuous insulin infusion (insulin pump therapy) rather than multiple injection therapy has been shown to enable a more strict diabetes regulation and also a significant reduction in the risk of severe hypoglycaemia (Pickup et al., 2008). However, severe hypoglycaemia is still a common and feared complication in type 1 diabetes (Anderbro et al., 2010).

Much effort has been put into the development of continuous glucose monitoring (CGM) systems. Ideally, CGM will provide a better protection against severe hypoglycaemia by frequent glucose measurements in the interstitial tissue and alarms based on actual glucose measurements or prediction algorithms. Large clinical studies have shown that the use of CGM enables a more tight glucose control without increased risk of hypoglycaemia, but so far CGM has not been shown to reduce the risk of severe hypoglycaemic events (The Diabetes Control and Complication Trial, 2009; Bergenstal et al., 2010; Tamborlane et al., 2008). Still, CGM studies have taught us that hypoglycaemia is much more common than previously thought and is likely to be significantly underreported (JDRF CGM Study Group, 2010). One shortcoming of CGM is that adherence to therapy seems to decline with long term use, so use of the device calculated as hours per week was reduced to 35-70% depending on age group already after six months of use in clinical trials (JDRF CGM Study Group, 2008).

2. EEG for hypoglycaemia detection

2.1 The concept of an EEG based biosensor as a hypoglycaemia alarm

While hormonal counterregulation and sympatoadrenal symptoms often diminish or disappear with long term diabetes, the devastating effect of low blood glucose on organ function persists. The most important dysfunctions arise from the glycopenic effects on the brain and the heart. Neuroglycopenia results in a gradual loss of cognitive functions. In the early stage, this may only be apparent during systematic cognitive testing. As the glucose concentration falls, the cognitive function continues to decline resulting in slower speed of reaction, blurred speech, loss of consciousness, seizures and ultimately death. The effect of hypoglycaemia on the heart is less well described but comprises prolongation of the QT-interval which is a known cause of cardiac arrhythmia. In fact death among younger patients with insulin treated diabetes is assumed often to be related to malignant cardiac arrhythmia.

The blood glucose threshold at which the organ function is affected varies both between and within diabetes patients. Diabetes patients with tightly controlled blood glucose and frequent hypoglycaemic events may not be severely affected despite a blood glucose level as low as 1.5 mmol/l or even lower. This means, however, that just a slight further reduction in the glucose concentration will result in the serious effects of severe hypoglycaemia.

The concept of a hypoglycaemia alarm based on biosensing involves continuous monitoring of organ function, a real-time signal processing and an alarm device. Preferably, such a biosensor should be able to sense subtle change in brain function (e.g. electroencephalography), cardiac function (e.g. electrocardiography) or any other organ changes preceding cognitive dysfunction which will preclude the patient from taking action and thereby avoid severe hypoglycaemia.

This chapter focuses on the possibility to construct a hypoglycaemia alarm system based on continuous EEG monitoring and real-time data processing by means of a multi-parameter algorithm. Such a device may comprise an alternative to self-glucose testing or continuous glucose monitoring as a guard against severe hypoglycaemia. Analysis of EEG changes as a predictor of severe hypoglycaemia was already proposed by Regan et. al. in 1956 (Reagan et al., 1956). Iaione published the development of an automated algorithm using digital signal processing and artificial neural networks with the aim of developing a hypoglycaemia detector system, and achieved a fair sensitivity and specificity in the detection of hypoglycaemia (Iaione et al., 2005). Our aim is to develop this further to a portable real-time hypoglycaemia alarm device, which can be used by type 1 diabetes patients with hypoglycaemia unawareness. For such a device to be suitable for clinical use, it must fulfil a number of criteria: It must have a high sensitivity with low occurrence of false positive alarms, preferably it should require little or no calibration, and it must be suitable for use over long periods with minimal discomfort for the patient.

2.2 Hypoglycaemia related EEG changes

The electroencephalogram (EEG) is usually measured on the scalp, using surface electrodes that are glued to the scalp with conducting gels. The surface EEG represents the electrical activity taking place inside the brain and originates from the firing neurons, mainly in the superficial part of the brain. When a neuron fires, a very small electrical charge is released, which in itself cannot be measured on the scalp. But the macro pattern that appears when many neurons fire in a synchronized manner, builds up larger electrical signals, which can be measured on the scalp. When measuring the EEG, all the micro changes in the firing pattern disappear due to the averaging effect through the scalp, and only the macro changes remain. The EEG, which is measured outside the scalp, can therefore be used to detect macro changes in the electrical behaviour of the brain. In general, during daytime, the healthy brain is less synchronized than during sleep, and only few daytime phenomena can be characterized and detected. During sleep, the brain is more synchronised and emits many characteristic wave patterns that reflect the different sleep phases (Iber et al., 2007). Many brain related diseases, like e.g. epilepsy, do result in synchronization of the brain waves, which can be seen in the EEG patterns. This is also the case for patients experiencing hypoglycaemia.

Glucose is an essential substrate for brain metabolism. Accordingly, low blood glucose resulting in neuroglycopenia can be assumed to result in EEG changes. In the 1950's, the first studies of hypoglycaemia related EEG changes (HREC) were published (Ross et al., 1951; Regan et al., 1956) and already by then, it was proposed that EEG might add information on whether a patient's blood glucose concentration falls below a critical threshold (Regan et al., 1956). Pramming et al studied EEG changes during insulin induced hypoglycaemia in type 1 diabetes patients (Pramming et al., 1988). They found that the EEG was unaffected when the blood glucose concentration was above 3 mmol/l. Following a gradual decline in blood glucose the EEG changes became apparent in all the patients. At a median blood glucose concentration of 2.0 mmol/l the alpha activity (8-12 Hz) decreased while theta activity (4-8 Hz) increased, reflecting a cortical dysfunction. Importantly, HREC disappeared when the blood glucose was normalized and a normal EEG was re-established when the blood glucose concentration exceeded a level of 2.0 mmol/l. It was concluded that "changes in electroencephalograms during hypoglycaemia appear and disappear at such a

narrow range of blood glucose concentrations that the term threshold blood glucose concentration for the onset of such changes seems justified".
A number of studies have further characterized the EEG-changes associated with hypoglycaemia (Bedtsson et al., 1991; Bjorgaas et al., 1998; Hyllienmark et al., (2005); Juhl et al., (2010); Tamburrano et al., 1988; Tribl et al., 1996). Although some discrepancy exists with respect to the spatial location of the EEG changes (see section 2.4) and the persistence of these changes after restoration of euglycaemia, it is well established that hypoglycaemia is associated with an increased power in the low frequency bands. Figure 1 shows an example of a single channel EEG recorded during euglycaemia and hypoglycaemia during daytime. Comparing the two signals, it is evident that the hypoglycaemic EEG originates from a process of lower frequency, which is more synchronized, leading to EEG of higher amplitude.

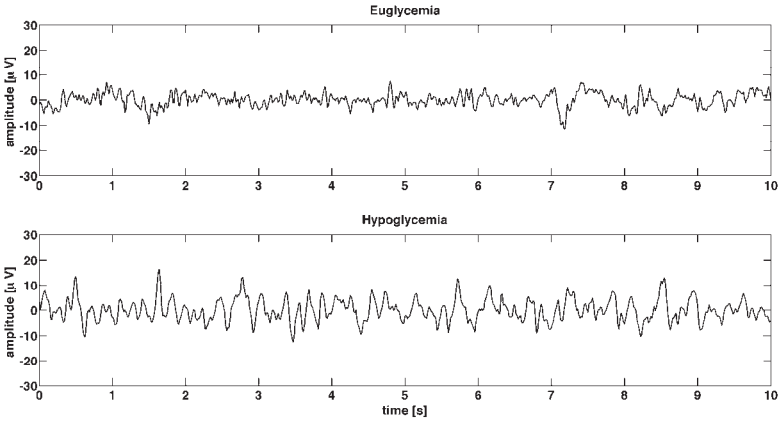

Fig. 1. Representative examples of single channel EEG recorded during euglycaemia and hypoglycaemia in the same person.

Bendtson et al. studied type 1 diabetes patients during sleep and found widespread occurrence of low frequency waves which could be differentiated from the delta and theta-band by the frequency (Bentson et al., 1991). These changes were only detectable in patients with lack of glucagon response. This observation has been challenged by our research team which found EEG changes irrespective of glucagon response (Juhl et al., 2010).
Though the two signals in Figure 1 are very easy to distinguish and the HREC paradigm is relatively well established, the HREC detection problem is not as trivial as it seems. The illustrated signals constitute textbook examples, and the exact signal characteristics vary considerably between subjects – both during euglycaemia and hypoglycaemia. In addition, many everyday activities induce EEG activity in the same frequency band as the HREC paradigm. Examples of this are low-frequency deep sleep patterns and broadband noise signals.

2.3 Long-term EEG recording: scalp vs. subcutaneous EEG

Using the brain as a biosensor for hypoglycaemia detection throughout the day requires a stable long-term EEG recording system. The usual 10/20 EEG system (Crespel et al., 2005)

with surface electrodes glued to the scalp is not an option, since surface electrodes are highly exposed to movement artefact. Therefore, in our setting, the EEG is measured by electrodes placed in the subcutaneous layer, a few millimetres below the skin, thereby giving the advantage of being more robust to noise and artefact signals. The subcutaneous measurements were tested compared to scalp electrodes and were found to be very similar, showing very high correlation.
In the initial experiments, four single subcutaneous electrodes were placed, while in the sleep studies a single electrode with three measuring points were inserted in the temporal area and connected to an EEG device.

2.4 Spatial considerations

In general, EEG patterns have different characteristics depending on the spatial location of the measurement. While some EEG changes are generalized and apparent on the entire surface of the brain, some paradigms are only present in smaller areas, which make detailed measurements in certain locations necessary.
Regarding the spatial distribution of the HREC, some discrepancy exists. The topographic maximum has been demonstrated to be located in the lateral frontal region during mild hypoglycaemia. This shifts towards the centroparietal and parieto-occipital region in deeper hypoglycaemia (Tribl et al., 1996). Hyllienmark et al on the other hand studied type 1 diabetes patients with a history of recurrent hypoglycaemia, and the EEG recording was conducted during a period of normal blood glucose. They found similar HREC characteristics as previously described, however predominantly in the frontal region. (Hyllienmark et al., 2005). In addition, this could indicate that EEG changes in some cases may become permanent.
In order to be able to detect HREC with a single or a few electrodes we investigated the spatial distribution of the changes. The hypoglycaemia changes are generally present on most of the scalp area. The spatial distribution of the artefacts particularly derived from muscle activity during facial mimicking, eating, eye movement and sleep related movements, should be taken into account when the optimal electrode placement is to be defined. In contrast to the HREC, these artefacts are more localized, making the location important. Artefact related to electrode movements and the mechanics of the electrode contact are not dependent on the spatial location. The ability to detect the HREC when artefact signals are present is illustrated in Figure 2, where the HREC signal is detected from a single electrode channel on five diabetes patients.

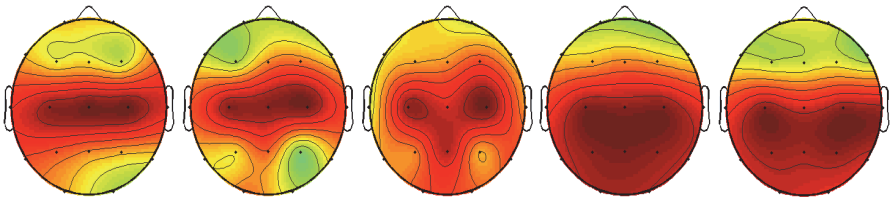

Fig. 2. Illustration of the spatial influence on the ability to detect the HREC paradigm. The red areas in the figure indicate that the HREC paradigm detection performance is high, whereas green areas indicate low performance.

Taking into consideration the spatial influence and the electrode type we have chosen the final measurement location shown in Figure 3.

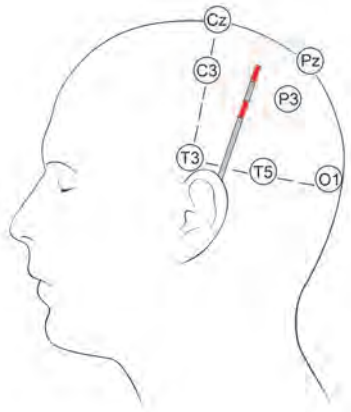

Fig. 3. Location of the subcutaneous EEG electrode. The subcutaneous electrode is inserted in a location behind the ear towards vertex cranii between Cz and Pz. The measurement points are shown in red, giving one differential channel.

3. The development of the algorithm

In the following paragraphs we describe in detail the development of the algorithm, which distinguishes HREC from normal daytime and sleep EEG. This process required a series of insulin-induced hypoglycaemia experiments with continuous improvements of the algorithm and repetitive testing. The series of clinical trials from which the data were obtained are outlined in Figure 4.

The measurement system used to acquire EEG data, samples the EEG at a sampling frequency of 512 Hz. The EEG is filtered so that all the frequency components above 32 Hz are removed, leaving us with a signal bandwidth of 32 Hz and a sampling frequency of 64 Hz for the HREC detection algorithm. The dynamic range of the measured signal is ± 512μV with a signal resolution (1 LSB) of 1μV. The internal noise level in the analogue data acquisition system is 1.3μV RMS.

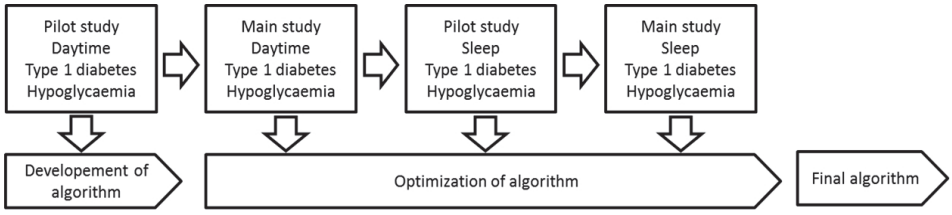

Fig. 4. Illustration of the flow of clinical studies leading to the development of the algorithm. Continuous optimizations were conducted on the basis of consecutive daytime and sleep experiments.

The HREC can be detected by visual inspection by a neurophysiologist, who inspects the waveforms of the EEG. However, if the EEG of the diabetes patients is to be analysed in real-time throughout the day this must be done automatically using an algorithm. The algorithm structure for hypoglycaemia detection is shown in Figure 5.

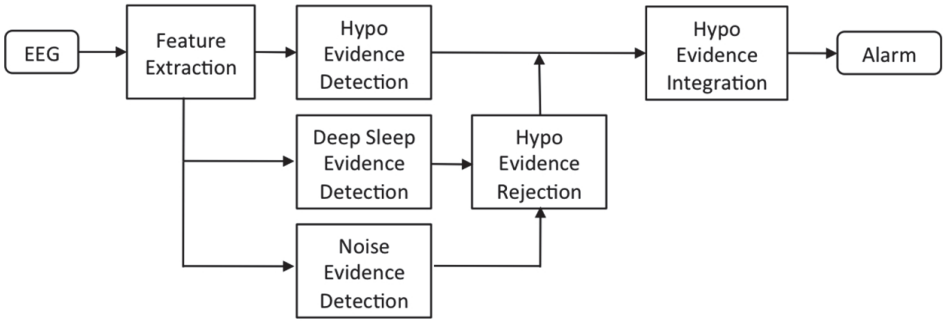

Fig. 5. Structure of the hypoglycaemia detection algorithm.

Overall, the algorithm works in four sequential levels that process the EEG signal and determines whether sufficient evidence of hypoglycaemia is present for an alarm to be triggered. At the first level, the feature extraction process maps the raw EEG into an appropriate feature space in which it is possible to distinguish HREC from normal EEG. The second level consists of three blocks, each of which analyses the features to determine if there is evidence of impending hypoglycaemia, deep sleep patterns, or noise contamination, respectively. At the third level, hypoglycaemia evidence is rejected when deep sleep patterns and/or noise are present. Lastly, taking the recent history into account it is determined whether or not a sufficient amount of hypoglycaemia evidence is present to constitute an alarm. Each of the algorithm blocks will be described in the following sections.

3.1 Feature extraction

The raw EEG signal waveform can easily be analysed by the trained human eye, which interprets the shape of the waves and draws a conclusion based on this. However, the raw waveform representation is not directly interpretable for a machine decision network, which needs the EEG in a different presentation. The feature extraction part of the algorithm maps the raw EEG into another form that represents the distribution of different kinds of waveforms. Since the hypoglycaemia paradigm in EEG is characterized by the existence of waveforms of specific frequency content, the features calculated are designed to reflect this.

The EEG waveforms are transformed to features by sending the EEG through an IIR filter bank, taking the 1-norm of the filtered signals, integrating the values in another filter, and by finally subsampling the integrated signal.

When analysing EEG, the signal is traditionally split into 5 frequency bands (delta, theta, alpha, beta, and gamma). However, this frequency resolution is not sufficient for an optimal performance of the hypoglycaemia detection system.

Our IIR filter bank consists of 32 filters where each filter has a bandwidth of 1Hz and a sub-band attenuation of 30 dB or more. In Figure 6, a 20-minute sample of EEG is represented in feature space.

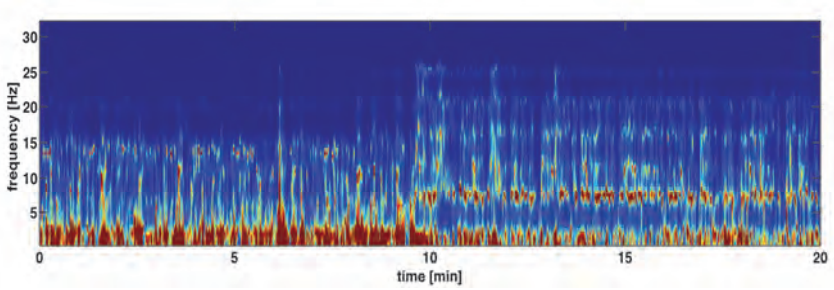

Fig. 6. Feature space representation of an EEG signal during a transition from euglycaemia (first 10 min) to hypoglycaemia (last 10 min), where HREC's are present. It is evident that a strong 7-8 Hz activity is present during hypoglycaemia in this sample.

We will see later (Figure 9) that many of the filter bands are irrelevant for the overall performance of the algorithm, but all bands have been included here to give a better understanding of the importance of each band. It should be noted that the fast Fourier transform (FFT) algorithm could easily substitute the IIR filter bank, if the process memory requirements are of no concern. Each filter in the filter bank consists of four sequential direct form-2 transpose 2nd order filter sections (Van den Enden et al., 1989). The direct form-2 transpose filters maintain the dynamic range of the signal in the fixed-point filter structure that we have chosen.

The output of the filters are normalized by the 1-norm and then integrated over a certain amount of time to get an estimate of the signal energy during this time period. We have used an IIR filter to facilitate the integration, which is a processing-wise cheap way of carrying this out. The integrator remembers the history approximately one second back in time. The integrator output is finally subsampled into a 1 Hz feature interval to eliminate redundant information. In this manner, feature vectors representing 1-second epochs are fed into the classifier.

3.2 Classifying evidence of hypoglycaemia

An important part of the algorithm is the classifier, which determines if there is evidence of hypoglycaemia in a small part of the EEG signal. The classifier bases its judgment on the extracted features, which represent the statistical properties of the EEG during 1-second epochs. The classifier combines the input statistics in a mathematical expression that results in either a "1" if the EEG has a hypoglycaemia pattern or a "0" otherwise.

There are many ways of setting up the mathematical classifier expression, and depending on this expression, the ability to classify the hypoglycaemia pattern varies. We have experimented with different kinds of classifier methods and found that the performance variation between them is small. The more advanced non-linear classifiers like support vector machines (SVM) (Joakims, 2002) and artificial neural networks (ANN) do however have small performance advantages over the more simple classifiers such as linear classifiers or the Bayes classifier with a Gaussian kernel (Bishop, 1998).

Based on our results, we have chosen to use a two-layer feed-forward ANN classifier structure to do all classification tasks in the hypoglycaemia alarm system. The ANN has a number of hidden units and uses the tanh sigmoid function for non-linear mappings.

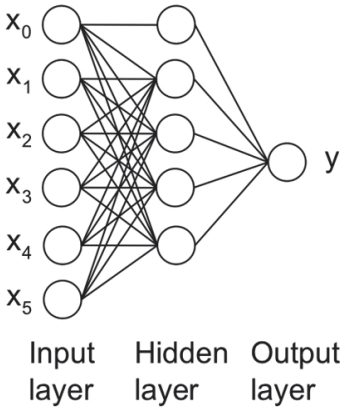

Fig. 7. Structure of the artificial neural network that detects HREC. It consists of a number of inputs and hidden layers, but only one final output determining whether or not the input epoch contains HREC.

The input layer values (x_0 - x_5) contain the feature values, where x_0 is a bias. The ANN classifier expression is shown in equation (1),

$$y_n = a\left(\sum_{h=0}^{N_h} z_h g\left(\sum_{i=0}^{N_i} w_{h,i} x_{n,i}\right)\right) \quad (1)$$

where $x_{n,i}$ is the input feature number i at time *n*, $w_{h,i}$ is the input feature weight for the mapping to the hidden unit h, N_h is the number of input features, g is the nonlinear mapping function (tanh), z_h is the output weight for the hidden unit h, N_h is the number of hidden units, a is the output activation function and y_n is the classifier output at time *n*. In our setting, the output activation function is simply a logic expression that determines whether or not the contained value has exceeded a threshold. The output y_n is shown as "1" if a HREC is detected, or otherwise, as "0".

3.3 Classifier training

The optimal parameters of the classifier ($w_{h,i}$ and z_h) can be estimated by using the back-propagation method (Bishop, 1998), based on a training set of labelled data points. We have used a neural network toolbox that applies a maximum a posteriori approach when finding the optimal weights (Sigurdsson et al., 2002). The precise classifier parameter optimization approach is of little importance in this application. Instead, the data labelling method impacts the classifier performance more. We have experimented with two data labelling approaches, where the first approach is based on expert labelling of experiment data, and the second approach is a flexible automatic labelling based on standard experiment parameters.

In the first data labelling approach, a neurophysiologist labelled a training set of EEG data, based on visual inspection of the raw EEG. The visual inspection is rather time consuming and is not feasible when larger amounts of data are used for training of the classifier. During the process of marking the data, the neurophysiologist was blinded to the timeline and

associated blood glucose sample values that had been measured while sampling the EEG. The neurophysiologist only knew that the EEG originated from a diabetes patient where both euglycaemia and hypoglycaemia situations were present in each experiment EEG dataset.

The second approach to data labelling is automatic and based on parameters that are associated with the experiment timeline and glucose values measured during the experiment. One direct advantage of using this approach is that all data can be used for modelling, and not just the data marked by the neurophysiologist. This allows for better modelling of the inter-subject variability. When using the second approach, the labelling is not predefined. Instead, time intervals with different reward functions are defined. Within such a time interval, the number of positive and negative labels rather than the exact timestamp of the label is used to determine the cost function of the classifier model. The time segments with different reward functions are shown in Figure 8, where β is the glucose threshold of 3.5 mmol/l that determines when an alarm may, but not necessarily will, be set off. T_0 is the point in time when cognition has deteriorated too much for the subject to be able to react to an alarm, $T_{0-\tau}$ is 10 minutes prior to T_0 and $T_{GL<\beta}$ are the times where the glucose level passes the threshold of 3.5 mmol/l.

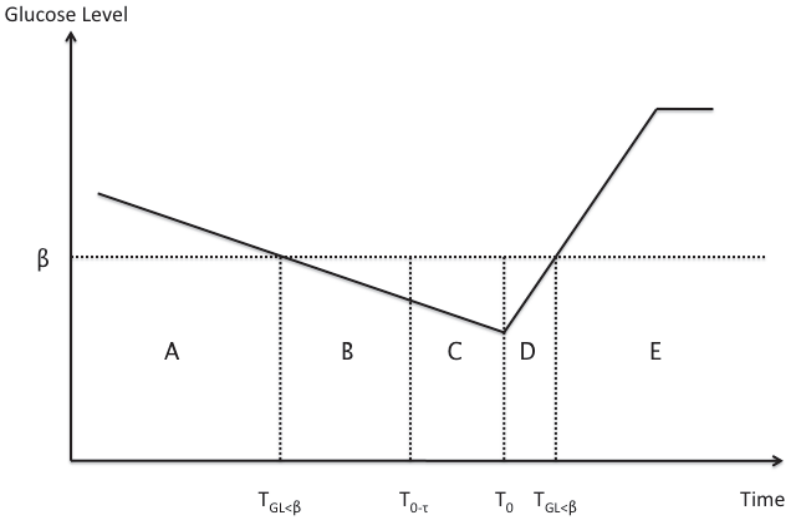

Fig. 8. Reward function time segments used to train the classifier.

In segment A and E, the classifier cost function is punished for detecting HREC, while rewarded in segment B and C. In segment D, the classifier is neither rewarded nor punished for its behaviour. The exact expression for the cost function is given in equation (2).

$$C = -\left(\sum_{A} y_n\right) + \left(\sum_{B} y_n\right) + \left(2\sum_{C} y_n\right) - \left(\sum_{E} y_n\right) \tag{2}$$

When the cost function expression is applied to a linear classifier with a single hidden unit, and optimized, we get the basic influences of the features. The classifier input weights $w_{h,i}$

show the importance of each feature. In Figure 9 the weights are shown for the linear classifier.

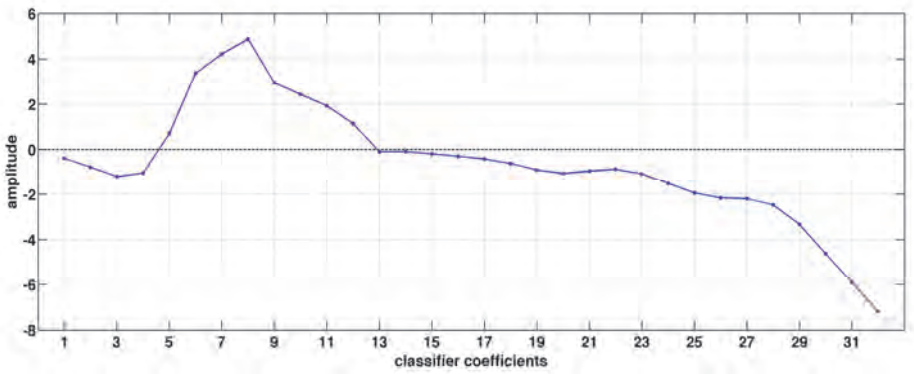

Fig. 9. Coefficients of a linear HREC classifier.

Many of the coefficients have small values and could be disregarded and many features could be joined since they have similar influence on the classifier output. It is evident that the HREC paradigm is characterized by high 6-8 Hz activity and some alpha activity.

3.4 Integration of evidence

Single events detected by the classifier do not make up sufficient evidence to trigger an alarm. The brainwaves are contaminated with noise and artefacts, leading to false detections. Furthermore, brainwaves similar to those seen during hypoglycaemia also appear sporadically during euglycaemia. It is therefore necessary to take the history of detected events into account before giving a hypoglycaemia alarm. We used the history by integrating the events that were detected during the past 10 minutes. The integrator is implemented as an IIR filter which makes it computationally cheap while only consuming little memory. The integration structure is shown in Figure 10.

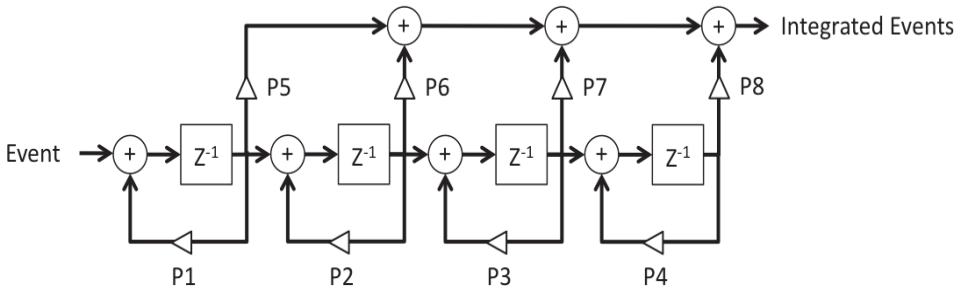

Fig. 10. Filter structure used for integration of evidence.

The coefficients P1-P8 are set to make the resulting time-function resemble a 5-minute square window. The shape of the integrator can easily be changed to have different weight and time perspectives, by changing the coefficients.

An example of the integrator output is shown in Figure 11, where a diabetes patient undergoes hypoglycaemia and recovers from the situation.

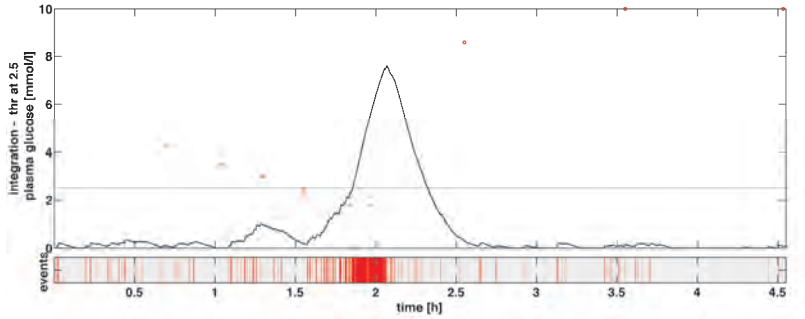

Fig. 11. Example of integrated evidence of the HREC. The red dots are blood glucose sample values sampled during the experiment. The solid line shows the value of the integration function, which alarms the subject when exceeding the predefined threshold of 2.5. The lower graph displays the events. One red vertical line represents an epoch in which HREC is detected.

3.5 Deep sleep algorithm

Initially, the hypoglycaemia algorithm was based on EEG from daytime experiments only. Figure 12 shows the output when it is applied on EEG recorded during sleep. The result is repeated detections of EEG changes compatible with hypoglycaemia during the night.

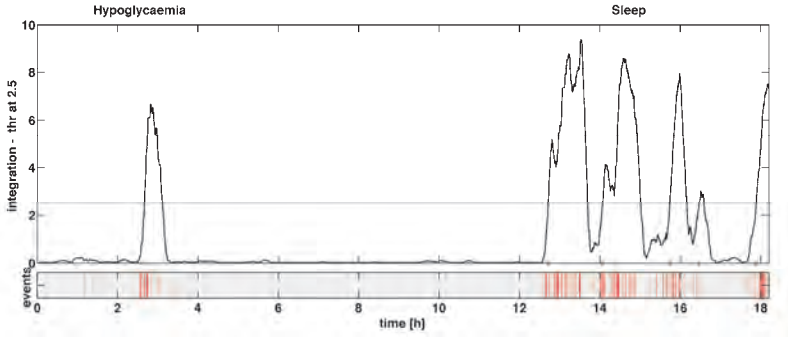

Fig. 12. Integrated events of EEG changes compatible with hypoglycaemia in a diabetes patient exposed to hypoglycaemia during the daytime and continued EEG recorded during sleep. The algorithm clearly detected repeated episodes during sleep as being consistent with hypoglycaemia.

Nocturnal hypoglycaemia thus encompasses a distinctive challenge with respect to a hypoglycaemia alarm. Not only do approximately half of all hypoglycaemic events take place during sleep (Woodward et al., 2009), but also the nocturnal EEG is distinctly different from the daytime EEG. During stages of deep sleep, the EEG pattern is characterized by slow wave patterns much like the hypoglycaemia EEG. It is therefore a challenge to

distinguish deep sleep EEG patterns from HREC. In order to suppress falsely detected hypoglycaemia events, we used a learning process that is similar to learning the HREC to construct a classifier that can detect when deep sleep patterns are contaminating the EEG signal. It should be noted that during the 27 insulin-induced hypoglycaemia night experiments that we have conducted so far, no deep sleep patterns have been present simultaneously with HREC.

3.6 Noise and artefact suppression

In an everyday life environment, the presence of noise and artefacts is substantial. Some of these operate in the same frequency band as the HREC, potentially leading to false alarms. Figure 13 shows an example of a false alarm detected during euglycaemia and normal daytime activities. The false alarm is caused by muscle activity when chewing. Many other daytime activities also come close to setting off false alarms.

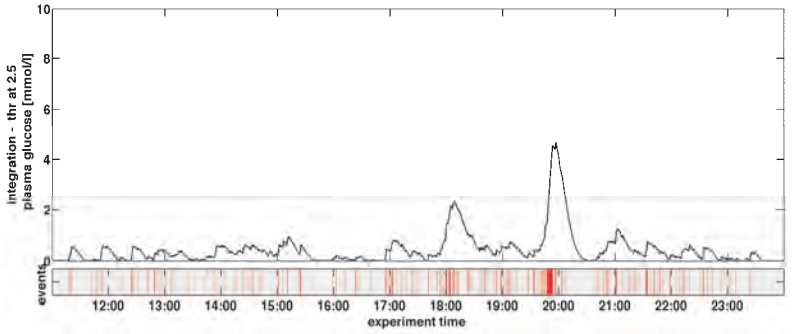

Fig. 13. Integrated HREC evidence during normal everyday activity. A false alarm is declared just before 20:00.

In order to suppress falsely detected hypoglycaemia events due to noises and artefact, we have constructed a classifier that can detect when noise and artefacts are contaminating the EEG signal using a learning process similar to learning the HREC. When this noise/artefact detection system is applied to the algorithm, the false alarm in Figure 13 is removed, and other false events are handled. The result is displayed in Figure 14. The integrated evidence is now generally lower during the normal situation, allowing us to make the HREC classifier more sensitive.

4. Clinical results

The following paragraph will focus on the clinical studies we have conducted. The focus of these studies has been the development of the algorithm for an EEG-based hypoglycaemia alarm device. The results we have achieved give an indication of the clinical applicability of the device. Here we will briefly summarize the results from the clinician's point of view.
Altogether, we have studied more than 50 patients. An important observation is that *all* patients studied so far have developed EEG changes compatible with previously described hypoglycaemia associated changes. This has allowed us to develop a general algorithm for EEG analysis, which can be applied to all diabetes patients.

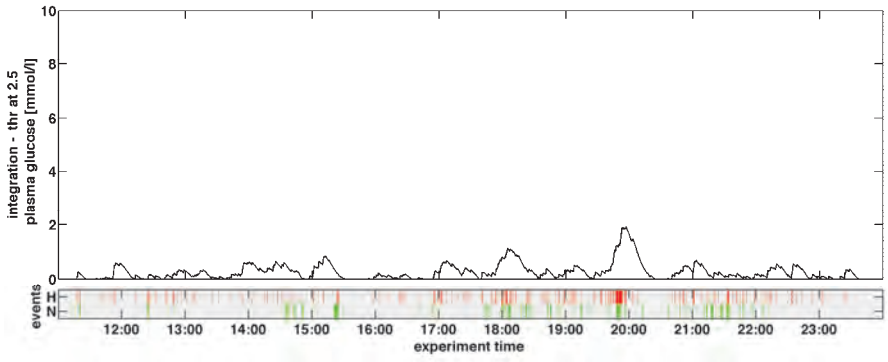

Fig. 14. Integrated HREC evidence after suppression of noise and artefacts. The vertical lines in the lower graph display the detected hypoglycaemia (red) and noise (green) events.

Initially, continuous EEG was recorded during insulin-induced hypoglycaemia experiments in 15 type 1 diabetes patients during daytime. Four subcutaneous electrodes located in the temporal region were applied along with a standard scalp 10/20 system recording. The cognitive function was evaluated by repeated cognitive testing (a backward counting test and a minus-seven test). Insulin infusion was terminated when plasma glucose reached 1.8 mmol/l or when the subjects showed obvious signs of cognitive dysfunction such as severely reduced speech velocity or heavy sweating. EEG was analysed post hoc by the automated mathematical algorithm. HREC were detected in all 15 subjects. Plasma glucose at the time of EEG changes above the threshold value indicating hypoglycaemia, ranged from 2.0 to 3.4 mmol/l and occurred 29±28 minutes (mean±SD)(range 3 – 113 minutes) before termination of insulin infusion. In this study, patients did not receive a real-time alarm, and therefore, it is not possible to state if they would have been able to react following an alarm. In 12 of 15 patients, however, EEG changes occurred before severe neuroglycopenia was apparent as evaluated by the cognitive testing. In three cases, the patients were moderately cognitively impaired at the time of EEG changes, they were, however, still awake. The presence and the time of alarm were independent of age, diabetes duration and glucose regulation (Juhl et al., 2010). Although this study did not prove that an alarm could be given in time for the patient to react, it indicated that it would in most cases.
Due to the characteristic EEG pattern during sleep, occasionally resembling HREC, it is essential to study the applicability of the algorithm during sleep. Initially, we performed a number of pilot experiments in type 1 diabetes patients exposed to insulin-induced hypoglycaemia during sleep. The original algorithm was trained on these data, and the algorithm was optimized to distinguish hypoglycaemia from deep sleep. Ten type 1 diabetes patients (mean age 47 years, diabetes duration 23.7 years, HbA1c 7.5%) all suffering from hypoglycaemia unawareness, were subsequently subjected to induced hypoglycaemia by graded insulin infusion both during daytime and during sleep at night-time. EEG was recorded from a single electrode with three measurement points placed subcutaneously in the temporal region and was analysed real-time. The patient received an auditory alarm when EEG-changes met a predefined threshold. The patients were instructed beforehand to consume a sandwich and a juice at the time of alarm. Figure 15 illustrates the procedure of a night experiment.

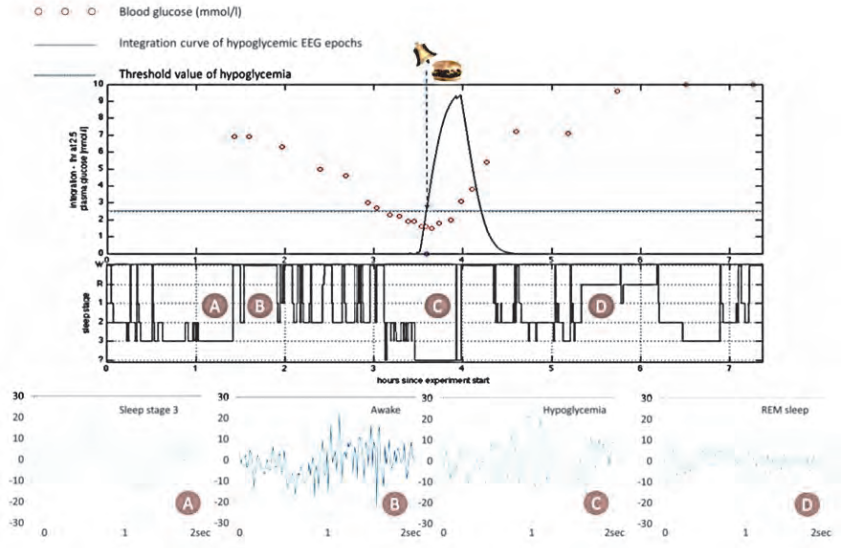

Fig. 15. Representative example of a night-time experiment. The upper panel shows the blood glucose profile (red circles) and the curve for integrated EEG-events of hypoglycaemia (black line). The integration curve rose steeply following hypoglycaemia. The patient received an alarm at blood glucose 1.8 mmol/l, where the integration curve crossed the threshold (blue dotted line). Blood glucose increased following ingestion of the meal, and the integration curve normalized accordingly. The middle panel shows the sleep stage according to AASM scoring. The patient clearly went through all stages of sleep during the night. After a short awake period following the hypoglycaemia event, the patient went back to sleep. The lower panels show two-second epochs of EEG while awake (B), REM sleep (D), stage three sleep (A) and hypoglycaemia (C).

If blood glucose fell to 1.7 mmol/l without triggering the alarm or if the patient was not able to react at the time of the alarm, hypoglycaemia was ceased by glucose infusion. The alarm was triggered for seven out of nine patients during daytime (mean blood glucose (BG) 2.7 mmol/l). Six of these seven patients were able to reverse hypoglycaemia by carbohydrate ingestion. During sleep, the alarm was triggered in nine out of ten subjects (mean BG 2.0 mmol/l) and eight awoke due to the alarm. Four corrected hypoglycaemia by food ingestion (mean BG 2.2 mmol/l) while the remaining four (mean BG 1.9 mmol/l) were supplemented with glucose due to cognitive impairment. Two events of false alarm were observed. EEG was also recorded from surface electrodes placed according to the 10/20 system and analysed by the American Academy of Sleep scoring manual to determine sleep stages (Iber et al., 2007). HREC occurred irrespective of the sleep stages and seemed to overrule physiological sleep related patterns.

By post hoc improvements of the algorithm (e.g. inclusion of hypoglycaemia evidence rejection due to deep sleep patterns and/or noise artefacts) it was possible to detect hypoglycaemia in all patients, while eliminating the false alarms. In addition, hypoglycaemia could be detected on average three (daytime experiments) and six (sleep experiments) minutes earlier than with the original algorithm, improving the sensitivity of the alarm.

Overall, it seems possible to detect hypoglycaemia in diabetes patients irrespective of the time of the day, duration of diabetes, awareness status and hormonal counter-regulation. The core question is whether this detection precedes serious cognitive impairment, allowing the patient to react. This is currently being tested in clinical trials.

5. An EEG based hypoglycaemia device for permanent use

The EEG based hypoglycaemia alarm system consists of two main parts: An implanted device that captures the EEG signal, and a non-implanted device, which stores and processes the EEG signal. This is illustrated in Figure 16.
The inner device is implanted subcutaneously, with the main part behind the ear and the electrode pointing towards the top of the head. The electrode has three measurement points, a length of 8 cm and a diameter of 1.1 mm.
Data is transmitted from the inner device to the outer device through a near field communication link. Therefore, the two devices have to be closely aligned for the system to function. The outer device is designed as an ear hanger, illustrated on the right panel of Figure 16. It is therefore easy to wear with a minimum of discomfort for the user. The outer device contains a sound generator and a light indicator to inform the user of critical events, e.g. impending hypoglycaemia.
The outer device contains a power source. When the outer device is placed behind the ear, the power source is shared with the inner device through the communication link. When the power source in the outer device is depleted, it must be recharged in a charging station. A full recharge allows for approximately 18 hours of use.

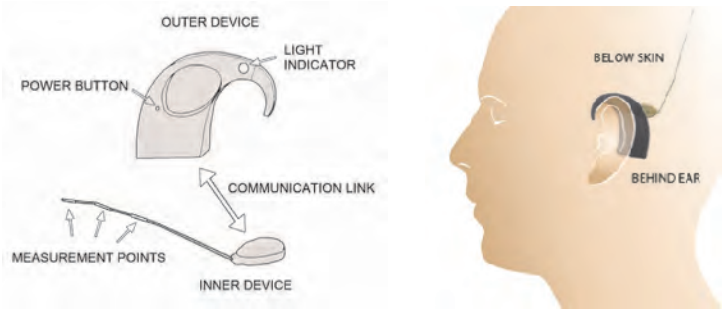

Fig. 16. The EEG based hypoglycaemia alarm system consisting of an inner and an outer device.

The implantation procedure is simple and takes approximately 15 minutes. The implanted device must be replaced only after two years of use.

6. Conclusion

Type 1 diabetes patients suffering from hypoglycaemia unawareness are significantly disposed to episodes of severe hypoglycaemia. This is associated with a risk of glucose metabolic dysregulation and a reduced quality of life (Anderbro et al., 2010; Barnard et al., 2010; Frier, 2008). Despite self-monitoring of blood glucose, the use of insulin analogues and increased knowledge of the mechanisms of unawareness, the risk of hypoglycaemia remains

a major barrier to optimized glucose control. If just one of the two components of hypoglycaemia associated autonomic failure (Cryer, 2005) (i.e. hypoglycaemia unawareness or reduced hormonal counter-regulation) could be re-established, these patients would be much less prone to severe hypoglycaemia.

The initial clinical studies of continuous EEG recording and real-time data processing during insulin-induced hypoglycaemia in type 1 diabetes patients indicate that it will be possible to predict incidents of severe hypoglycaemia before the patients are severely cognitive impaired both during daytime and sleep. The studies conducted so far, though, have taken place in clinical research units. We are now testing the hypoglycaemia alarm in an out-patient setting.

It is of utmost importance that an alarm device has a high sensitivity and specificity. False alarms may be annoying to the patients yet they are not dangerous. Missed alarms, on the other hand, may render the patient with a false feeling of security. On the other hand, a sensitive and reliable alarm device will allow the patient to achieve a better glucose control with less fear of hypoglycaemia events. The studies conducted so far hold promises that an EEG based device might fulfil these goals.

7. Acknowledgement

First of all, we would like to thank the patients who volunteered to participate in the clinical trials. Conducting these studies was essential in the development of the algorithm. Thanks to Marianne Bötcher, Lone Jensen, and Charlotte Olsen for excellent technical assistance during the conduction of the hypoglycaemia studies. Thanks to Poul Jennum and Michaela Gjerstadt for analyses of and advice regarding the recording and analysis of sleep EEG.

8. References

Amiel, SA.; Pottinger, RC.; Archibald, HR.; Chusney, G.; Cunnah, DT.; Prior, PF. & Gale, EA. (1991). Effect of antecedent glucose control on cerebral function during hypoglycemia. *Diabetes Care*, Vol.14, No.2, pp. 109-118.

Anderbro, T.; Amsberg, S.; Adamson, U.; Bolinder, J.; Lins, PE.; Wredling, R.; Moberg, E.; Lisspers, J. & Johansson UB. (2010). Fear of hypoglycaemia in adults with Type 1 diabetes. *Diabet Med*, Vol.27, No.10, pp. 1151-1158.

Barnard, K.; Thomas, S.; Royle, P.; Noyes, K. & Waugh, N. (2010). Fear of hypoglycaemia in parents of young children with type 1 diabetes: a systematic review. BMC Pediatr, 10:50.

Bendtson, I.; Gade, J.; Rosenfalck, AM.; Thomsen, CE.; Wildschiodtz, G & Binder, C. (1991). Nocturnal electroencephalogram registrations in type 1 (insulin-dependent) diabetic patients with hypoglycaemia. *Diabetologia*, Vol. 34, No.10, pp. 750-756.

Bergenstal, RM.; Tamborlane, WV.; Ahmann, A.; Buse, JB.; Dailey, G.; Davis, SN.; Joyce, C.; Peoples, T.; Perkins, BA.; Welsh, JB.; Willi, SM. & Wood, MA. (2010). Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes. *N Engl J Med*, Vol.363, No.4, pp.311-320.

Bjorgaas, M.; Sand, T.; Vik, T. & Jorde, R. (1998). Quantitative EEG during controlled hypoglycaemia in diabetic and non-diabetic children. *Diabet Med*, Vol. 15, No.1, pp. 30-37.

Bishop, CM. (1998). *Neural Networks for Pattern Recognition*. 1st ed. Oxford University Press, New York, USA.

Crespel, A. & Gélisse, P. (2005). *Altas of Electroencephalography.* 1st ed. John Libbey Eurotext, Montrouge, France.

Cryer, PE. (2005). Mechanisms of hypoglycemia-associated autonomic failure and its component syndromes in diabetes. *Diabetes*, Vol.54, No.12. pp. 3592-3601.

Frier BM. (2008). How hypoglycaemia can affect the life of a person with diabetes. Diabetes Metab Res Rev 2008 Vol. 24, No.2, pp. 87-92.

Geddes, J.; Schopman, JE.; Zammitt, NN. & Frier, BM. (2008). Prevalence of impaired awareness of hypoglycaemia in adults with Type 1 diabetes. *Diabet Med*, Vol.25, No.4, pp. 501-504.

Gold, AE.; MacLeod, KM. & Frier, BM. (1994). Frequency of severe hypoglycemia in patients with type I diabetes with impaired awareness of hypoglycemia. *Diabetes Care*, Vol.17, No.7, pp. 697-703.

Hammer, M.; Lammert, M.; Mejias, SM.; Kern, W. & Frier, BM. (2009). Costs of managing severe hypoglycaemia in three European countries. *J Med Econ*, Vol. 12, No.4, pp. 281-290.

Hojlund, K.; Wildner-Christensen, M.; Eshoj, O.; Skjaerbaek, C.; Holst, JJ.; Koldkjaer, O.; Møller Jensen, D. & Beck-Nielsen, H. (2001). Reference intervals for glucose, beta-cell polypeptides, and counterregulatory factors during prolonged fasting. *Am J Physiol Endocrinol Metab*, Vol.280, No.1, pp. E50-E58.

Howorka, K.; Pumprla, J.; Saletu, B.; Anderer, P.; Krieger, M. & Schabmann, A. (2000). Decrease of vigilance assessed by EEG-mapping in type I diabetic patients with history of recurrent severe hypoglycaemia. *Psychoneuroendocrinology*, Vol. 25, No.1, pp. 85-105.

Hyllienmark, L.; Maltez, J.; Dandenell, A.; Ludvigsson, J. & Brismar T. (2005). EEG abnormalities with and without relation to severe hypoglycaemia in adolescents with type 1 diabetes. *Diabetologia*, Vol.48, No.3, pp. 412-419.

Iaione, F. & Marques, JL. (2005). Methodology for hypoglycaemia detection based on the processing.; analysis and classification of the electroencephalogram. *Med Biol Eng Comput*, Vol.43, No.4, pp. 501-507.

Iber, C.; Ancoli-Isreal, S.; Chesson, A.; & Quan, SF. (2007). The AASM Manual for the Scoring of Sleep and Associated Events, Rules, Terminology and Technical Specifications. 1st ed. American Academy of Sleep Medicine, Westchester, Illinois.

JDRF CGM Study Group. (2010). Prolonged nocturnal hypoglycemia is common during 12 months of continuous glucose monitoring in children and adults with type 1 diabetes. *Diabetes Care*, Vol. 33, No.5. pp. 1004-1008.

JDRF CGM Study Group. (2008). Continuous glucose monitoring and intensive treatment of type 1 diabetes. N *Engl J Med*, Vol. 359, pp. 1464–1476.

Joakims, T. (2002). *Leaning to Classify test using Support Vector Machines*. 1st ed. Kluwer Academic Publishers. Boston, USA.

Juhl, CB.; Hojlund, K.; Elsborg, R.; Poulsen, MK.; Selmar, PE.; Holst, JJ.; Christiansen, C & Beck-Nielsen, H. (2010). Automated detection of hypoglycemia-induced EEG changes recorded by subcutaneous electrodes in subjects with type 1 diabetes-The brain as a biosensor. *Diabetes Res Clin Pract*, Vol.88, No.1, pp. 22-28.

Lammert, M.; Hammer, M. & Frier, BM. (2009). Management of severe hypoglycaemia: cultural similarities.; differences and resource consumption in three European countries. *J Med Econ*, Vol.12, No.4, pp. 269-280.

Monami, M.; Marchionni, N. & Mannucci, E. (2009). Long-acting insulin analogues vs. NPH human insulin in type 1 diabetes. A meta-analysis. *Diabetes Obes Metab*, Vol. 11, No.4, pp. 372-378.

Pedersen-Bjergaard, U.; Pramming, S.; Heller, SR.; Wallace, TM.; Rasmussen, AK.; Jorgensen, HV.; Matthews, DR.; Hougaard, P & Thorsteinsson, B. (2004). Severe hypoglycaemia in 1076 adult patients with type 1 diabetes: influence of risk markers and selection. *Diabetes Metab Res Rev*, Vol.20, No.6, pp. 479-486.

Pickup, JC. & Sutton, AJ. (2008). Severe hypoglycaemia and glycaemic control in Type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion. *Diabet Med*, Vol.25, No.7, pp. 765-774.

Pramming, S.; Thorsteinsson, B.; Stigsby, B. & Binder, C. (1988). Glycaemic threshold for changes in electroencephalograms during hypoglycaemia in patients with insulin dependent diabetes. *Br Med J (Clin Res Ed)* Vol.296, No.6623, pp.665-677.

Pramming, S.; Thorsteinsson, B.; Bendtson, I.; & Binder, C. (1990). The relationship between symptomatic and biochemical hypoglycaemia in insulin-dependent diabetic patients. *J Intern Med*, Vol.228, No.6, pp. 641-646.

Regan, PF. & Browne-Mayers, AN. (1956). Electroencephalography, frequency analysis and consciousness, a correlation during insulin-induced hypoglycemia. *J Nerv Ment Dis*, Vol.124, No.2, pp.142-147.

Ross, IS. & Loeser, LH. (1951). Electroencephalographic findings in essential hypoglycemia. *Electroencephalogr Clin Neurophysiol*, Vol.3, No.2, pp. 141-148.

Sigurdsson, S.; Larsen J.; Hansen LK.; Philipsen PA. & Wulf, HC. (2002). Outlier estimation and detection: Application to Skin Lesion Classification. *Proceedings of IEEE International conference on acoustics.; speech and signal processing*.

Tamborlane, WV.; Beck, RW.; Bode, BW.; Buckingham, B.; Chase, HP.; Clemons, R.; Fiallo-Scharer, R.; Fox,LA.; Gilliam,LK.; Hirsch, IB.; Huang, ES.; Kollman, C.; Kowalski, AJ.; Laffel, L.; Lawrence, JM.; Lee, J.; Mauras, N.; O'Grady, M.; Ruedy, KJ.; Tansey, M.; Tsalikian, E.; Weinzimer, S.; Wilson, DM.; Wolpert, H.; Wysocki, T. & Xing, Dl. (2008). Continuous glucose monitoring and intensive treatment of type 1 diabetes. *N Engl J Med*, Vol.359, No.14, pp.1464-1476.

Tamburrano, G.; Lala, A.; Locuratolo, N.; Leonetti, F.; Sbraccia, P.; Giaccari, A.; Busco, S. & Porcu, S. (1988). Electroencephalography and visually evoked potentials during moderate hypoglycemia. *J Clin Endocrinol Metab*, Vol.66, No.6, pp. 1301-1306.

The Diabetes Control and Complications Trial Research Group. (2009). The effect of continuous glucose monitoring in well-controlled type 1 diabetes. *Diabetes Care*, Vol.32, No.8, pp. 1378-83.

Tribl, G.; Howorka, K.; Heger, G.; Anderer, P.; Thoma, H. & Zeitlhofer, J. (1996). EEG topography during insulin-induced hypoglycemia in patients with insulin-dependent diabetes mellitus. *Eur Neurol*, Vol.36, No.5, pp. 303-309.

Van Den Enden, AWM. & Verhoeckx, NAM. (1989). Discrete-time signal processing. Prentice Hall. Hertfordshire, UK.

Woodward, A.; Weston, P.; Casson, IF. & Gill, GV. (2009). Nocturnal hypoglycaemia in type 1 diabetes-frequency and predictive factors. QJM, Vol.102, No.9, pp. 603-607.