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IMPORTANCE OF EEG FEATURES IN ACTIVE AND QUIET SLEEP FOR ASSESSMENT OF NEWBORN BRAIN MATURATION AT NEONATAL CENTRES

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АНАЛИЗ ЗНАЧИМОСТИ ЭЭГ В БЫСТРОЙ И МЕДЛЕННОЙ ФАЗАХ СНА ДЛЯ ОЦЕНКИ РАЗВИТИЯ МОЗГА НОВОРОЖДЕННЫХ В НЕОНАТАЛЬНЫХ ЦЕНТРАХ

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Newborn brain development can be analysed and interpreted by EEG-experts scoring maturity-related features in sleep electroencephalogram (EEG). These features widely vary during the sleep hours, and their importance can be different in quiet and active sleep stages. The level of muscle and electrode artefacts during the active sleep stage is higher than that in the quiet stage that could reduce the importance of features extracted from the active stage. In this paper, we use Bayesian methodology of averaging over Decision Tree (DT) models to assess the newborn brain maturity and explore importance of EEG features extracted from the quiet and active sleep stages. The use of DT models enables to find the EEG features which are most important for the brain maturity assessment. The method has been verified on EEG data recorded from 995 patients of neonatal centres under a project of the University of Jena (Germany) in 2004. The research has been supported by the Leverhulme Trust (UK), and anonymised EEG recordings have been made available for public research under support of the University of Bedfordshire (UK).

Keywords: newborn electroencephalogram, feature importance, sleep stages, Bayesian classification, decision trees

Для решения задач оценки развития мозга новорожденных эксперты неонатальных центров в Европе и Северной Америке используют электроэнцефалограммы (ЭЭГ), записанные во время сна новорожденных, для последующего распознавания и анализа прогностических признаков. Эти признаки, однако, варьируют в течение сна, в то время как их параметры различаются в медленной и быстрой стадиях сна. Уровни мускульных

и электродных артефактов, как правило, наблюдаются высокими в быстрой фазе сна, что снижает прогностическую значимость признаков в этой фазе. Представлен новый метод, который использует Байесовские древа решений для оценики значимости ЭЭГ признаков, выявленных в медленной и быстрой фазах сна. Использование таких моделей позволило выявить признаки, которые обладают наибольшей прогностической значимостью, и, что крайне важно для снижения риска ошибочных решений, оценить ожидаемые интервалы прогнозов при вариабельности признаков. Результаты были верифицированы на большой выборке ЭЭГ записей, сделанных на 952 пациентах неонатальных центров по проекту университета Йены (Германия). Разработка нового метода была поддержана фондом Leverhulme Trust (Великобритания). ЭЭГ записи были сделаны доступными для исследований при поддержке университета Бедфордшира (Великобритания).

Ключевые слова: электроэнцефалограммы новорожденных, прогностическая значимость, фазы сна, Байесовский метод, древо решений

Newborn's brain development can be assessed by experts observing the maturity-related patterns in sleep electroencephalograms (EEG) [1, 2]. Clinical experts use these patterns to estimate a newborn's physiological age [3], although these patterns widely vary during sleep hours and between patients so that the analysis becomes difficult and laborious. For assisting experts in the interpretation, automated analysis of the maturity-related patterns has been proposed and shown promising [2, 4, 12].

Typically, sleep EEG is recorded during a few hours and comprises one or more cycles of the active sleep (AS) and quiet sleep (QS) stages. These cycles or stages are recognizable in sleep EEG, and the EEG features extracted from these stages make different contribution to the maturity assessment [5].

The sleep stages are recognizable in newborn EEG since approximately 30 weeks post-conception. At this age, the QS is recognized as a pattern with high voltage bursts of *delta*, *theta* and *alpha* activity interrupted by periods with very low voltage. In contrast, the AS pattern is recognized as a longer period of uninterrupted medium-voltage *theta* and *delta* activity. The cyclic variations in the voltage and frequency corresponding to the sleep stages become more distinguishable with the brain maturation. For full-term newborns, the AS pattern is characterized by low-to-moderate voltage activity in *theta*, *alpha* and *beta* bands, whereas the QS pattern is often characterized by a high voltage *delta* activity [2, 5, 6].

The QS and AS patterns were found significantly different in terms of voltage, powers in the *delta* and *theta* bands, as well as in terms of the number and length of pseudo-stationary segments [7].

Such a feature as the dimensional complexity of neonatal EEG has been explored and shown to be significantly higher during the AS [8]. An attempt to discriminate the sleep stages by using a set of 88 statistical features representing the voltage, frequency and cepstral coefficients has been described in [9]. Another approach has been undertaken by segmenting newborn EEG into pseudo-stationary intervals which are then clustered by the mean frequency and voltage. It has been shown that the EEG intervals from the QS and AS stages were assigned to different clusters [10]. Another study has shown that the importance of features extracted from the QS and AS stages was different. Particularly, the powers in *theta* and *beta* bands were most informative during the AS, whereas the *alpha* band was prevalent during the QS [11]. A recent study [18] showed that important maturational features related to synchrony of EEG activity can be extracted from QS stage.

The above findings inspired us to explore the importance of EEG features extracted from the QS and AS stages for the assessment. In this research we use the methodology of Bayesian averaging over classification models, in particularly, over decision tree (DT) models [13, 14]. These models are widely used in practice due to their explanatory ability. The use of DT models has been also shown promising for estimating EEG feature importance [15, 17]. The Bayesian averaging enables estimation of the full predictive posterior probability distribution that is required for accurate estimation of uncertainty in assessments.

Aim of the investigation: Development of a new method for reliable evaluation of brain maturity in newborns at risk of developmental pathologies for EEG experts of neonatal centres

Material and Methods. In our experiments we used 952 EEG obtained in different clinics from newborns of age from 36 to 45 weeks of post-conception. Each of the 10 age groups has been made including around 100 recordings. The recordings were made with the C3-T3 and C4-T4 electrodes with a sampling rate 100 Hz. The electrodes were positioned according to the standard 10-20 electrode system.

Newborns sleep EEG are weak signals with average amplitude around 50 μV. During sleep hours EEGs are contaminated by noise and artifacts, so that there is the need of cleaning EEG data. Before processing, EEGs are normally rectified to make all amplitudes positive.

The variability of an EEG recorded during sleep hours of a newborn is quite high and can additionally affect the accuracy of recognition of age-related patterns in EEG.

We found that the Mean-to-Deviation Ratio (MDR), defined as m/s, was around 1.0, where m and s are the mean and standard deviation of rectified EEG amplitudes.

The common artifacts, such as muscle, cardiac, eye blinking, breathing, and electrode movement, can be labeled by an expert and then removed from EEG data. In our EEG data, the rate of labeled artifacts widely ranged from 0.01 to 0.5, and the average rate of artifacts was around 0.1.

The EEGs were recorded in a number of clinics, and artifacts were labeled by different EEG experts. Consequently, we could not expect that the EEG artifacts were labeled consistently and so decided to remove from the EEG data only amplitude artifacts. We defined these artifacts as EEG samples with abnormally high amplitudes. Such artifacts can be automatically detected by using the standard method of adaptive thresholding [16].

The idea of this method is based on the observation that the probability of abnormal EEG samples is distinctly smaller than that of normal samples. For stationary signals, the abnormality of samples can be adequately estimated in terms of their amplitudes. However, EEG are non-stationary signals, and abnormalities should be estimated within a window sliding over the EEG recording. The standard deviation over samples in a window has been shown providing more accurate estimates of the abnormality than the mean over sample amplitudes as

its value is more sensitive to the non-stationarity of EEG [16].

In our implementation, a window of length W is moved over an EEG of length N, and the deviation d_i over samples in the window is counted for its central sample

$$i=\frac{W}{2}+1, \ldots, N-\frac{W}{2}.$$

The probability distribution over d_i is estimated in order to find the most frequent value d, as well as the maximal deviation d_{max}. Consequently, we expect that the normal EEG samples appear most frequently with the deviation d, and the abnormal samples appear with a higher deviation. This allows us to count probability q_i that the ith sample with deviation d_i is an artifact:

$$q_i=\frac{(d_i-d)}{d_{max}}, d\le d_i\le d_{max}.$$

Given an acceptable probability of artifacts in the window, q_0, we can then label a sample as an artifact if its deviation exceeds the threshold d_0:

$$d_0=d+(d_{max}-d)\, q_0.$$

The above technique is based on finding a reasonable trade-off between the accuracy of artifact detection and the amount of normal EEG samples being removed. In our experiments, we found that such a trade-off is achieved with a sliding window of 10-s duration and q_0=0.225.

Figure 1 shows an example of removing artifacts from a sleep EEG. The upper plot shows the raw EEG which was contaminated by artifacts visible as samples of a high amplitude. The second plot shows the labels of these artifacts, whose rate was 0.116. The third plot shows the clean EEG. We see that the MDR of the raw EEG was 0.97, and for the clean EEG it increased to 1.06 due to removal of the amplitude artifacts.

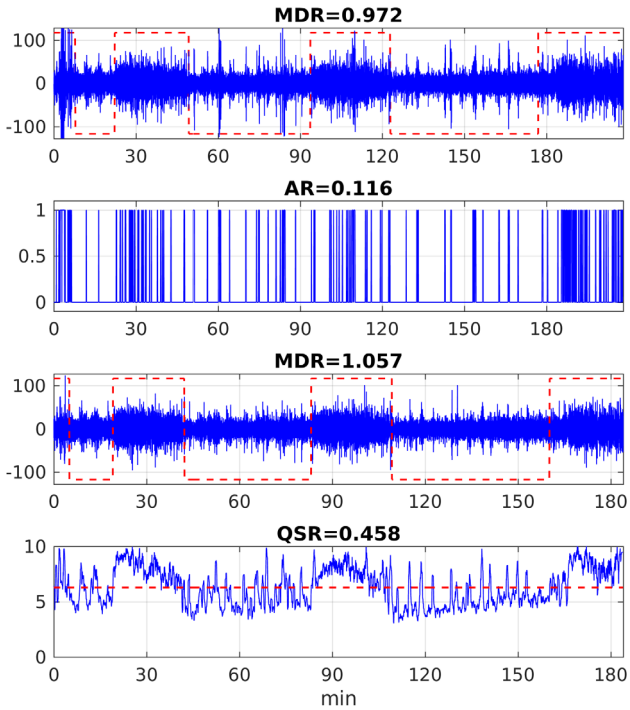

Fig. 1. Segmentation of QS stages in EEG

The background information about sleep patterns in EEG given in the Introduction inspired us to segment EEG into QS and AS sleep stages. Similarly to the above technique of detecting EEG artifacts, these sleep stages can be segmented by adaptive thresholding. Within this technique, duration of the window and threshold value are made adjustable in order to achieve the best accuracy of segmentation on EEG data labeled by an expert. Besides, the information about a minimal duration of QS stage and a maximal duration of breaks, which can happen during QS, are used to improve the segmentation accuracy.

In our experiments, a threshold was adapted to an EEG recording as follows. First, we counted the deviation of samples, d_k, k=1, …, K, in a window sliding over an EEG recording, where $K=Ent\left(\frac{N-W}{L}\right)$ is the number of windows counted in an EEG, and L is the window shift step. Then we counted a probability distribution histogram, p_i, i=1, …, M, over the deviation values v_i, where M is the number of bins in the histogram. Namely, the probabilities p_i are the portions of samples whose deviation values are between v_i and v_{i+1}. Thus, given a probability P_0, we can find a bin M_0:

$$\sum_{i=1}^{M_0} p_i \simeq P_0,\ M_0\le M,$$

and then choose a corresponding deviation interval, whose center is defined as the desired threshold. In this context, probability P_0 is normally associated with a prior on the frequency of an event detected by the segmentation technique.

In our experiments on EEG with the labeled QS stages, we have set P_0=0.5 to reflect the fact that the QS intervals represent, on average, a half of an EEG recording. The best accuracy of segmentation was achieved when the maximal duration of QS break intervals was set equal to one min. The minimal duration of QS intervals was set to seven min to enable segmenting QS intervals fragmented at the beginning and at the end of an EEG recording.

The QS segmentation of an EEG is illustrated in Figure 1. The upper plot shows the EEG as the solid line. The dashed line in this plot shows the detected QS stages. The second plot shows the amplitude artifacts which were detected during the QS stages. The third plot shows the EEG cleaned from the artifacts. The lower plot illustrates the process of thresholding detection of QS stages in the clean EEG. The dashed line in the third plot shows the result of QS detection. As the segmentation is made on the clean EEG, finally we extend the duration of sleep stages to the artifacts removed from the raw EEG. The resultant QS labels are shown in the upper plot as the dashed line.

The upper plot shows that the QS stages have been properly segmented despite the high level of artifacts shown to be detected in the second plot. The window duration W and shift L were set to 30 s and 1.5 s, respectively.

The labeled QS and AS intervals were used for extracting EEG features for classification of brain maturity within the methodology of Bayesian averaging over DT models. The details of implementation of the Bayesian method can be found in [17].

Results and Discussion. After cleaning and segmentation, the EEG data were represented by 9 features, namely the spectral powers in the six frequency bands, (1) *Subdelta*, (2) *Delta*, (3) *Theta*, (4) *Alpha*, (5) *Beta*, and (6) *Beta2* (features 1–6), and three features of EEG discontinuity, described in [17]. The spectral powers have been computed with fast Fourier transform over 6-s epochs, which then were averaged within each band in order to represent an EEG by a six-element vector. The artifacts were detected and removed, and the sleep stages in each EEG were segmented into QS and AS intervals.

Table 1 shows the rates of artifacts removed from the QS and AS intervals as well as from the whole EEG. This rate includes EEG samples which have been detected as artifacts within the proposed segmentation technique. The artifact rates are shown with the mean and 2σ intervals counted over the EEG recordings. We can observe that the rate of artifacts detected in the QS intervals is

more than twice higher than that in the AS intervals. The second plot in Figure 1, which shows the labeled artifacts in the raw EEG, confirms that the artifact rate in the QS intervals is higher than that in the AS intervals.

Table 1

Artifact rates in the sleep stages

Sleep stage	Rate
QS	0.12±0.21
AS	0.05±0.07
QS and AS	0.09±0.13

In the first two experiments with the Bayesian classification, we used the features extracted from the QS and AS intervals. The third experiment has been run with the features extracted from the whole, unsegmented EEG in order to compare the importance of features within the Bayesian classification.

Table 2 shows the accuracy of the Bayesian classification obtained with the above settings within a 10-fold cross validation for the features extracted from the QS and AS stages as well as from the whole EEG. The accuracy is evaluated within three intervals of weeks post-conception commonly used by the EEG experts.

Table 2

Accuracy of assessment for 10 groups within three intervals

Sleep stage	Performance, %, week intervals			Entropy
	0	±1	±2	
QS	25.2±7.4	64.8±8.8	85.5±8.3	206.1±11.7
AS	26.7±9.9	60.8±10.0	82.5±7.1	210.6±11.8
Both	28.8±5.5	63.9±9.0	82.9±7.5	207.1±9.8

The performance is shown by the mean accuracy within 2σ standard deviation intervals. The entropy E is counted over an ensemble of K DT models, in order to estimate the uncertainty of the ensemble: $E = \sum_{i=1}^{K} p_i \log_2(p_i)$, where p_i are the class posterior probabilities provided by the DT models.

Figure 2 shows the importance of features extracted from the QS and AS intervals. Observing the results, we see that the most important feature extracted from the AS intervals is related to the discontinuity (feature 7). In the QS intervals, the powers in the *Delta*, *Theta* and *Alpha* bands are also shown to be important.

Conclusions. In this paper, we explored the importance of EEG features used for the newborn brain maturity assessment within the methodology of Bayesian averaging over decision tree (DT) models. This methodology has been shown providing the most accurate estimates of class posterior distribution, while the use of DT models has been shown capable of finding features making valuable contribution to the assessment.

Based on clinical observations that the EEG features in various sleep stages are different, we assumed that there exist EEG intervals which provide the most informative features, which can be extracted from intervals of quiet sleep.

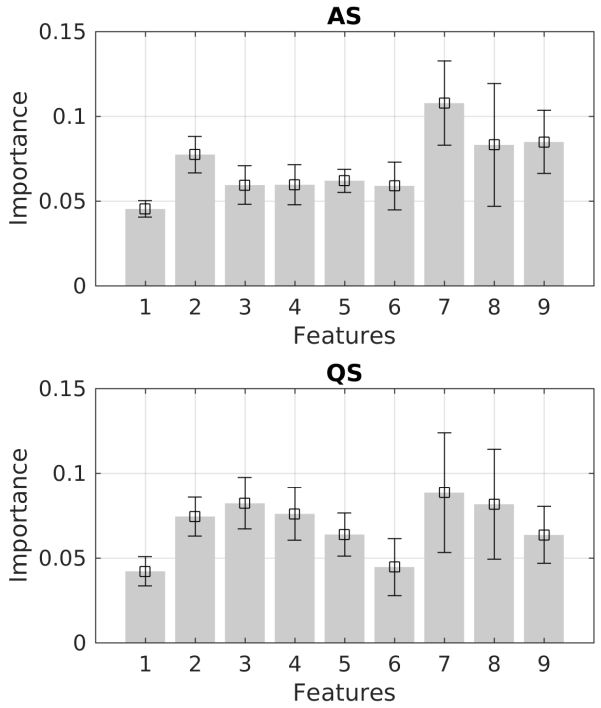

Fig. 2. Mean and standard deviation of importance of features extracted from AS and QS stages

For testing this assumption, the EEGs were automatically segmented into the quiet and active sleep intervals. Before the segmentation, the EEGs were automatically cleaned from the amplitude artifacts. Both the segmentation and artifact detection have been made with the standard adaptive thresholding techniques. For each sleep stage, the segmented EEG intervals have been split into epochs and represented by the standard spectral bands. Finally, each band has been averaged over the epochs to represent the EEG intervals by a vector entry.

In our experiments, we used the EEG data recorded from newborns of age 36 to 45 weeks post-conception. We found that the EEG features extracted from the quiet sleep intervals have provided more accurate age classification in the comparison with the features extracted from the active sleep intervals.

The above allows us to conclude that intervals of the quiet sleep in EEG are more informative for the newborn brain maturity assessment within the methodology of Bayesian averaging over DT models. Obviously, this result is conditioned on the methods chosen in our research for segmenting EEG into sleep intervals, extracting features from the segmented EEG intervals as well as for classification of age-related patterns.

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CHANGES IN CALCIFEDIOL CONCENTRATIONS IN INFANTS DEPENDING ON THE CHOLECALCIFEROL DOSE AND DURATION OF THERAPY

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ДИНАМИКА КАЛЬЦИДИОЛА У ДЕТЕЙ ГРУДНОГО ВОЗРАСТА В ЗАВИСИМОСТИ ОТ ДОЗЫ И ДЛИТЕЛЬНОСТИ ПРИЁМА ПРЕПАРАТОВ ХОЛЕКАЛЬЦИФЕРОЛА

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The paper presents an analysis of the relationship between the duration of cholecalciferol supplementation at different doses and the 25(OH)D concentration in infants during their first year of life. We evaluated 496 infants aged 1 month to 12 months who were divided into four groups depending on the duration of vitamin D supplementation: up to 8 weeks, 8–15 weeks, 16–24 weeks, and over 24 weeks.