ARTICLE IN PRESS

Early Human Development xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Unobtrusive assessment of neonatal sleep state based on heart rate variability retrieved from electrocardiography used for regular patient monitoring

ARTICLE INFO

Keywords:
Active sleep
Quiet sleep
Heart rate variability
Support vector machine
Automated
Separation

ABSTRACT

As an approach of unobtrusive assessment of neonatal sleep state we aimed at an automated sleep state coding based only on heart rate variability obtained from electrocardiography used for regular patient monitoring. We analyzed active and quiet sleep states of preterm infants between 30 and 37 weeks postmenstrual age. To determine the sleep states we used a nonlinear kernel support vector machine for sleep state separation based on known heart rate variability features. We used unweighted and weighted misclassification penalties for the imbalanced distribution between sleep states. The validation was performed with leave-one-out-cross-validation based on the annotations of three independent observers. We analyzed the classifier performance with receiver operating curves leading to a maximum mean value for the area under the curve of 0.87. Using this sleep state separation methods, we show that automated active and quiet sleep state separation based on heart rate variability in preterm infants is feasible.

1. Introduction

Newborn infants show two distinct sleep states defined as active sleep (AS) and quiet sleep (QS) [1]. In full-term infants AS is traditionally associated with rapid eye movements (REM), increased variability in cardiorespiratory rates, low muscle tone, and body movements in combination with specific continuous patterns of the electroencephalography (EEG). In contrast, QS is associated with absence of REM, decreased variability in respiratory rates and fewer body movements in combination with a discontinuous EEG pattern. Even in very preterm infants, rudimentary sleep states can be identified from 26 weeks postmenstrual age (PMA) [2].

The important role of sleep states on brain development is only beginning to be understood. It has been shown that sleep cycles are necessary for normal sensory and cortical development of the fetus and newborn [3,4]. AS is important in providing the early stimulation and activity requirements of the growing brain. During AS several organizational events take place such as the topographic alignment of the somatosensory, auditory and the visual system and their connection to the cortex structures [3,4].

The time spend in AS and QS has been shown to be associated with maturation [4–6]. The distribution changes from 80% AS and 18% QS at early gestational age (GA) to around 60% AS and 30% QS at term age (see Fig. 1) [7]. The neonatal intensive care unit (NICU) environment has a profound detrimental effect on sleep pattern development. Significant differences are found in sleep behavior between fetuses and preterm infants at the same postmenstrual age. It has been shown that preterm infants spend less time in AS and more in QS compared to fetuses at comparable age [3,8,9] The difference can be related to the clinical condition of the preterm infant or to the interaction with the “hostile” NICU environment with a variety of noxious stimuli and painful procedures [9,10].

Therefore, investigation of sleep states in preterm infants provides the opportunity to gain more insight in preterm brain development and identify which factors support or disrupt preterm brain development. Currently, polysomnography (PSG) is considered to be the standard for sleep assessment. PSG employs audio and video recording of the infant as well as the typical recordings of respiration, heart rate (HR), electromyography, electro-oculography and EEG. However, the instrumentation required for these studies is only found in sleep laboratories and not in a typical NICU setting. Furthermore, PSG requires placement of multiple electrodes and sensors which are not tolerated by the skin of the vulnerable preterm infant.

Recent advances in technology allow to collect a variety of physiological data in the clinical setting and to process and analyze these in an

Abbreviations: AM, Antedependence models; AS, Active sleep; AUC, Area under the curve; CFS, Correlation based feature selection; ECG, Electrocardiogram; EEG, Electroencephalogram; FSMC, Minority class based feature selection; GA, Gestational age; HR, Heart rate; HRV, Heart rate variability; LDA, Linear Discriminant Analysis; LVQ, Learning Vector Quantization; LOOCV, Leave one out cross validation; MLP, Multi Layer Perceptron; NREM, Non rapid eye movement (sleep); PMA, Postmenstrual age; PSG, Polysomnography; QS, Quiet sleep; REM, Rapid eye movement (sleep); ROC, Receiver Operating Characteristic; SVM, Support vector machine

http://dx.doi.org/10.1016/j.earlhumdev.2017.07.004

0378-3782/

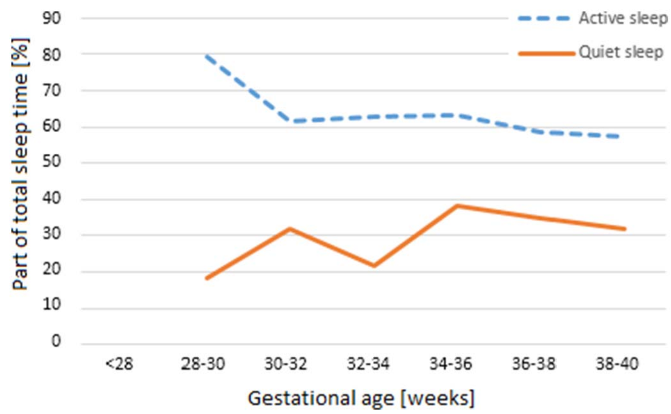

Fig. 1. Percentage of active and quiet sleep of the total sleep time over the gestational age. Active sleep at low gestational age is dominant with around 80% it lowers to around 58% until term age. Vice versa, at low gestational age quiet sleep is less strong represented with around 18%. It increases over the course of development to around 32% at term age. The data is accumulated from several publications, published in [7].

automated fashion. Various methods have been explored to develop sleep state separation techniques that require only a subset of standard PSG measures [11–13]. Automated sleep staging (or sleep state classification) based on e.g. heart rate variability (HRV) is already successfully implemented in adults [14–17]. For newborns, however, automated sleep scoring is still in the exploration phase, while the development of stable EEG based algorithms is only recently emerging (see Table 1). The first research was introduced in the late eighties by Harper et al. [18] and Haddad et al. [19]. Harper et al. used cardiorespiratory signals with a discriminant analysis on 25 term infants over a period of 6 month to separate AS, QS and wake. They created different models depending on age and achieved an overall agreement with the manual observations of 85%. Haddad et al. [19] exceeded the results of Harper et al. classifying only AS from QS based on respiratory variability with an accuracy of 99% on detecting AS and of 93% on detecting QS using Kolmogorov Smirnov distances. These good results might be explained by the age of the subjects, varying from 44 to 56 weeks PMA. Sleep state separation becomes easier with increasing maturation as each sleep state becomes more pronounced and can be separated more clearly. This was also found by Sadeh et al. [20] who separated AS, QS and wake only using actigraphy. They created several movement-based features which were analyzed with an linear discriminant analysis (LDA) for 41 term infants with age ranging from birth (term) to one year of age. The classification accuracy increased over the curse of development from 89 to 97% for sleep and wake distinction. Nason et al. [21] confirmed this observation when they used wavelet analysis in combination with LDA and antedependence models (AM) to separate sleep and wake on one subject over a duration of 4 month. Performance increased over age from 75 to 90% with an LDA and 90–96% with AM.

In 2004, the group of Lewicke and Schuckers used the CHIME study for sleep staging in term infants based on HRV. Lewicke et al. [22] first compared the use of HRV against actigraphy for sleep staging with a learning vector quantization (LVQ) neural network. They reported that the use of HRV resulted in a correct detection of sleep in 90% and wake in 57%, respectively. The use of accelerometer measurements led to 92% for sleep and 42% for wake detection, respectively. The lower agreement for wake could be explained with the use of accelerometer measurements which might not detect wake episodes with less or no movement. In addition, the generally lesser amount of data on wake episodes in term infants can reduce neural network performance as it is directly linked to the quantity of training data. In a second study [23], they applied two additional classification methods together with the LVQ on an extended data set of 190 early term infants. In that study, they used only HRV as input for the LVQ, Multilayer perceptron neural network and a support vector machine (SVM). With a huge amount of 57,000 30s epoch for each training, test and validation set, they were able to increase the correct prediction for wake to 80%. The SVM created the highest scores with a detection accuracy of 90% for sleep and 79% for wake. This was the first time that such amount data was analyzed for automated sleep staging for early term infants. It could be postulate that this was the first stable sleep staging algorithm for early term infants. Automated analysis of preterm infant sleep using cardiorespiratory signals has been published in 2016. Similar to Haddad et al., Isler et al. [12] created a threshold-based algorithm where the threshold was derived from the normalized instantaneous breathing rate variance and respiration variability. By replicating the manual scoring process and tailoring the analysis specifically to the dataset they reached a 100% agreement with the observer annotations. The more general performance of their method ranges from 78% to 92% agreement with the observer annotations.

In 2017, Dereymaeker et al. [25] and Koolen et al. [26] published a classification algorithm of preterm infant sleep states using EEG signals. Dereymaeker et al. focused mainly on identifying QS, where they based their analysis on the heightened discontinuity of the EEG during QS. Using a cluster-based adaptive sleep staging method they achieved very high results from the "Receiver Operating Characteristic" (ROC) with an area under the curve (AUC) of 0.97 for detecting QS from other sleep states out of preterm infant data stream. Koolen et al. used six features on a nonlinear SVM classifier, resulting in an AUC of 0.83 for preterm infants $<$ 32 weeks PMA and 0.87 for infants $>$ 32 weeks. PMA. A more complete overview on sleep state classification based on EEG is given in another article of this special issue by Dereymaeker et al.

As most previous studies were based on term newborns, in this paper we aimed to investigate the feasibility of classifying AS and QS based on HRV only for preterm infants. This would be complementary to the studies by Koolen et al. and Dereymaekers et al. (focusing on EEG analysis) as well as the work by Isler et al. (focusing on respiratory analysis).

2. Material and methods

2.1. Population

In this retrospective study we analyzed eight healthy and stable preterm infants born at a mean gestational age of 30 $\pm$ 2.6 weeks, who were studied at a mean postmenstrual age of 34 $\pm$ 2.8 weeks. The mean birth weight was 1646 $\pm$ 309 g. The infants were admitted to the neonatal department at Máxima Medical Center Veldhoven, the Netherlands. Ethical approval was given by the medical ethical committee of the hospital and written consent was given by the patient's parents.