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Electrophysiological studies of neonatal sleep stages

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1 Introduction

Electroencephalography (EEG) and magnetoencephalography (MEG) are noninvasive ways to study the electric activity of the brain. They can be successfully applied to studies of human infants. In this work, spontaneous MEG, EEG and ECG signals recorded from neonates in the context of somatosensory response study are analyzed. The analysis focuses on looking for differences in certain signal measures between the two sleep states observed in neonates. This kind of information would be useful in development of an automatic neonatal sleep stage classification system. Sleep stage scoring performed by experienced infant researchers is used as a basis for the comparisons.

In chapter 2, some relevant background information on infant MEG and EEG studies and sleep stages is presented. Chapter 3 briefly describes the measurement setup. In chapter 4, the signal processing methods utilized in this work are explained. The results are presented in chapter 5, and some discussion follows in chapter 6.

2 Background

2.1 EEG and MEG in infant studies

The activity of neurons in the brain gives rise to electric and magnetic fields. It is possible to measure these fields outside of the brain. In EEG, the potential variations on the scalp are measured with electrodes. In MEG, ultrasensitive magnetic field sensors are used to measure the weak magnetic fields outside the head. Both methods can be used in infant studies, though there are some special challenges.

Infant EEG is well established in clinical and research use. The first measurements were performed by Hans Berger in 1935 on a 35-day old child. The electric activity of the infant brain can be registered from gestation week 19 onwards [5]. In research use, infant EEG has been used mainly for event-related potential (ERP) studies. Clinically it can be used to get information about seizures and other abnormal conditions.

In contrast to EEG, very few MEG studies of infants have been published to date. MEG is a relatively new technique that requires expensive hardware and usually a special shielded room. The use of MEG in infant studies is particularly challenging for various reasons. The head of the infant should stay immobile with respect to the sensors, and this can be difficult to accomplish. Current multichannel MEG devices are designed for adult heads, which means that the size of the helmet-shaped sensor array is too large and relatively few channels are able to see the signals from the brain. In the future, these problems should be alleviated by MEG instruments specially designed for infant measurements. The main advantage of MEG in infant studies is the ability to perform source localization, that is, locating the neural generators in the brain that give rise to the measured field. This is difficult to do with EEG because the conductivity details of the head have to be taken into the account in solving the inverse problem.

2.2 Sleep stages

Newborn infants have two different sleep stages that occur in alternating cycles of tens of minutes [6]. These stages have been termed active sleep and quiet sleep, corresponding respectively to REM sleep and NREM sleep in adults. Active sleep is characterized by

irregular breathing, saccadic eye movements and small bodily movements and twitches. In contrast to adult REM sleep, peripheral motor pathways are not depressed during active sleep in neonates, making movements possible. During quiet sleep, breathing is regular, and eye and bodily movements are absent. The states have EEG correlates: EEG in quiet sleep shows either continuous high-voltage low-frequency (HVLF) activity or trace alternant, in which HVLF activity alternates with quiet periods in cycles of few seconds. In active sleep, the EEG is relatively quiet.

The sleep stages also have an effect on the activity of the heart. The average heart rate is higher in active sleep [7]. This is consistent with the higher metabolic demand caused by nervous system and muscle activity in active sleep. Porges et al. [7] reported a sleep stage effect also on respiratory sinus arrhythmia (RSA), observing that RSA in quiet sleep was significantly higher than in active sleep. RSA is the natural arrhythmia cycle that occurs through the influence of breathing on the output of the vagal pathway. During inhalation, the activity of the vagus nerve is suppressed, resulting in increased heart rate. During exhalation, the pattern is reversed. Therefore, quiet sleep seems to be associated with increased vagal tone.

3 Measurements

MEG signals were acquired with a 306-channel Vectorview device (Neuromag Ltd.). It has 102 sensor units with two planar gradiometers and one magnetometer in each. The sensors are arranged in a helmet-shaped array designed to accommodate adult heads. In this study, the device was operated in supine mode and the baby was lying on a bed on its side, head inside the helmet. Since the radius of curvature of the helmet is too large for infants, only relatively few channels (about 10 gradiometers) are able to detect signals from the brain. The device is located inside a special magnetically shielded room.

EEG was measured with 5 disposable electrodes attached to the scalp of the baby. The electrode locations corresponded to P3, P4, Cz, between F3 and C3, and between F4 and C4. The reference electrode was placed at right mastoid. The built-in EEG acquisition system of the Vectorview was used to record the EEG.

The infants (6 subjects) were fed before the measurements. The somatosensory stimulation was done on either the finger or the palm with a pressure-operated tactile device. In the context of this work, we ignore the presence of the somatosensory responses. The light stimulation does not affect the normal sleep cycles of the baby and the somatosensory responses are so small compared to the spontaneous activity during sleep that their effect on the appearance of the data and spectral analysis is negligible. Data was acquired in blocks of approximately 10 minutes, with 4-5 blocks per subject. Both quiet and active sleep episodes were observed in each subject.

The subjects were fed before the measurement. During the measurements, two persons were usually present in the shielded room to make sure the baby is well and the stimulator stays attached, and to make notes about movements etc.

4 Methods

4.1 Data preprocessing

The data processing and analysis was done in Matlab environment on a Linux workstation. The Vectorview system saves data in its own format called FIFF. The FIFF Access package by Kimmo Uutela [10] was used to read this file format in Matlab.

After acquisition, the data was first downsampled by a factor of three to save disk space. The original sampling frequency is 989.2 Hz. After downsampling, the frequency content of the signal extends to 164.9 Hz. Finally, the data was bandpass filtered using zero-phase filtering with a fourth order elliptic bandpass filter. This is done to remove low-frequency noise (EEG drifts due to changing skin potentials etc.) and high-frequency noise (especially line noise). The passband for data visualization was from 1 to 20 Hz.

4.2 The Pan-Tompkins algorithm

For detection of the heart rate from ECG signal, it is necessary to be able to detect QRS complexes. Various methods can be used for this. One popular algorithm was presented by Pan and Tompkins [1]. In this work, we use a slightly modified version to detect first the QRS intervals and then find the R-wave peaks by searching those intervals. This type method was also used in [4].

The different processing phases of this algorithm are shown in figure 1. The bandpass filtering (step 1) emphasizes the QRS frequency range, removing slow drifts and high-frequency noise. The passband was chosen to be 6–30 Hz, based on experiments conducted in [4]. A Butterworth IIR filter of order 6 was used. Since we are interested in the fast transients of the QRS complex, differentiation of the signal (step 2) enhances the signal-to-noise ratio. Squaring (step 3) will further enhance the peaks and remove negative values. Finally, by filtering with a moving-average filter we remove undesirable noise and get a well-defined broad peak centered at the QRS complex. By finding the rising and falling edges of this peak, we can detect the approximate borders of the QRS interval. The R-wave is detected as the maximum of the signal between these borders.

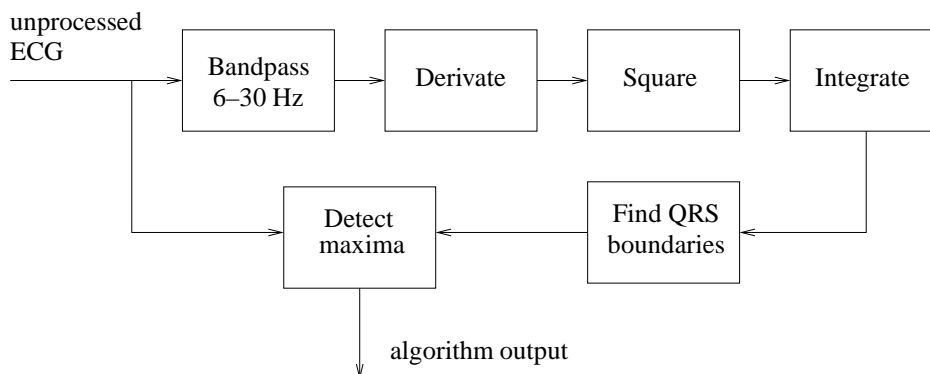


Figure 1: The processing stages of the Pan-Tompkins algorithm

Physiologically, the QRS complexes cannot occur closer than 200 ms to each other. If any two R-wave peaks occur faster than this, the later peak is considered an artifact. The algorithm requires only one parameter, which is the threshold value for detection of the rising and falling edges of the averaged signal. This varies from recording to recording,

according to the amplitude of the ECG signal. However, it was found that a threshold that worked for every recording was twice the mean of the integrated ECG signal.

An example infant ECG signal in the different processing phases is shown in fig. 2. The algorithm rarely makes false detections or misses beats, but one type of erroneous detection seen couple of times is illustrated here. Around $t=336$ s, a spiky artefact halfway between two QRS complexes is detected as a beat. Even the majority of these false detections could probably be avoided by adding some extra logic to the algorithm, such as investigation of the width of the original R-wave. However, for the purposes of the present study the algorithm performs sufficiently well as it is.

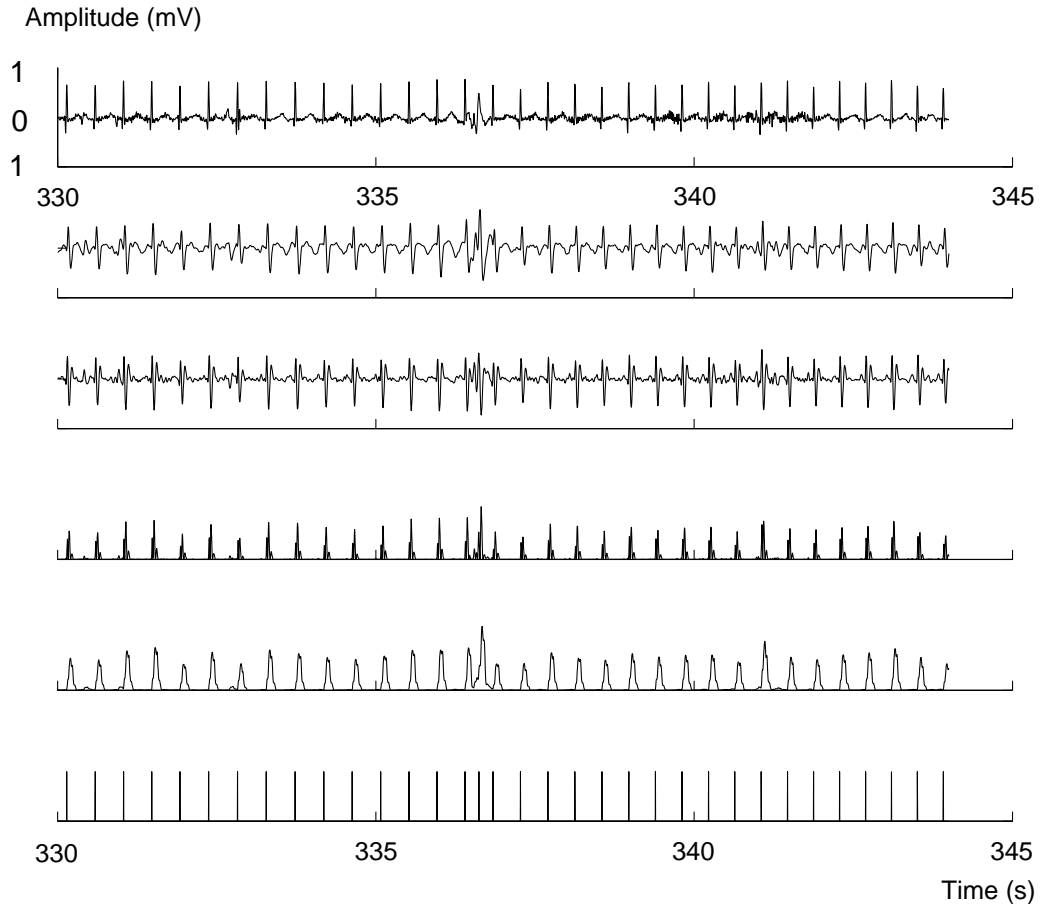


Figure 2: The ECG signal in different stages of processing. From up to down: original signal, bandpass filtered signal, differentiated signal, squared signal, integrated signal, and pulses corresponding to detected R-wave peaks. Notice the artefact at $t=336$ s.

4.3 Spectral estimation

The power spectra of different sleep stages were estimated using the Welch method, as discussed in [2]. In this method, the data is divided into overlapping segments and the segments are windowed by a specified window function. Then modified periodograms are calculated from each segment by fast Fourier transform, and the results are averaged to form the spectrum estimate. The parameters to choose are the length of the segment, the amount of overlap and the type of window function. The length of the segment represents a tradeoff between the variance and resolution of the spectral estimate. If the length

is short, more periodograms will be available for averaging, which reduces the variance of the estimate. However, a short periodogram length implies a decrease in spectral resolution. Spectral resolution is important, for example, when there is a need to separate closely-spaced narrowband peaks in the signal. A length of 6 seconds with 50% overlap was used here. The choice is not critical here, because it was found that there are no closely located spectral peaks that we would like to separate. For windowing, the commonly used Hamming window was selected.

5 Results

5.1 MEG and EEG data

Figures 3 and 4 show representative MEG and EEG signals from quiet and active sleep stages. It is seen that MEG data of good quality is obtainable from neonates with this measurement setup. In quiet sleep, MEG shows signal features quite similar to EEG. As seen in fig. 4, some EEG features are seen on certain MEG channels but not on others. The reason may be that the gradiometers pick up signals more locally, making it possible to distinguish activity from different sources better. The amplitudes of spontaneous signals are large in both MEG and EEG. This is because the signal sources are quite close to the gradiometers, due to the small size of the infant head. In EEG, there is also less attenuation caused by the skull, which is not fully developed in neonates. The quiet sleep example shows the typical tracé alternant pattern. In active sleep, the signals are relatively small.

The data has been bandpass filtered from 1 to 20 Hz to suppress low-frequency noise. Some information is lost this way, because there is evidence that meaningful brain activity in neonates extends down to DC levels [8]. However, the EEG system used is not DC capable, and for meaningful comparison of the signals the MEG is filtered in the same way.

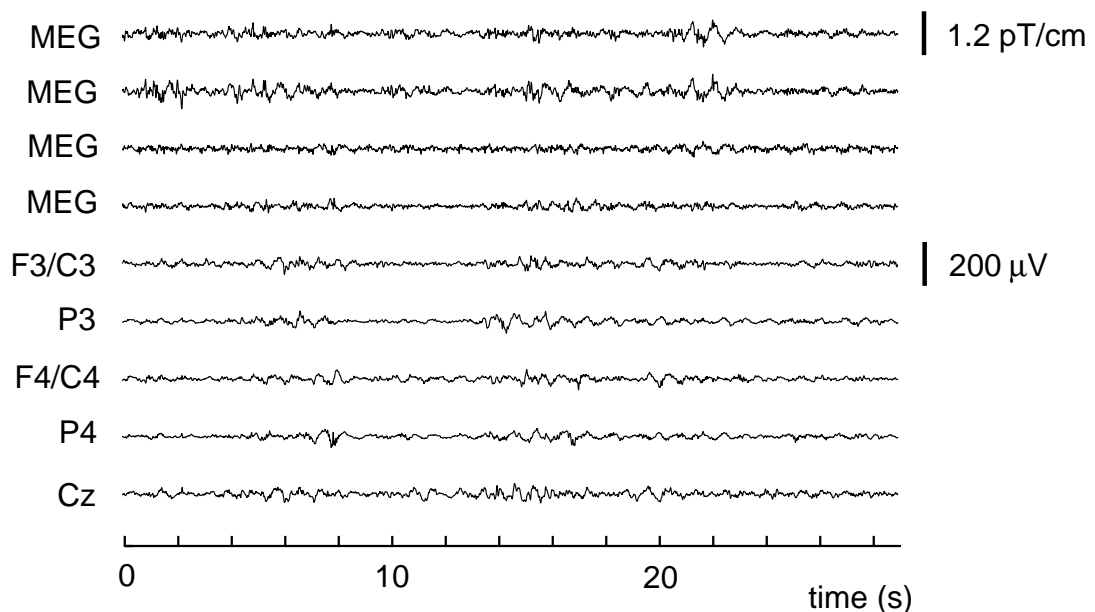


Figure 3: MEG and EEG signals in active sleep

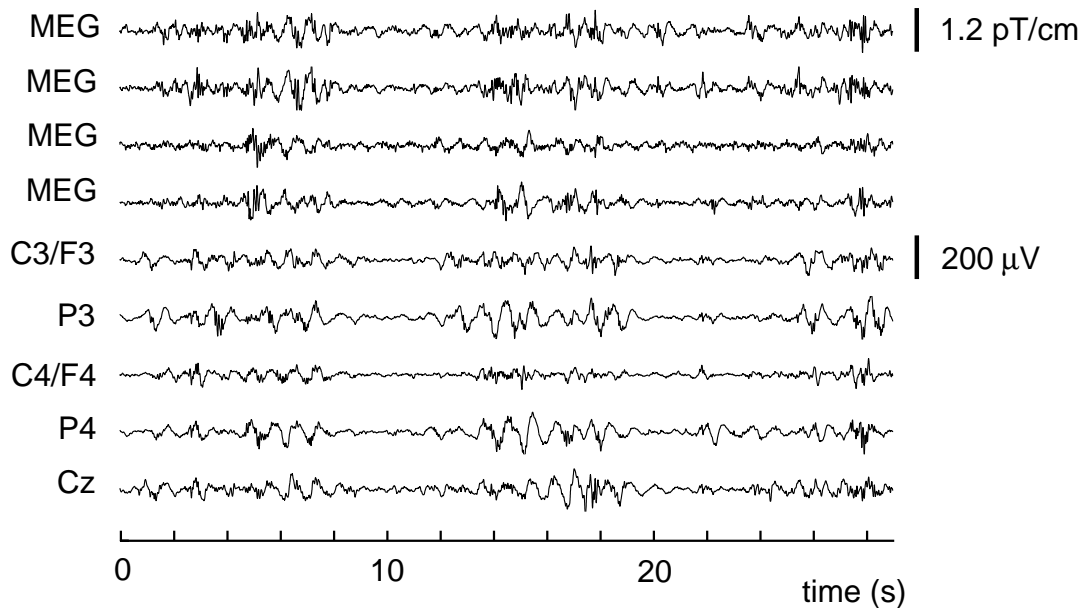


Figure 4: MEG and EEG signals in quiet sleep

5.2 Spectral distribution of power in QS and AS

For comparison of the sleep stages in the frequency domain, a 50 second artefact-free period of quiet and active sleep was chosen from each subject. For EEG, channel Cz was used. For MEG, the head position is slightly different from each subject, so a good channel for each subject was chosen by visual inspection. Spectra were then computed as explained in section 4.3 and averaged across subjects. The results are shown in figure 5. The increase in activity in quiet sleep is mainly in the 1-10 Hz range. The difference in spectra are similar in EEG and MEG. In MEG, the high frequency activity is relatively larger. It is known that MEG is able to see high frequency brain signals better EEG, because the skull acts as a lowpass filter for the electric fields. A part of the high frequency activity is probably caused by the larger environmental noise in MEG and possibly by heart activity of the baby picked up by the gradiometers. However, heart noise was found to be very small or undetectable in the gradiometer channels selected for the inspection. The signals have been bandpass filtered from 0.5 to 40 Hz.

The increase of activity in quiet sleep seems to be distributed over a broad frequency band. There are no characteristic peaks that would result from narrowband rhythmic activity.

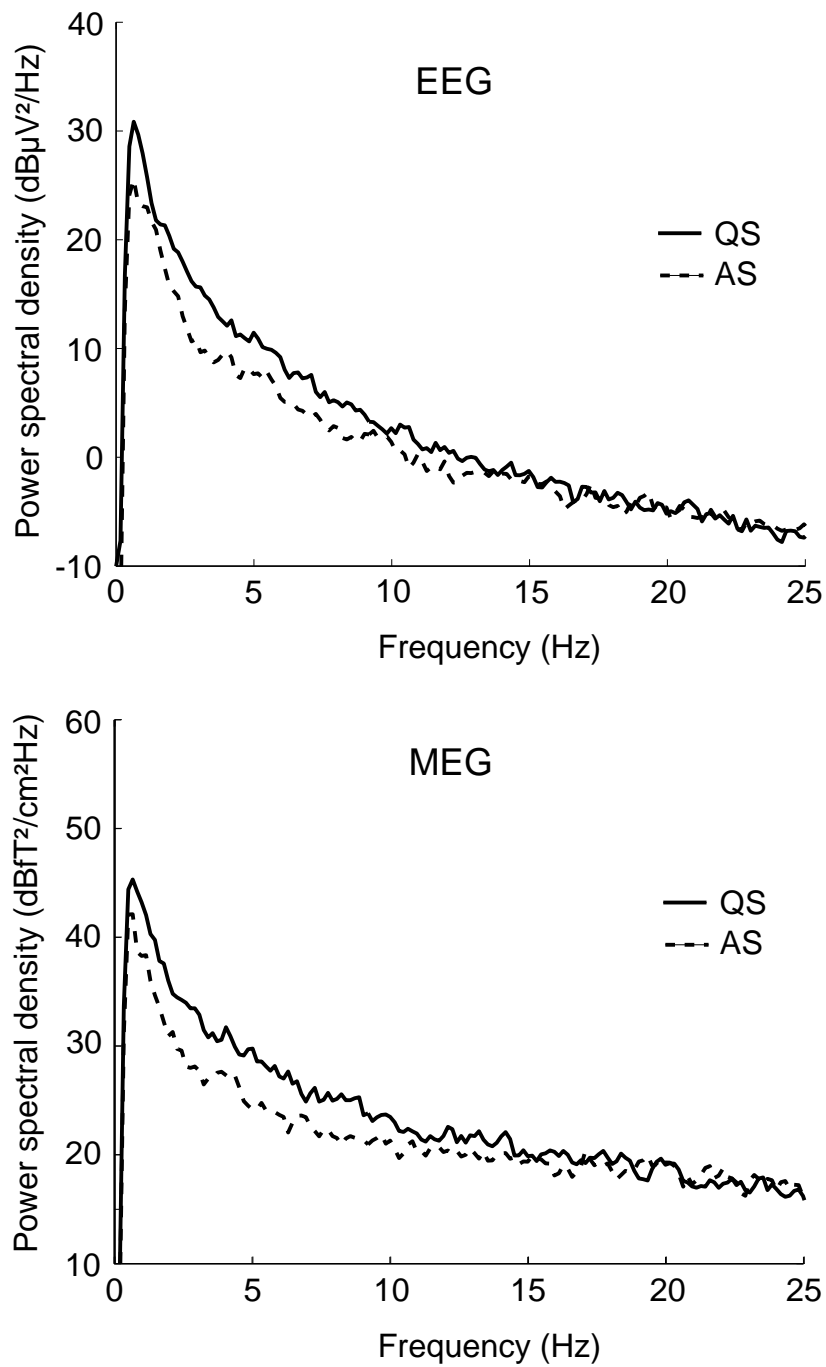


Figure 5: EEG and MEG power spectra in active sleep (AS) and quiet sleep (QS), averaged across the subjects. The power spectral density is plotted on logarithmic scale.

5.3 Heart rate variations

The instantaneous heart rates as a function of time were computed for the same 50-s classified segments that were used for the spectral comparisons. The results are shown in fig. 6. The fast oscillations (about 1 cycle in 2 seconds) seen in quiet sleep data represent the RSA. The difference in RSA amplitude between active and quiet sleep is very clear even from the raw signals. In active sleep, there is an increased amount of slower variations in the heart rate, corresponding to changing metabolic demands during active sleep events such as movements.

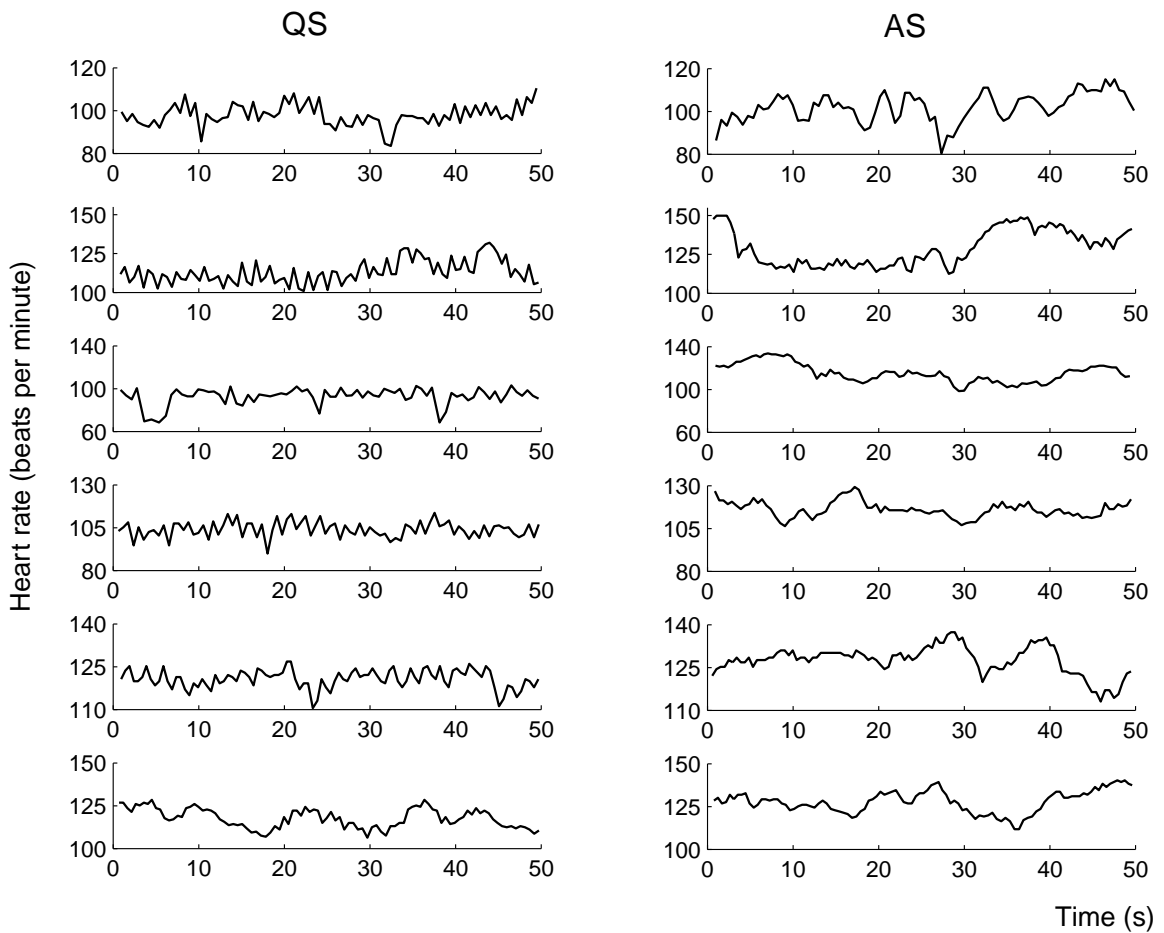


Figure 6: Heart rates as a function of time for quiet sleep (left column) and active sleep (right column). Every pair of plots (one row) is from one subject.

6 Discussion

It was found that good spontaneous MEG data similar to EEGs is obtainable with this measurement setup. The power spectra are similar and support this observation.

For evoked response studies, classification of sleep stages is important, as the responses depend on the sleep stage. The classification is usually performed manually by an expert, which is time-consuming and tedious. Automated adult sleep stage classifiers based mostly on neural networks have been implemented (for example by Shimada et al. in [3]), but as they depend on the specific features of mature sleep stages (delta activity, K-complexes etc.) they will not work on neonatal data. A good classifier for neonatal data will be harder to implement, mainly because the EEG of the neonate has a much smaller number of distinctive features. Another difficulty for classification is that intersubject variability among neonates is large, because they are in a stage of very rapid brain development and small differences in age will affect the EEG significantly. However, even a primitive kind of automated scoring would be useful to support the manual evaluation. It could be used to detect rough errors in manual scoring and quickly obtain an overview of a recording.

Turnbull et al. [9] implemented an automated tracé alternant detection system based on the discrete wavelet transform. As they note, this is the most distinct feature of neonatal sleep EEG and therefore easiest to detect. However, detection of TA is not enough for reliable sleep stage classification. Not all neonates exhibit TA, and it is not always seen during quiet sleep even in the ones that do. Moreover, they seem to have tested the algorithm only on sleep segments that actually have TA, so it is not clear if it makes false detections in other types of sleep stages.

Based on the data obtained here, two potentially useful features to distinguish between AS and QS would be the average EEG or MEG power spectral density on a broad low-frequency band (about 1 to 10 Hz), and the RSA amplitude derived from the ECG. To extract the RSA amplitude, one could for example perform spectral analysis on the instantaneous heart rate signals. Such an approach would also permit easy extraction of the slower heart rate variations observed in AS. Features derived from EMG and EOG signals, if these are available, would probably be useful to support the classification. The easiest approach for implementing a neonatal polygraphy classifier would be to use an existing adult data classifier design as a basis, and just change the feature set.

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