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EEG Analyses—Sleep Scoring in Man and Mammals

Automated Scoring of Sleep in the Neonatal Lamb

*Daniel A. Grant, *†Terri L. Davidson and †James E. Fewell

*The Departments of *Obstetrics and Gynaecology and †Medical Physiology, University of Calgary, Calgary, Alberta, Canada*

Summary: The study of sleep is an important and rapidly expanding area of research that generates large bodies of data. Manual scoring of sleep states from polygraph recordings is a laborious and often subjective task. Even when care is taken, the opportunity for disagreement between investigators and between laboratories remains great. To avoid this difficulty and to reduce the subjectivity of sleep state scoring we have designed a computer-based algorithm for scoring sleep state in the lamb. The algorithm underlying the system relies upon spectral analysis of the electrocorticogram and upon amplitude analysis of the electrooculogram and nuchal electromyogram. Partitioning the spectral power observed within the electrocorticogram (1–4 Hz frequency range) reliably identifies deep quiet sleep. Wakefulness and active sleep are then identified based upon threshold crossings of the electrooculogram and of the electromyogram of the nuchal muscles. We compared the sleep states returned by the algorithm to those scored visually by trained personnel for 1 hour of data collected from each of five 19-day-old lambs. There was good agreement between the two methods of scoring sleep. The percents agreement between the algorithm-derived scores and visual scores were as follows: active wakefulness 97%, quiet wakefulness 87%, quite sleep 85% and phasic active sleep 82%. As such, our algorithm provides a fast, reliable and objective method for scoring sleep state in the young lamb. **Key Words:** Sleep scoring—Automatic analysis—Automatic sleep stager.

The scoring of sleep state is often based upon guidelines established for the adult or the newborn human (1,2). Even when care is taken, significant variability in scoring sleep is reported both within and between laboratories (3–5). The subjectivity of visual scoring is compounded in the animal research laboratory, where physiological data are recorded from species that have sleep–waking characteristics that differ from those of the human. Within our laboratory, sleep state determination for the neonatal lamb is based upon the criteria of Anders et al. (1). Generally, three sleep states are defined; wakefulness, quiet sleep and active sleep (6). Wakefulness and active sleep are easily defined in the lamb because the electrocorticogram activity is well differentiated, even in the near-term fetal lamb (4). However, as with the human (7), the transition from wakefulness to quiet sleep is often more difficult to score.

Attempts to automate the scoring of sleep states to overcome the above-mentioned difficulties (7–13) have met with varying degrees of success. Moreover, many of these systems have limited usefulness because they employ variables for determining sleep state, such as cardiorespiratory variables, that are themselves often the subject of investigation. Thus they do not allow for the simultaneous analysis of many physiological variables that may be influenced by sleep. Because of the need for standardization of sleep state determination, both within and between experimental protocols, we designed and tested a computer-based system for scoring sleep state in the lamb that interacts with commercially available data acquisition and analysis software.

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Address correspondence and reprint requests to Daniel A. Grant, Monash University Medical Centre, Centre for Early Human Development, 246 Clayton Road, Clayton, Melbourne, Victoria, Australia 3168.

METHODS

Animal preparation and recording environment

Sleep data were recorded from five young lambs (19 days old, mixed western breed). Newborn lambs were delivered to the University of Calgary's Animal Resource Centre and housed in Plexiglas cages located within environmental chambers where the temperature (25°C), humidity (40%) and light cycle (12-hour light : dark) were controlled. Each lamb was housed with a companion lamb and had continuous access to food (Lamb Milk Replacer, Land O'Lakes, Inc., Fort Dodge, IA, U.S.A.).

At 2 days of age, each lamb was instrumented for the experiment using sterile surgical techniques. Each lamb was pretreated with atropine sulfate (0.2 mg/kg subcutaneously) and then anaesthetized with 5% halothane in oxygen delivered by mask. The lambs were then intubated and ventilated with 1.0–1.5% halothane in oxygen. Electrodes, necessary for identification of sleep state, were implanted as previously described (6). In brief, teflon-coated, multi-stranded, stainless steel wires (AS633, Cooner Wire Co., Chatsworth, CA, U.S.A.) were implanted through burr holes over the parietal cortex to record the electrocorticogram (ECoG). Similar electrodes were positioned at the inner and outer canthus of the right eye to record the electrooculogram (EOG) and positioned in the dorsal cervical musculature to record the nuchal electromyogram (EMGn). Each electrode pair was referenced to a single wire implanted under the scalp.

After recovering from surgery [in an intensive care unit for small animals (Shorline, Schroer Manufacturing Company, Kansas City, MO, U.S.A.)], the lambs were returned to the environmental chambers. Antibiotics (penicillin G and dihydrostreptomycin) were given daily for 5 days.

Conditions of study

Prior to the study the lamb's cage was partitioned to prevent the lamb from turning around. Lambs continued to be able to move forward and backward and had free access to food. Having previously been exposed to these conditions, the lambs remained quiet during the study.

An open-ended fluid-filled catheter, positioned either intravascularly or upon the lamb's back, was used to detect when the lamb was standing up or lying down. We connected this catheter to a calibrated (0–60 mm Hg) strain gauge manometer (Gould P23ID, Gould Inc., Oxnard, CA, U.S.A.) and amplifier (Low Level Preamplifier, Model 7P1J, Grass Medical Instruments, Quincy, MA, U.S.A.). A change in the lamb's body position produced a step change in the pressure as the vertical distance between the catheter tip and the pressure transducer changed. The electrodes were connected to differential high-impedance probes (7HIP5G, Grass Medical Instruments) that in turn were connected to AC preamplifiers (Model 7P5 Wide Band AC EEG Preamplifier, Grass Medical Instruments) located outside the environmental chamber. Electrophysiological signals were high-pass filtered using the ½ amplitude low frequency response control on the AC preamplifiers (ECoG 0.3 Hz, EOG 1.0 Hz and EMGn 3.0 Hz). All data signals were also low-pass filtered at 35 Hz to conform with the Nyquist criterion and prevent aliasing.

Physiological variables were recorded from each lamb for a 6-hour period on a strip chart recorder (Grass Model 7 Polygraph, Grass Medical Instruments). These signals were also digitized at 167 Hz (Zenith AT computer, Data Translation 2801A A/D, DataQ WFS-200 Hardware Scroller and Codas Data Acquisition software) and stored for off-line analysis. From each 6-hour data file the first 1-hour period that contained a minimum of one of each type of sleep state (as determined by visual scoring [1]) was analyzed further.

Data analysis—sleep scoring algorithm

Automated sleep staging was performed using a sleep staging algorithm incorporated within the commercially available data analysis software package CVSOFT (Odessa Computer Systems Inc., Calgary, Canada). The algorithm incorporated a series of decisions (Fig. 1) based on information derived from the three electrophysiological signals and from the pressure catheter.

The average spectral power of the ECoG over the frequency range of 1–4 Hz was calculated using a Fast Fourier transform ($\sin^3$ window). This frequency range was selected because it consistently provided the best discrimination in spectral power values between different sleep states (Figs. 3, 4 and Results). This frequency range also identifies delta waves associated with deep quiet sleep in humans (1,2). We determined ECoG thresholds that would consistently reflect quiet sleep and quiet wakefulness as identified by trained observers. To do this, we determined the entire range of spectral power values observed in the original 6-hour pre-experiment periods and partitioned them into threshold values as described in Fig. 3. The threshold for quiet sleep was set at 25% of the total range of the ECoG spectral power values, whereas transitional periods were set at 12.5% (Fig. 3). Amplitude threshold crossing routines were used to determine the presence of EOG and tonic EMGn activity and to determine the lamb's body position (pressure catheter). Threshold values for EOG and tonic EMGn were determined as the voltages observed during several periods of well-defined quite sleep, where EOG approaches zero, and during several periods of well-defined active sleep, where tonic EMGn approaches zero. During active sleep, phasic EMGn activity can exist and can exceed EMGn amplitude thresholds, falsely indicating the presence of tonic EMGn activity. To compensate for this activity, the user can select the maximum number of allowable threshold crossings that may occur before EMGn activity is determined to have exceeded the threshold.

After determining the necessary threshold values, automated sleep state scoring was performed on sequential 13-second epochs of data (Fig. 1). The sleep

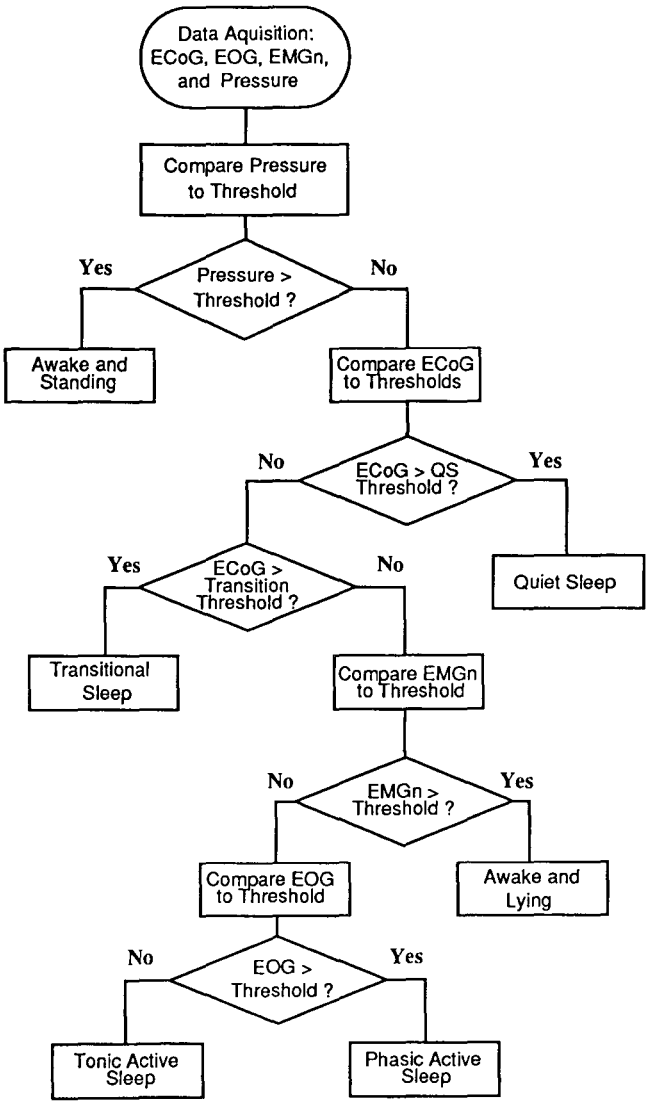

FIG. 1. Automated sleep state scoring incorporated a series of decisions based on information derived from the three electrophysiological signals and the pressure monitoring catheter acquired by the computer. The pressure recorded by the fluid-filled catheter was compared to a threshold value (predetermined when the lamb was standing up). If pressure exceeded this threshold, a score of awake and standing was assigned. If the lamb was lying down a Fast Fourier transform was performed on the ECoG and the spectral power determined for the 1–4 Hz frequency range. Whenever the spectral power exceeded the predetermined threshold for quiet sleep, a score of quiet sleep was assigned. If the spectral power did not exceed the quiet sleep threshold but exceeded the transitional threshold, a score of transitional was assigned. If the spectral power did not exceed the transitional threshold, the EMGn was analyzed for the presence or absence of nuchal tone. When EMGn tone was present a score of quiet wakefulness was assigned. When EMGn tone was absent a score of phasic or tonic active sleep was assigned based on the presence or absence of rapid eye movements (EOG activity), respectively.

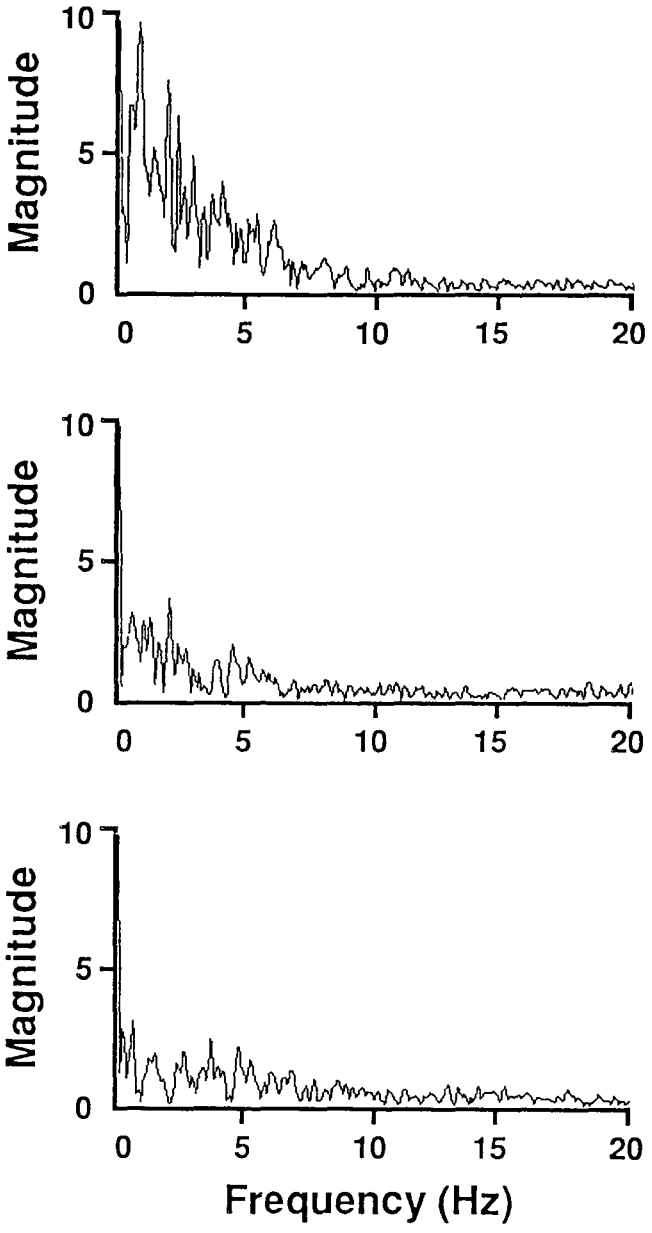

FIG. 2. An example of the average spectral power calculated for a period of well-defined quiet sleep (Top), quiet wakefulness (Middle) and active sleep (Bottom). The greatest difference in spectral power between states was found within the 1–4 Hz frequency range.

staging algorithm initially determined if the lamb was standing up or lying down by comparing the average pressure recorded from the fluid-filled catheter during this period to that pressure recorded during a period when the lambs were known to have been standing up. If the lamb was standing up, the sleep state assigned was awake and standing. If the lamb was lying down, the algorithm calculated the spectral power of the ECoG and compared it to the threshold values. If the spectral power exceeded the quiet sleep threshold, the epoch was scored as quiet sleep. If the spectral power was below the quiet sleep threshold but above the transitional threshold, the epoch was scored as transitional sleep. Whenever the sleep state was assigned a score of either transitional or quiet sleep, the analysis was

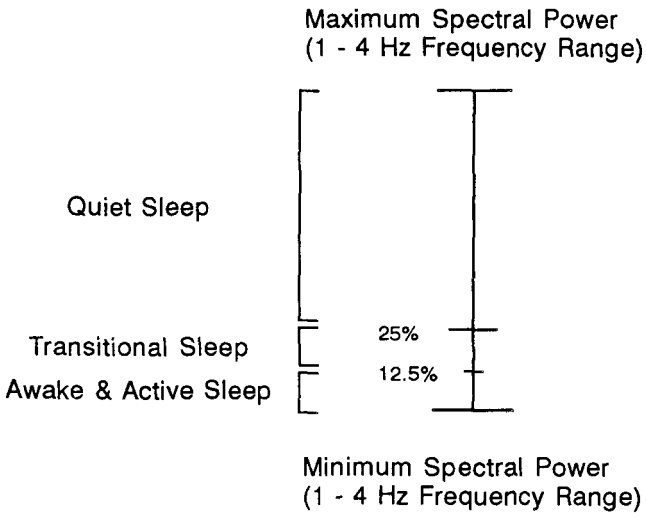

FIG. 3. The ECoG thresholds for the various states ranging from awake/active sleep to quiet sleep were set to give the best concordance between the visual and automated scoring of sleep states. This occurred when the difference between the maximum and minimum spectral powers observed in the 6-hour data files was partitioned as shown. The minimum spectral power plus 12.5% of the difference between minimum and maximum spectral power determined the transitional threshold. The transitional threshold value plus an additional 12.5% of the difference between the minimum and maximum spectral power determined the quiet sleep threshold.

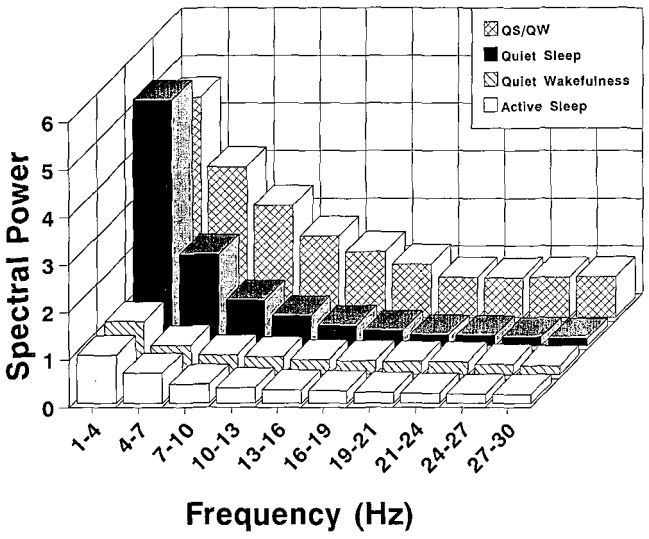

FIG. 4. The average spectral power was calculated for 1-minute periods of well-defined quiet sleep (QS), quiet wakefulness (QW) and active sleep. The greatest difference in spectral power between QS and QW was found in the 1–4 Hz frequency range ($p \leq 0.05$, ANOVA for repeated measures and Student-Newman-Keuls test). Similarly, the greatest relative difference, as reflected by the ratio of the spectral power in QS to that in QW (QS/QW), was also recorded in the 1–4 Hz frequency range ($p \leq 0.05$). Values represent the mean values from five lambs.

complete and the process was repeated on the next 13 seconds of data. If the spectral power of the ECoG was below the transitional threshold, the amplitude of EMGn was compared to its threshold value to determine if nuchal muscle activity was present. The epoch was scored as awake if the EMGn activity was present and active sleep if absent. When scored as active sleep the EOG amplitude was then compared to its threshold value to determine if rapid eye movements were present. The epoch was scored as phasic active sleep when rapid-eye-movements were present and tonic active sleep if absent.

Data analysis—visual scoring

The results obtained by the sleep scoring algorithm were compared to those determined visually. Polygraph recordings of the 1 hour of data analyzed by the algorithm were partitioned into sequential 13-second epochs and then visually scored for sleep state by three experienced laboratory personnel. These individuals were asked to score each epoch as awake and standing, awake and lying down, transitional periods, quiet sleep, phasic active sleep and tonic active sleep. These 13-second epochs were presented in sequential order because scoring of sleep states is routinely aided by reference to the amplitude of the ECoG in the preceding and subsequent epochs. A score of wakefulness was assigned if the ECoG was of low voltage and high frequency and EMGn tone was present. Wakefulness was further classified into periods of standing up or lying down by assessing the pressure recorded by the fluid-filled catheter. Active sleep existed when the ECoG was of low voltage and high frequency and EMGn tone was absent. Active sleep was further classified into tonic (no rapid eye movements) or phasic (rapid eye movements) periods. The remaining periods were assigned as either transitional sleep or quiet sleep. Because the visual classification of the transition from wakefulness to quiet sleep is the area where most disagreement occurs between scorers (7), we asked our visual scorers to base their analysis upon the following subjective criteria. Quiet sleep was to be determined as those periods where high-voltage, low-frequency (1–4 Hz) ECoG activity occurred and where the magnitude of the ECoG appeared to be $\geq 50\%$ of the maximum ECoG amplitude observed throughout the data file. Transitional sleep was therefore determined to exist if the ECoG amplitude was in excess of that in wakefulness but less than that in quiet sleep. Because visual scores often disagreed, we utilized the modal score for each period of data. Those periods in which at least two of three scorers did not agree were excluded from further comparison.

RESULTS

Calculations of the average spectral power (Fig. 2) for a series of frequencies showed that the greatest

TABLE 1. *A comparison of sleep state scores determined by the algorithm to those determined by visual examination of the records. Values represent the percentage of agreement when comparing the automated score to the visual score*

	Visual					
Algorithm	Awake standing up	Awake lying down	Transitional sleep	Quiet sleep	Active sleep (tonic)	Active sleep (phasic)
Awake (standing up)	97.4%	1.2%				
Awake (lying down)	2.6%	87.0%	29.7%	0.5%	12.5%	11.8%
Transitional sleep		8.1%	52.0%	13.6%	29.2%	4.9%
Quiet sleep		1.2%	13.8%	85.0%	4.1%	
Active sleep (tonic)		1.5%	3.7%	0.7%	37.5%	0.7%
Active sleep (phasic)		1.0%	0.8%	0.2%	16.7%	82.6%

A total of 116 active wakefulness, 408 quiet wakefulness, 246 transitional sleep, 433 quiet sleep, 24 tonic active sleep and 144 phasic active sleep epochs of 13-second lengths were included in this analysis.

relative difference between spectral power existed in the 1–4 Hz frequency range. The transition from quiet sleep to either active sleep or wakefulness was accompanied by a significant reduction in spectral power in the lower frequency ranges [1–4 and 4–7 Hz bins, $p \leq 0.05$, analysis of variance (ANOVA) for repeated measures and Student-Newman-Keuls test], with the greatest relative change occurring in the 1–4 Hz frequency range ($p \leq 0.05$, Fig. 4). Spectral power in the upper frequency ranges did not change during this transition.

The sleep states defined using the algorithm corresponded closely to those scored visually (Table 1). In >97% of the periods in which the lambs were visually scored to be standing, the automated sleep stager assigned the same score. When visually determined to be awake and lying down, the algorithm assigned the same score in 87% of the cases. The visual and automated scoring for quiet sleep and phasic active sleep also compared favorably (85% and 83% agreement, respectively). The agreements between the visual and automated scores of transitional sleep and of tonic active sleep were weaker (52% and 38%, respectively). In the majority of cases, disagreement between the visual and automated scores for awake, transitional sleep and quiet sleep reflected the inconsistency of visual scorers in judging ECoG amplitude or power (Table 1). Data that were visually scored as awake were consistently scored (>95% of the time) as either awake or transitional by the algorithm. A similar inability to partition the ECoG amplitude can account for the discrepancies observed for quiet sleep. Even with these difficulties, the algorithm and visual scores were in agreement >80% of the total time analyzed.

DISCUSSION

We have designed a computer-based system that reliably scored sleep states in the lamb and that interacts with a commercially available data acquisition/analysis software system. The concordance between the automated and visual scoring of data exceeded 90% for wakefulness (standing and lying combined), 87% for quiet wakefulness, 85% for quiet sleep and 83% for phasic active sleep. These agreement scores correspond well with those of other automated sleep scoring algorithms (3). The algorithm uses information derived from a Fast Fourier transform analysis of the ECoG and subsequent amplitude threshold analysis of the EMGn, EOG and position catheter and is, thus, independent of changes in cardiorespiratory variables. This algorithm reduces the subjectivity of scoring sleep states within a laboratory setting and allows the user to objectively compare sleep states under varying experimental conditions. By virtue of its interaction with a complete data analysis program, it also allows the user to assess the influence of sleep state upon other physiological variables.

Harper et al. (19) used cardiorespiratory variability to accurately define sleep state in human infants. This approach has merit when the definition of sleep state is the only goal. If, however, the goal of the study is to assess cardiorespiratory responses to various interventions during sleep, as is often the case within animal laboratories, these same cardiorespiratory variables cannot appropriately be used to define state (19). In these situations it is necessary to employ alternative measurements, such as the electrophysiological variables used here. As we outline below, the accuracy of the scoring system based upon electrophysiological criteria equals that of Harper et al. (19).

The largest source of disagreement between visual and automated scoring was in subjectively partitioning the transition from wakefulness to quiet sleep by the visual scorers. Lacking the benefit of power spectrum analysis, our visual scorers often scored epochs as awake and lying down that were scored as transitional by

algorithm. A similar disagreement was evident for transitional and quiet sleep. Our results confirm the difficulty of visually partitioning the transition from wakefulness to quiet sleep (7,14) and emphasize the usefulness of power spectral analysis in determining sleep states in the lamb by virtue of its consistency.

Disagreement between the visual and automated scoring systems also existed for epochs in which a change in state occurred. State changes accounted for 100% of the discrepancy observed when determining if the lamb was awake and standing versus awake and lying down and almost 40% of the discrepancies in tonic and phasic active sleep. We could not eliminate this type of disagreement.

The ability of the algorithm to score phasic active sleep, although exceeding 80% agreement with the visual score, was hindered by the presence of phasic EMGn activity. This difficulty has been noted by others (11) to affect sleep state scoring during periods of active sleep with large amounts of phasic nuchal muscle activity. To reduce this problem, the algorithm was designed to allow the user to adjust the number of threshold crossings acceptable before the EMGn activity exceeded the threshold. Disagreements of this type were easily detectable during review of the original polygraph recordings (an essential component of data analysis even when using automated systems).

Although the agreement between sleep state determined visually and using the algorithm was good for most states, the agreement for tonic active sleep was poor (38%). The amount of tonic active sleep in the lamb is small (accounting for $<2\%$ of the total time analyzed in this study). In the lamb, tonic active sleep occurs primarily at the beginning or end of an active sleep epoch and is usually of a much shorter duration than is phasic active sleep. Because of its short duration compared to the length of the sample window, the sample period of tonic active sleep seldom contained a period of pure tonic active sleep but instead often included a change in state. If a change in state is included in the sample window, the spectral analysis of the ECoG or the EMGn threshold analysis will score an "incorrect" state. Indeed, state transitions accounted for $>50\%$ of the errors in automatically scoring tonic active sleep. This type of disagreement reflects the inherent inaccuracy that arises from attempting to discretely classify the continuous process of sleep (14).

We have based our analysis upon the assessment of spectral power in the 1–4 Hz range for the ECoG. This frequency range, which reflects delta waves, was utilized because it is this frequency range in which most power is found in the adult (15), neonatal (16) and near-term fetal lamb ECoG (13). It is also the dominant frequency range found in deep quiet sleep in the adult and neonate (1,2). It is within this frequency range that the greatest differences in spectral power exist between sleep states. We confirmed that this is the case in the neonatal lamb (Figs. 2 and 4) because spectral power in this frequency range decreased with a change from quiet sleep to wakefulness.

The strength of our algorithm rests in its ability to consistently return the same sleep score for any given period of data. This greatly reduces variability in sleep scoring both within and between laboratories. This sleep scoring system allows us to standardize sleep scoring within and between experimental protocols and allows the user to make quantitative statements concerning the distribution of sleep states (e.g. before and after drug treatment). In addition, the other variables, such as heart rate or blood pressure, can be assessed within a consistent sleep state—both within and between animals. We did not try to determine the sleep state strictly based upon the manuals for sleep state determination (1,2). Instead, we based our determination loosely upon those criteria, as done in the past within this laboratory (17,18). In essence the criteria are the same for wakefulness and for active sleep but vary in the assessment of quiet sleep. The assessment of these states using the clinical criteria is impractical in the animal laboratory, where vast amounts of data are recorded from animals that may not mimic the human. For this reason we have not related transitional and quiet sleep states specifically to the clinical states of 1–4. In addition, the length of the sample window used in our program is less than half of that used for clinical sleep staging (1,2). This reduces the possibility of multiple state changes occurring within a given sample window and so increases the accuracy of the sleep state determination.

In summary, we have designed an automated method for scoring sleep states that operates in conjunction with a commercially available data analysis program (CVSOFT). Based upon information derived from electrophysiological signals commonly used to score sleep state, the algorithm reliably identified wakefulness, quiet sleep and active sleep. Our sleep scoring system is flexible because it allows the user to define all of the threshold values and thus fine tune the program to his/her needs. Although we have not tested our algorithm on other species, we believe it will be applicable for other species that display similar ECoG, EOG and EMGn patterns during sleep.

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