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The REM–NREM Sleep Cycle: Renewal Process or Periodically Driven Process?

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Summary: The question of the serial dependence of successive REM–NREM sleep cycles was examined. The experiments were performed in two different settings: 309 sleep episodes of 11 healthy young sleepers (age range, 20–36 years) were recorded under entrained conditions in the sleep laboratory; 5 of these subjects also slept in an isolation unit (underground apartment) with free-running sleep–wake cycles for a total of 107 sleep episodes. The covariances between the first three REM–NREM cycles were computed using an intraindividual cross-night approach. Significant negative covariances were observed. This result confirmed the assumption of serial dependencies between successive REM–NREM cycles. These data agree with the features of a periodically driven process and are incompatible with the alternatively hypothesized renewal model. The periodically driven process is similar in concept to the basic rest–activity cycle. **Key Words:** Sleep—REM–NREM cycle—Ultradian periodicity—Basic rest–activity cycle.

The alternation of REM and non-REM (NREM) episodes is a basic feature of sleep. A sequence of two such sleep episodes is termed a REM–NREM cycle.[1] It is known that the variability of the REM–NREM cycle is large (Lewis, 1974) and that there exist systematic trends in cycle length over a sleep episode (Feinberg and Floyd, 1979). These observations have raised serious questions about the supposed periodic nature of the REM–NREM cycle. As in the case of circadian periodicities, it would be useful to define criteria which have to be fulfilled before assumptions about the periodic properties of the cycle may be confirmed. In this paper two different mechanisms are examined which may regulate the succession of REM–NREM cycles.

The simplest statistical approach is to imagine that REM–NREM cycles occur

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[1] A REM–NREM cycle is defined as either a NREM cycle or as a REM cycle. A NREM cycle begins with a NREM episode and contains the succeeding REM episode, while a REM cycle begins with a REM episode and contains the succeeding NREM episode.

as a result of a renewal process (Cox, 1962) (Fig. 1). In this case, the first cycle is triggered by sleep onset. The length of this cycle constitutes a random variable. A basic assumption is that the length of the succeeding cycle 2 is again a random variable which is independent of the length of cycle 1. The same holds for the further REM–NREM cycles during the night.

Experimental data from many studies on the REM–NREM cycle fit this model. Different studies have shown that intervening wakefulness lengthens the REM–NREM cycle (Březinová et al., 1975; Gaillard and Tuglular, 1976; Schulz, 1978). Moses et al. (1977) demonstrated that the estimation of the cycle length is greatly disturbed by intervening wakefulness and becomes more stable after the elimination of this variable. These results are consistent with the model of a renewal process: if sleep is interrupted by wakefulness, the process starts anew with the next trigger signal (sleep onset). On the basis of this model, the REM–NREM cycle is a sleep-dependent event which is terminated by awakening.

Basically, the renewal process has no "memory" of past events. This results in a succession of REM–NREM cycles that are independent of one another within a bedrest and, consequently, across consecutive bedrests.

An alternative to the renewal process is the periodically driven process. In this case, the cyclic alternation of NREM and REM sleep is seen as an overt rhythm which is controlled by a process of higher precision. This periodic process is

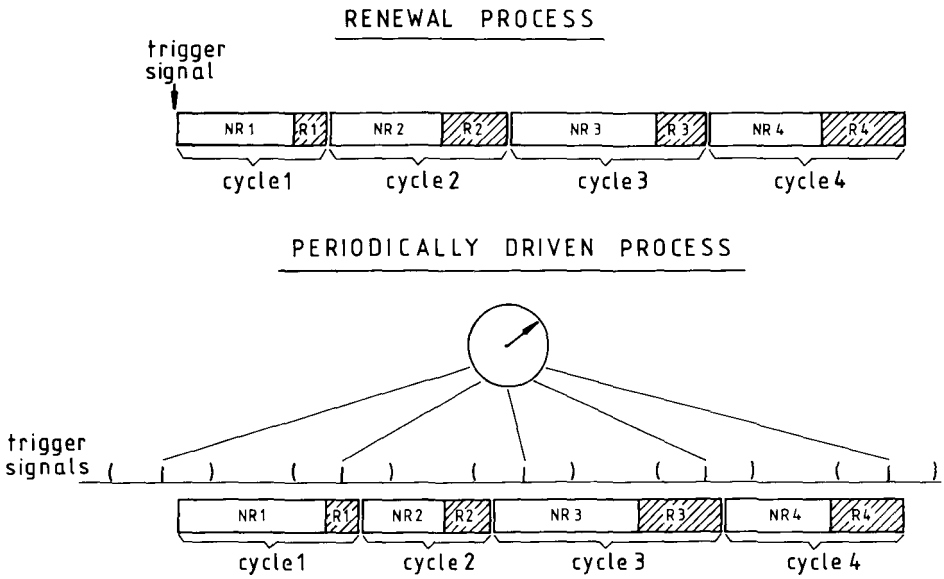

FIG. 1. Schematic representation of two alternative models for the description of the REM–NREM cycle. In the renewal process the cycles are independent realizations of randomly varying cycle lengths. The trigger signal represents sleep onset. NR and R are the NREM and REM part of the REM–NREM cycle. The model of a periodically driven process assumes a driving force, represented by a clock, which controls the overt REM–NREM rhythm. The clock delivers trigger signals at equal time intervals. The brackets represent zones where the probability of REM sleep is high. This control by a clock effects negative correlations between successive REM–NREM cycles.

illustrated as a clock in Fig. 1. According to this model, the lengths of adjacent cycles are not independent but negatively correlated. Thus, a deviation in the length of one cycle is corrected in the following cycle. In a long-term observation of this process, the starting points of the cycles occur mainly in the temporal neighborhood of certain clocktimes.

The periodic process, outlined here, shares some important properties with the basic rest–activity cycle (BRAC) which was proposed by Kleitman (1969). The BRAC was conceived as a sleep-independent driving force which generated the sequence of NREM and REM episodes during sleep. In contrast to the BRAC hypothesis, the periodic process emphasizes the correction of the length of successive REM–NREM cycles.

In 1975 we reported on some longitudinal sleep studies in which subjects displayed a NREM–REM pattern which was not a submultiple of 24 hr, but drifted from night to night (Schulz et al., 1975). These data are compatible with the assumptions of a periodically driven process and incompatible with those of a renewal process.

In the present paper we test the hypothesis as to whether successive REM–NREM cycles are interrelated in the sense of a correction of the cycle length. This will be done by an estimation of cycle parameters across sleep episodes. Furthermore, the question of whether or not periodic components are detectable in single sleep episode patterns will be examined. This approach should facilitate the choice between the two models.

METHODS

Experimental Procedure

Eleven healthy subjects (4 females, 7 males; age range, 20–36 years) took part in the experiments. All of them slept under undisturbed conditions in the sleep laboratory. In addition, 5 of them lived for some time under conditions without external *zeitgebers* in an isolation unit (underground apartment) where sleep was also recorded. Table 1 gives the number of consecutive sleep episodes per subject which were selected for analysis. While the sleep–wake cycle was entrained to 24 hr in the sleep lab, sleep episodes were self-selected in the isolation unit. Isolated subjects were trained to prepare the hookup for polygraphic sleep recording by themselves. While applying the electrodes, they informed the experimenter in the control room, by a buzzer, that the bedrest would start soon. Only in the first isolation experiment, with subject CMB, did the experimenter enter the isolation chamber to attach the electrodes.

Under both experimental conditions the following variables were recorded: horizontal and vertical electro-oculogram (EOG), electroencephalogram (EEG, C4-A1, C3-A2), chin electromyogram (EMG), and body movements, using an inductive device (actogram). In the sleep laboratory, sleep-onset time varied between 2230 and 0100 hr. The distribution was unimodal, being centered around 2330 hr.

Only two of the subjects had a fixed lights-off time (CML and CWL). In another subject (DAL) lights-off was delayed by 4 min/24 hr. Lights were turned off

TABLE 1. *Subject characteristics and number of sleep episodes*

Subject[a]	Sex	Age (years)	Sleep episodes analyzed (*n*)
CML	F	28	30
CWL	M	23	30
DAL	M	21	29
GRL	F	36	25
STL	F	24	30
BGL	M	21	28
KOL	M	31	26
SPL	F	20	29
AFL	M	21	23
MCL	M	25	29
WML	M	30	30
CMB	F	28	23
AFB	M	21	22
MCB	M	25	22
WMB	M	30	20
WLB	M	27	20

[a] Subjects CM, AF, MC, and WM slept under internally synchronized conditions in the sleep laboratory (L) and in the isolation unit (B).

immediately after the subject lay down; however, subject GTL, who was accustomed to reading for 30–60 min before lights-off, was asked to continue this behavior in the sleep lab.

Data Analysis

All sleep episodes were analyzed twice. In the first analysis only sleep onset, end of sleep, and the first and last epoch of each REM episode were scored. Sequences of REM sleep epochs were combined into one REM episode if the interval between them was 15 min or less. This criterion fits with the criteria used by others (Feinberg and Floyd, 1979; McNew et al., 1971). No minimal duration for a REM episode was defined. In the second analysis, sleep episodes were scored by epoch according to the criteria of Rechtschaffen and Kales (1968). The present data rely mainly on the first analysis described.

Data Processing

In the present paper, we use two methods of testing the hypotheses of periodicity and renewal for the REM–NREM. First, an analysis of the structure of each sleep episode was carried out. Then, an intraindividual statistical evaluation across sleep episodes was done.

Single Sleep Episodes Analysis. In the following, a sequence of equidistant points will be called a grid. The grid interval, constant over a given grid, is variable between grids. For each sleep episode a grid was sought that "hit" each REM episode once and only once. By "hit" we mean the coincidence of one grid point

with one REM episode. If such a matching grid was found, the respective sleep episode was classified as periodic, since its structure would then be compatible with the above-stated model of periodicity. If a matching grid did not exist, then the sleep episode was classified as nonperiodic.

Moreover, if a sleep episode was classified as periodic by this procedure, there exist matching grids of minimal and of maximal intervals which hit all REM episodes exactly once. The values of these intervals provide an estimate of the period of the REM–NREM cycle. Moreover, it was possible to compute a value, M, that may be regarded as an optimal period estimate as defined in Fig. 2.

Across Sleep Episodes Analysis. As described above, the analysis of a single sleep episode does not permit a choice between the two hypotheses, i.e., periodic versus renewal process, since each sleep episode is too short for a time series analysis. Therefore, an across sleep episodes analysis was based on the following consideration. Let z_1, z_2, and z_3 be the durations of the first three REM–NREM cycles. Let var (z_n), $n = 1, 2, 3$, be the variances of the cycle lengths. In addition to the random variables z_1, z_2, z_3, we define the sum of the cycle lengths $z_1 + z_2 + z_3$. Let var$(z_1 + z_2 + z_3)$ be the variance of this random variable. A general property of sums of random variables is

$$\text{var}(\sum z_n) = \sum \text{var}(z_n) + 2 \sum_{n \neq m} \text{cov}(n,m) \ .$$

In the case of a renewal process with uncorrelated cycle lengths, this reduces to

$$\text{var}(\sum z_n) = \sum \text{var}\ (z_n)$$

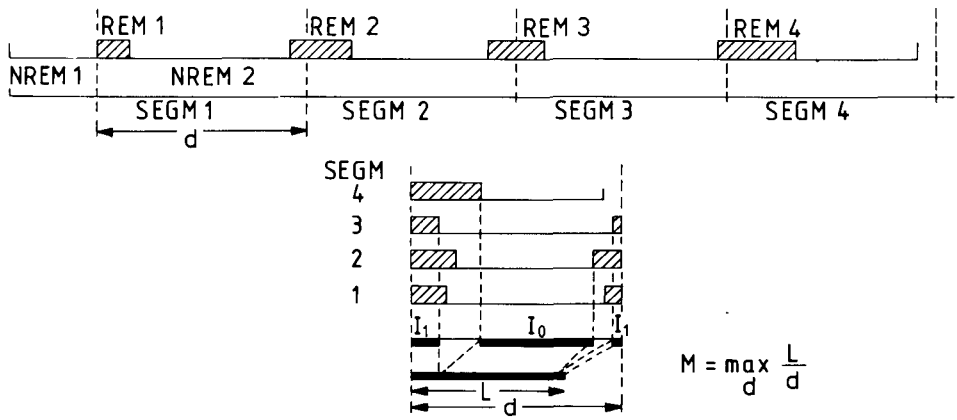

FIG. 2. **Top:** The REM–NREM sequence is divided into segments of equal length d, where d is the grid interval. **Bottom:** The segments are then superimposed. If the grid with distance d is a matching grid, the intervals I_1 and I_0, where either all (I_1) or no (I_0) REM is present, have a length greater than zero. Let L be the pooled lengths of the intervals of type I_1 and I_0. L is a function of the grid interval d, which assumes a maximal value M when d is varied through the interval from d_{min} to d_{max} (see text). The grid interval d at which M is assumed is used as an optimal estimate of the REM–NREM cycle.

or, defining a quantity Q as

$$Q = \frac{\text{var}(\sum z_n)}{\sum \text{var}(z_n)},$$

we have

$$Q = 1.$$

In the case of an overt rhythm, driven by a periodic process as defined above with negative covariances between different cycles, the following inequality holds:

$$\text{var}(\sum z_n) < \sum \text{var}(z_n).$$

Therefore, in this case,

$$Q < 1.$$

The variances may be estimated intraindividually by an across sleep episodes computation, and the Q values can be subject to statistical analysis.

RESULTS

Single Sleep Episode Analysis

The results of the single sleep episode classification procedure are summarized in Table 2. Clearly, sleep episodes with few cycles are more likely to be classified as periodic than sleep episodes with more cycles. Therefore, in Table 2, column I, the average number of cycles for each subject is given, and in column II the percentages of sleep episodes classified as periodic. A comparison of the values

TABLE 2. *Parameters used to classify sleep episodes as periodic or nonperiodic*

Subject	I	II	III	IV	V	VI	VII
CML	4.23	93.3	50.0	86	104	115	63.0
CWL	4.87	46.7	10.0	79	103	108	56.9
DAL	4.48	41.4	6.9	72	97	131	55.7
GRL	3.80	64.0	20.0	88	118	158	71.0
STL	4.87	53.3	23.3	77	98	115	58.5
BGL	4.14	51.7	25.0	94	111	132	63.9
KOL	4.04	73.1	34.6	77	105	159	59.8
SPL	4.59	37.9	3.5	77	98	131	57.4
AFL	4.52	56.5	21.7	76	102	131	59.3
MCL	3.59	82.8	36.7	97	128	171	77.6
WML	4.63	56.7	33.3	77	97	119	63.4
CMB	4.78	78.3	43.5	78	99	124	66.1
AFB	5.91	27.3	9.1	77	91	115	56.8
MCB	4.82	54.5	22.7	89	111	129	53.6
WMB	6.10	30.0	25.0	73	90	106	53.0
WLB	3.40	50.0	20.0	84	118	156	74.4

Columns are as follows: I, average number of REM–NREM cycles for each subject; II, percentage of sleep episodes classified as periodic; III, percentage of sleep episodes classified as periodic with the mean optimal cycle duration; IV, minimal grid interval (min); V, mean value of optimal grid interval (min); VI, maximal grid interval (min); VII, intraindividual mean value of parameter M (%).

for subjects SPL and CML shows that great interindividual differences in the proportion of periodic sleep episodes exist; these cannot be explained by different numbers of cycles.

Columns IV and VI of Table 2 show the overall minimal and maximal period estimates for each subject. Column V contains the intraindividual mean values of the optimal period estimates. For each periodic sleep episode, we can determine whether a grid whose interval coincides with this mean value is a matching grid in the sense defined above. If this is the case, then this sleep episode is compatible with the mean optimal period. Column III presents the proportion of sleep episodes compatible with the mean optimal period for each subject. Column VII shows the intraindividual mean values of the parameter M obtained in the procedure for estimating the optimal period; it varies only between 53.0% (subject WMB) and 77.6% (subject MCL). This indicates a remarkably stable structure of the REM–NREM cycle, even in different subjects and under different experimental conditions. A well-known fact, which is confirmed by the figures presented here, is the relatively small variation of the mean length of the REM–NREM cycle, varying between 90 and 128 min. The results so far reported, do not yet allow a choice of which of the two suggested models is a more appropriate description of the REM–NREM cycle.

Across Sleep Episodes Analysis

We now turn to the results from an intraindividual across sleep episodes analysis, based on the variance ratio Q defined above (Table 3). In the computation, only nights with at least three complete REM and NREM episodes were included. Therefore, in some cases, the number of sleep episodes (column I), differs from the numbers given in Table 1. Column II shows the variance ratio values for the first and second NREM cycles, while column IV gives the respective values for the second and third cycles. Column III presents the Q values for the first and third cycles, which are not adjacent. Finally, column V shows the Q values for the combined first three NREM cycles. Respective values for the REM cycles are found in columns VI–IX.

Concerning the Q values for the combination of two successive cycles, there are only two significant deviations from the expected value of $Q = 1$ for the renewal process hypothesis. The mean values of $Q = 0.88$ and 0.75 (column VII) for the combination of REM cycles 1 and 3 are significantly smaller than 1.0 under both experimental conditions (t-test, one-tailed; $p < 0.05$).

From the four mean Q values, which result from the combination of the first three cycles, NREM or REM, three are significantly smaller than unity: NREM, isolation experiment, $Q = 0.61, p < 0.05$ (column V); REM, sleep lab, $Q = 0.78, p < 0.01$; and REM, isolation experiment, $Q = 0.69$, $p < 0.05$, t-test, one-tailed (column IX). We have not tested the effect of the combination of more than three REM–NREM cycles so as to avoid the problem of comparing different subsamples of sleep episodes within a subject.

These results show that when a deviation in the duration of one cycle occurs, there is a significant tendency for an appropriate correction to be made in the next

TABLE 3. *Variance quotient Q for different combinations of REM–NREM cycles*

Subject	I Sleep periods (*n*)	II NREMC1 NREMC2	III NREMC1 NREMC3	IV NREMC2 NREMC3	V NREMC1 NREMC2 NREMC3	VI REMC1 REMC2	VII REMC1 REMC3	VIII REMC2 REMC3	IX REMC1 REMC2 REMC3
CML	30	0.99	0.88	0.71	0.69	0.59	0.98	0.73	0.60
CWL	28	1.08	1.12	1.03	1.17	1.06	1.16	1.01	1.13
DAL	27	0.49	0.78	1.38	0.72	0.96	1.06	0.64	0.71
GRL	19	0.82	1.23	0.92	0.96	1.23	0.82	0.92	0.99
STL	30	1.15	1.28	1.00	1.37	1.13	1.00	0.82	0.94
BGL	26	0.88	0.57	0.78	0.45	0.70	0.76	1.19	0.82
KOL	23	0.60	1.03	0.76	0.62	1.09	0.81	0.58	0.66
SPL	27	1.04	0.53	0.77	0.54	0.45	0.55	1.29	0.50
AFL	22	1.64	0.96	0.81	1.29	0.93	0.56	1.11	0.74
MCL	16	0.79	1.39	0.67	0.90	0.78	0.85	0.54	0.44
WML	29	1.09	1.01	1.07	1.07	1.03	1.16	0.88	1.07
$\bar{x}$		0.96	0.98	0.90	0.89	0.91	0.88	0.88	0.78
s		0.31	0.28	0.21	0.31	0.24	0.21	0.25	0.23
t		0.42	0.24	1.59	1.19	1.29	1.83[a]	1.55	3.16[b]
CMB	20	1.04	0.71	0.87	0.73	1.12	0.63	1.10	0.92
AFB	21	0.84	0.62	0.99	0.58	0.64	0.84	0.91	0.59
MCB	21	0.58	0.59	1.08	0.48	0.92	0.65	0.66	0.46
WMB	19	0.86	1.21	0.69	0.95	0.91	1.06	0.86	0.90
WLB	9	0.26	0.77	0.94	0.33	0.90	0.57	0.89	0.56
$\bar{x}$		0.72	0.78	0.91	0.61	0.90	0.75	0.88	0.69
s		0.30	0.25	0.15	0.24	0.17	0.20	0.16	0.21
t		2.10	1.96	1.31	3.67[a]	1.33	2.78[a]	1.65	3.34[a]

[a] $p < 0.05$ (t-test, one-tailed).
[b] $p < 0.01$ (t-test, one-tailed).
NREMC, sleep cycle starting with a NREM episode; REMC, sleep cycle starting with a REM episode.
t and s: $t_{N-1} = \dfrac{|\bar{x} - \mu|\sqrt{N}}{s_{N-1}}$ (Diem and Leutner, 1975) where the hypothesis is that the empirical mean value $\bar{x}$ is equal to the expected mean μ. In the present case, the expected $\mu = Q = 1$.

cycles, in accordance with the hypothesis of an overt rhythm driven by a periodic process. This effect is not very strong when comparing pairs of successive cycles, but it is remarkable for combinations of at least three adjacent REM–NREM cycles. Negative covariances between successive cycles cannot be explained by a renewal model, but are, in accordance with the assumptions of the periodicity model.

DISCUSSION

The most important finding of the present study is the demonstration of significant negative covariance between successive REM–NREM cycles. The length of one cycle depends on the length of the preceding cycles. This tendency to correct the cycle length presupposes a "memory." This feature of the REM–NREM cycle is incompatible with the assumptions of a renewal model but favors the periodicity model. Although this result is valid for entrained as well as free-running sleep–wake cycles, there are some important limitations. If pairs of cycles are combined, only the REM cycles 1 + 3 combination yields significant negative covariances (for both experimental conditions). Only the combination of the first three REM–NREM cycles shows a clear effect. It has yet to be tested whether the combination of more than three cycles, which is possible for long sleep periods, yields even greater reductions of variance. There are some differences between the results from the sleep lab and the isolation unit. The mean Q values are somewhat smaller for the isolation condition, in which the time and the duration of bedrests were self-selected. This may point to an important interaction between internal and external factors in the 24 hr condition of the sleep lab.

If it is true that the overt rhythm is driven by a periodic process, then the percentage of sleep episodes classified as periodic is surprisingly small. In the present approach, sleep episodes were classified as either periodic or nonperiodic according to a rigid criterion. To satisfy this criterion, all REM episodes of a particular sleep episode must be distributed equidistantly. This approach is not sensitive to systematic within-night trends of the length of the REM–NREM cycle, which were evaluated by Feinberg and Floyd (1979). Another cause of nonperiodicity can be local disturbances of the sleep process. The main reason could be sleep interruptions by spontaneous awakenings, which lengthen the REM–NREM cycle (Březinová, 1974).

The observation that the overt REM–NREM rhythm is frequently nonperiodic suggests that this rhythm is controlled by more than one trigger mechanism. While sleep onset may control the occurrence of REM sleep at the beginning of a sleep episode, other clocklike mechanisms may regulate the REM–NREM cycle later in the night (Schulz et al., 1975; McPartland and Kupfer, 1978).

Nevertheless, the observed negative correlation between successive REM–NREM cycles weakens the hypothesis of a renewal process as an appropriate model. This result may be a new argument in the lively debate on the question of whether the REM–NREM cycle may be understood as the manifestation of the putative basic rest–activity cycle (Lavie, 1980) during sleep.

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