A Model-Based Approach to Homeostatic and Ultradian Aspects of Nocturnal Sleep Structure in Narcolepsy

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Study Objective: We present a mathematical model of sleep-EEG structure applied to the analysis of sleep patterns in narcoleptics by combining the 2-process model of sleep regulation and the reciprocal interaction model of REM regulation suggested by McCarley and Hobson. The aim was the individuation of parameters characterizing narcoleptic sleep in comparison to controls.

Design: Polysomnographic data were drawn from a previous study about sleep in narcolepsy. The mathematical model was fitted to quantitative EEG data by an optimization procedure.

Setting: Polysomnographic data were recorded in single and sound attenuated hospital rooms, for one night following an adaptation night.

Participants: 9 narcoleptic subjects (7 males, 2 females, mean age 39.6±4.3 years) and 9 age- and sex- matched controls.

Measurements: Slow Wave Activity (SWA) time series were evaluated by spectral analysis. The sleep model was fitted to SWA profile for each recording and to the averaged SWA profile for each group. Bartlett and Kolmogorov-Smirnov test were used to evaluate the goodness of fit and the accuracy of model predictions.

Results: In both controls and narcoleptics the optimization procedure produced a good fit of SWA raw data. The only significant difference between the groups were the RemOn /RemOff coupling parameters, reflecting an enhanced strength of the REM oscillator in narcoleptics.

Conclusions: The mathematical model of sleep provides a substantial description of empirical patterns for both controls and narcoleptics. The variation of values in the parameters describing the strength of RemOn /RemOff interaction is the major feature characterizing narcoleptics; it can explain sleep onset REM periods (SOREMPs) and variations of REM-NREM sleep cycle duration.

Keywords: Narcolepsy, model of sleep regulation, REM sleep, slow wave activity

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INTRODUCTION

SLEEP STRUCTURE AND ITS DISTRIBUTION OVER THE 24 HOURS ARE REGULATED BY SEVERAL MECHANISMS WHICH INTERACT WITH ONE ANOTHER IN A RATHER regular manner. Mathematical models of sleep-wake time course and intranight dynamics of physiological human sleep have been proposed, offering a conceptual framework for the analysis and interpretation of sleep regulatory processes. Among the available models, the 2-process model of sleep regulation has been evaluated and corroborated most frequently and has been able to simulate and predict sleep behavior in different physiological and experimental conditions. In the 2-process model of sleep regulation the power density of the delta (0.5 - 4.5 Hz) band, called slow wave activity (SWA) and obtained by spectral analysis of sleep EEG, is supposed to reflect the variations in a homeostatic recovery process (Process S) that increases in a saturating exponential way during wakefulness. Its decrease is expressed by the exponential decline in SWA during sleep. Sleep deprivation elicits an SWA rebound in the recovery night. The homeostatic pressure interacts with circadian and ultradian oscillations of sleep propensity leading to the nocturnal distribution of sleep and to the NREM-REM periodic alternation during sleep.

Sleep structure and sleep distribution in humans with narcolepsy differ from normal subjects. The sleep of narcoleptic patients is characterized by a polyphasic distribution over the 24 hours and by frequent occurrence of REM sleep onsets. It has been suggested that these phenotypic sleep features could be ascribed to an alteration of the strength of the homeostatic process or to a disequilibrium between homeostatic and sleep-wake regulatory rhythms (circadian and ultradian rhythms). Deprivation and bed rest study protocols have shown that the homeostatic regulation of sleep is preserved in narcoleptics. In particular, it has been shown that after 16 or 32 hours of forced wakefulness, the nocturnal sleep structure of narcoleptics becomes compact, and the SWA during sleep decays exponentially with a time-constant similar to normal subjects. However, despite the effect of sleep deprivation, narcoleptic patients still had a high frequency of REM sleep onsets and showed longer NREM-REM sleep cycles than controls, even though the amount of wakefulness during the night was similar in the 2 groups.

In our preliminary work, we have tried to simulate sleep features of narcoleptic and normal subjects by combining a 2-process model of sleep regulation, describing overnight dynamics of SWA, with the reciprocal-interaction model of REM regulation suggested by McCarley and Hobson. The reciprocal interaction model proposes that REM inhibiting neurons (RemOff cells) of the dorsal raphe (DR) and locus coeruleus (LC) have an inhibitory collateral autofeedback that eventually stops their own activity and allows the neurons (RemOn cells) of the laterodorsal tegmental (LDT) and pedunculopontine (PPT) nuclei to gain ac-
tivity and generate REM sleep; the strength of these autofeedback connections accounts for intervals between REM episodes.4,14

Leaving unaltered the pressure of the homeostatic process and empirically doubling the strength of the REM oscillator, we were able to simulate the REM sleep onset in narcoleptics and the longer duration of sleep cycle maintaining the regular exponential decline of SWA during sleep.12,13

In this paper to confirm statistically the accuracy of our model, for both normal and narcoleptic patients, we estimate the model parameters using an optimization procedure.

MATERIALS and METHODS

Subjects

Polysomnographic data were obtained from a previous study performed at the Sleep and Wake Disorders Unit, Gui-de-Chauliac Hospital, Montpellier (France), concerning ultradian rhythms and sleep in narcolepsy.10,11

Nine narcoleptic subjects (7 males and 2 females, aged 20-55 years, mean 39.6 SD 4.3 years) all showing 2 or more sleep onset REM episodes on a previous MSLT (multiple sleep latency test), cataplectic episodes, and excessive diurnal sleepiness (less than 5 minutes of mean sleep latency on the MSLT) were included. All patients were either untreated or withdrawn from stimulant and anti-cataplectic drugs for at least 3 weeks before recordings. Nine healthy subjects made up a control group; they were age- and sex-matched to a patient. Both narcoleptics and controls were recorded in the context of a bedrest condition protocol.10

After an adaptation night (23:00-07:00), the subjects were prevented from sleeping for 16 consecutive hours, while under continuous laboratory staff supervision. Then, 24 hours after start of adaptation night, starting at 23:00, they were recorded for 32 hours. The first 8 hours of recording represented the baseline night analyzed in this study.

Recording Procedure and Data Processing

EEGs were derived from electrodes positioned at C3-A2 and C4-A1. EMG and eye movements were also recorded. EEGs were lowpass filtered at 40Hz high pass filtered at 0.5 Hz, and online digitized at a sampling rate of 128 Hz by a STC-PC 12-16200 card (SMZI France) on a computer. Both EEG signals were processed online by a FFT routine that was implemented on a WE DSP32 digital processor card. The epoch length was 4 seconds and a Hamming window was applied. Records were scored according to the standardized criteria of Rechtschaffen and Kales in 20 sec epochs. Power spectra were calculated by the Welch method (i.e., 9 epochs with 2 seconds overlapping) resulting in an average spectrum every 20 seconds. To synchronize power spectra and visual scores of paper recording, a time signal was generated and recorded both on EEG paper and on the computer. This enabled us to eliminate epochs with artifacts by visual inspection of the records and to calculate power spectra per cycle. For the present study, only the power in the 0.5-4.5 Hz (slow wave activity; SWA) range was considered; the term power is used to designate the integrated power density values over the specified frequency range. The data series obtained had a length of 1440 data points covering a total time of 8 hours of sleep.

Data Analysis

For each subject (controls and narcoleptics) the SWA time series were first normalized with respect to the mean SWA values for the whole time span (8 hours); they were then smoothed, using a 5-point moving average method.

NREM-REM cycles were defined according to the criteria of Feinberg and Floyd (1979) by the succession of an NREM sleep episode lasting at least 15 minutes and a REM sleep episode of at least 5 minutes. In narcoleptics, REM sleep onset episodes were defined as the occurrence of REM sleep in the first 20 minutes of sleep, and the cycles were defined as the succession of REM-NREM episodes.

For each subject we separated NREM from REM episodes. NREM episodes relative to the same cycle in controls and narcoleptics were aligned by a translation, shifting on the respective maximum SWA peak. We repeated the operation for the REM intervals, centering all the subseries on the minimum SWA peak. Inside each NREM and REM episode, we averaged the subseries in both controls and narcoleptics, obtaining a mean SWA value with a confidence interval of 99% for standard error. This method enables to synchronize the subseries in the consecutive cycles without any distortion in shape and permits to define reasonable standard interval lengths of cycles.

Finally, composing in succession all the NREM and REM episodes, we obtained 2 time series, one for controls and one for narcoleptics, of the averaged SWA time course throughout the night.

Description of the Model and Equations

The mathematical model we used for simulating the sleep characteristics comprised 4 nonlinear differential equations describing the dynamics of homeostatic Process S, SWA time course, and REM sleep coupled oscillators, i.e., the 2-process model that describes the intranight dynamics of SWA,5 modified by the inclusion of RemOn and RemOff system of equations.4,5

The circadian rhythm process, (inserted in the 2-process model as a permissive condition for sleep occurrence) was not included in this work. It will be considered in the extended version of this model applied to simulate 32 hours of Bed Rest condition.

The first order linear differential equation (Equation 1) describes the trend in the homeostatic Process S during sleep episodes: the first term describes the saturating exponential increase of S as function of its distance from the upper asymptote Su, at the rise rate rs, prevailing during wakefulness and REM sleep episodes; the second term describes the asymptotically exponential decrease of S as function of SWA, with the gain constant gc, prevailing during NREM sleep episodes.

The second order nonlinear differential equation (Equation 2) describes the ultradian oscillations of Swa during sleep, obtained as consequence of a coupling term (fcR, fall constant of Swa), with the Process S and with the RemOn function, which determines the falls of Swa due to RemOn time function. The ultradian oscillation is also regulated by the rise constant of Swa rc, which determines the rise of Swa together with level of S. Finally, SwaL means the lower asymptote of Swa. The interaction of S with the REM pulses defines the timing of REM and NREM sleep, where the threshold allowing REM sleep occurrence is defined by the RemOn values overlapping the S values. RemOn values lower than S values define NREM Sleep. This condition is valid also...
for sleep onset, since we fixed sleep onset at the maximum value of RemOn pulse with S close to its maximum value, allowing the possibility of a SOREMP in both controls and narcoleptic patients.

The REM oscillator, characterized by 2 coupled differential equations (Lotka-Volterra type), has been added on the basis of the reciprocal interaction model suggested by McCarley and Hobson.\textsuperscript{4} It consists of 2 coupled, nonlinear differential equations describing the dynamics of RemOn and RemOff variables, where the strength of interactions is denoted by the coupling parameters.

In the third system of equations, the parameters alpha and gamma are the timing parameters for the RemOn and RemOff time courses, and the parameters beta and delta explain the coupling describing the RemOn and RemOff reciprocal interaction.

\begin{align*}
\frac{dS(t)}{dt} &= r_s(S_u - S(t)) - g_c Swa(t) \\
\frac{dSwa(t)}{dt} &= \frac{r_c}{S_c} Swa(t) S(t) (1 - \frac{Swa(t)}{S(t)}) - \frac{f_a}{S_c} (Swa(t) - Swa_u) RemOn(t) \\
\frac{d RemOn(t)}{dt} &= \alpha RemOn(t) - \beta RemOn(t) RemOff(t) \\
\frac{d RemOff(t)}{dt} &= -\gamma RemOn(t) RemOff(t) + \delta RemOn(t) RemOff(t)
\end{align*}

Where briefly:

- $S(t)$ = homeostatic process; $S_u$ = upper asymptote of $S$;
- $Swa$ = slow wave activity; $Swa_u$ = lower asymptote of $Swa$;
- $r_s$ = rise rate of $S$; $g_c$ = gain constant of $S$; $r_c$ = rise constant of $Swa$;
- $f_a$ = fall constant of $Swa$;
- RemOn, RemOff = RemOn and RemOff activities;
- $\alpha$, $\gamma$, $\beta$, $\delta$ = RemOn / RemOff timing parameters; $\beta$, $\delta$ = RemOn / RemOff interaction parameters.

### Parameters Estimation and Optimization

Initial values of parameters used by the optimization procedure for estimating the best parameters are the same as that reported in literature. In particular, as for the parameters of the S and Swa differential equations (Equations 1 and 2), ($r_s$, $S_u$; $g_c$; $r_c$; $f_a$; Swa,) the values are expressed in min$^{-1}$, we adopted the values of the 2-process model.\textsuperscript{3} Regarding REM sleep equations system (Equations 3), we used the parameters adopted in the McCarley and Hobson model\textsuperscript{4} after rescaling for compatibility with the timing step of the other 2 differential equations (Table 1, first data column).

The software Matlab 6.5 was used for the interactive study of the model and its response to parameter changes; the optimization tool was used to estimate the parameter values and initial conditions by a best-fit method using experimental data.

The references against which the model was tested were both the 9 time series of raw data and the time series of averaged SWA for both controls and narcoleptics. We used the raw data series to obtain 9 sets of parameters for controls and 9 for narcoleptics to draw an estimate of the mean values of parameters with a confidence interval of 99\% for standard error. The 2 time series of averaged SWA in controls and narcoleptics were used to test the goodness of fit of the optimized model. A stochastic search of parameters was involved, using a multidimensional unconstrained nonlinear minimization (Nelder-Mead method), to find a local minimizer point of the error function and successively applying a least error criterion. The error function was the sum of the absolute values of the differences between the SWA data-point calculated by the model and the empirical data (L1-norm). The optimization terminated successfully if the termination criteria, including the convergence of the error function in a maximum number of 10,000 iterations with a parameter precision of 4 significant digits was satisfied.

The system of differential equations was solved with a numerical method using the Runge-Kutta 4/5 algorithm.

### Statistical Tests

The system of differential equations solved in the time data points represented the theoretical data (expected), while the 2 time series of averaged SWA (controls and narcoleptics) represented the empirical data (observed). Bartlett’s test of normality was performed on autocorrelation function of residuals to find significant differences between expected and observed data, with an alpha level of 0.05. The hypothesis that the model could predict the REM sleep timing and duration in narcoleptics and controls was tested by the 2-sample Kolmogorov-Smirnov goodness-of-fit test; default value for alpha was 0.05. The hypothesis that the duration of the REM sleep episodes increased more significantly in normal sleepers than in narcoleptics in both raw data and model predictions was tested by Kolmogorov-Smirnov goodness-of-fit test, and the rise rate of growth was determined by polynomial regression.

### RESULTS

#### Optimization

The optimization procedure provided a solution satisfying the termination criteria for each subject in both narcoleptic and control groups, as well as for the 2 average time series. The parameter values obtained from the optimization procedure applied to the raw data series are shown in Table 1. The parameters obtained for the controls were not significantly different from the references

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**Table 1—Parameter Values**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Initial values</th>
<th>Final Values for Controls</th>
<th>Final Values for Narcoleptics</th>
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<tbody>
<tr>
<td>Alpha</td>
<td>0.151</td>
<td>0.128 (0.039)</td>
<td>0.112 (0.060)</td>
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<tr>
<td>Beta</td>
<td>1.150</td>
<td>1.409 (0.461)</td>
<td>1.362 (0.186)*</td>
</tr>
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<td>Gamma</td>
<td>0.151</td>
<td>0.184 (0.044)</td>
<td>0.194 (0.084)</td>
</tr>
<tr>
<td>Delta</td>
<td>1.150</td>
<td>1.196 (0.394)</td>
<td>0.914 (0.159)*</td>
</tr>
<tr>
<td>Rs</td>
<td>0.283</td>
<td>0.256 (0.108)</td>
<td>0.214 (0.144)</td>
</tr>
<tr>
<td>Su</td>
<td>564.00</td>
<td>361.02 (234.94)</td>
<td>435.11 (72.34)</td>
</tr>
<tr>
<td>Fcr</td>
<td>0.236</td>
<td>0.290 (0.117)</td>
<td>0.318 (0.136)</td>
</tr>
<tr>
<td>Swa_u</td>
<td>10.000</td>
<td>13.901 (6.803)</td>
<td>8.678 (4.916)</td>
</tr>
<tr>
<td>Gc</td>
<td>0.008</td>
<td>0.001 (0.003)</td>
<td>0.015 (0.006)</td>
</tr>
<tr>
<td>Rs</td>
<td>0.0009</td>
<td>0.0007 (0.0005)</td>
<td>0.0009 (0.0002)</td>
</tr>
<tr>
<td>RemOn(0)</td>
<td>0.950</td>
<td>1.084 (0.587)</td>
<td>1.086 (0.375)</td>
</tr>
<tr>
<td>RemOff(0)</td>
<td>0.010</td>
<td>0.011 (0.002)</td>
<td>0.013 (0.010)</td>
</tr>
<tr>
<td>SWA(0)</td>
<td>66.000</td>
<td>47.691 (33.927)</td>
<td>53.988 (32.195)</td>
</tr>
<tr>
<td>S(0)</td>
<td>410.00</td>
<td>233.19 (184.22)</td>
<td>349.32 (108.79)</td>
</tr>
</tbody>
</table>

First column: the initial conditions used for optimization in both controls and narcoleptics. Second column: best values found for parameters (mean values and standard errors) obtained with optimization procedure of 9 controls as reference. Third column: best values found for parameters (mean values and standard errors) after optimization procedure of 9 narcoleptics as reference. The * symbol refers to significant values of difference (P<0.01).
parameters. The parameters calculated by the optimization procedure for the narcoleptics were statistically different as for beta and delta parameters (P<0.01), which represent the reciprocal interaction between RemOn and RemOff neurons.

Figure 1 shows the solution of the model by plotting the overnight time course of each process. The initial parameters are those reported in literature. Figure 2A shows the solution of the model in the controls, using as reference the parameters obtained from the optimization procedure applied to the averaged SWA data series. The patterns are quite similar to the ones showed in Figure 1, with narrow balanced peak of RemOn and RemOff activities. The initial pattern is magnified in order to highlight the relationships between the different processes at sleep onset. In Figure 2B the averaged SWA time series for the controls and the SWA solution as obtained by the optimization procedure are superimposed. The matching between the two time series is good. Bartlett’s test for the autocorrelation function of the differences (residuals) confirmed the goodness of fit between observed and expected data (P<0.05).

Figure 3A shows the solution of the model in narcoleptics using as reference the parameters obtained from the optimization procedure applied to the averaged SWA data series. Changes in model parameters, particularly the ones representing RemOn – RemOff interaction, produced a different pattern with wider unbalanced peaks of RemOn and RemOff activities and consequently longer NREM-REM cycles. The imbalance between RemOn and RemOff activities highlighted at sleep onset may promote SOREMPs.

In Figure 3B the averaged SWA time series of narcoleptics and the SWA solution, as obtained by the optimization procedure, are superimposed. In this case too, the good matching between the 2 time series was confirmed by Bartlett’s test for the autocorrelation function of the differences (residuals) between observed and expected data (P<0.05).

REM Episode Duration

The optimized model obtained in control subjects showed an REM oscillator periodicity of about 90 minutes, (exactly 88.2 ± 3.4, mean and standard deviation); empirical data showed a mean interval of 93 ± 8.6 minutes.

The Kolmogorov-Smirnov test showed no significant differences between the model and the raw data for the timing and duration of REM episodes in controls (P<0.05).

The optimized model obtained in narcoleptic subjects showed a REM oscillator periodicity of about 120 minutes (121.3 ± 0.1); empirical data showed a mean interval of 118 ± 7.6 (SD) minutes. As in controls, the Kolmogorov-Smirnov test showed no significant differences between the model and raw data for timing and duration of REM sleep in narcoleptics (P<0.05).

Finally, the time course of REM-sleep-episode duration for the controls was significantly fitted (Fisher test, P<0.05) by a polynomial regression (R^2 = 0.95) with a rise rate of 2.12 ± 0.75 (SD) per hour.

The time course of REM-sleep-episode duration for narcoleptics was fitted by a polynomial regression (R^2 = 0.851) with a rise rate of 0.54 ± 0.82 (SD) per hour, but it was not significant at the default confidence level.
DISCUSSION

Our model depicted the temporal evolution of SWA in both controls and narcoleptics matching the raw data with a good approximation. In both groups, SWA showed a progressively declining trend over cycles, thus confirming that the homeostatic regulation of sleep was preserved in narcoleptics.\(^8\)\(^-\)\(^1^1\) The optimization procedure confirmed the hypothesis we made in a preliminary study,\(^1^2\)\(^,\)\(^1^3\) given that the parameter values of the optimized model for the controls were not different from the initial ones; on the other hand, in the case of narcoleptics, the optimization procedure showed a statistically significant difference for the RemOn and RemOff equation parameters. Indeed, in narcoleptic subjects the variation of connectivity coefficient between RemOn and RemOff cells could reproduce the temporal course of SWA progressive decline via a lower number of longer cycles. As to REM timing and duration, the enhanced strength of RemOn accounted for the enhanced probability of SOREMPs, a longer period (120 min) of NREM-REM cycles and a lower increase in REM duration throughout the night with respect to controls.

The simulation we have proposed is grounded on models of sleep regulation developed by other authors.\(^4\)\(^,\)\(^5\) Our contribution consists chiefly in the assumption that REM pulse can play a role in allowing both the onset and offset of sleep cycles. As in the 2-process model proposed by Achermann and Borbely\(^5\) to describe the intranight dynamics of SWA, the level of Process S is linked to the momentary level of SWA; the rise in S is permanently activated during sleep (being a linear function of the distance between the current S level and its asymptote \(S_u\)) and is counteracted by the increase in SWA during NREM sleep. While in the 2-process model the decrease in SWA during REM sleep is obtained using a switch represented by an external function (REM trigger signal) obtained from empirical REM episodes, in our model both Process S and SWA levels are coupled with a function, included in the model, expressing the dynamic of a REM oscillator continuously operating during sleep. Either REM or NREM sleep may then occur depending on the balance among the relative values of Process S, SWA, and REM oscillator. Maximum SWA levels are obtained in correspondence to high levels of Process S relative to low values of RemOn activity. REM sleep is allowed when the relative values of the RemOn oscillator approximate and surpass the momentary level of Process S. Analogously, the decline of the RemOn oscillator with respect to the level of Process S allows the exit from REM sleep. Thus, the relationship between the level of Process S, which decreases during the night depending on the relative amount of SWA, and the level of RemOn oscillator, distributed uniformly during sleep, is sufficient to account for longer REM sleep episodes throughout the night without imposing homeostatic or circadian dependencies on REM sleep.

Several propositions have already been advanced for ways of

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incorporating the REM oscillator as an intrinsic part of the model, however, in these models, the possibility of a REM episode at sleep onset is not foreseen. The limit cycle proposed by Mas-Carbonell and McCarley introduces an a priori circadian regulation of REM sleep distribution.

The possibility of a shorter REM sleep latency has been simulated by using different assumptions; for example the reduced latency of REM episodes observed in depressed subjects has been obtained hypothesizing a weaker aminergic inhibition effect of the RemOff oscillator facilitating a quicker release from inhibition of the cholinergic REM promoting neurons. It has also been observed that a reduced amplitude, or a phase advance, of the circadian rhythm would allow low levels of aminergic activity at sleep onset, thus facilitating abnormalities of the first REM sleep episode. In our model, the same weaker inhibition effect of the RemOff oscillator was obtained in narcoleptics, and a similar imbalance between RemOn and RemOff neurons was present at sleep onset producing the release from inhibition of the cholinergic REM promoting neurons immediately at sleep onset, thus allowing sleep onset REM periods in narcoleptics. We were able to simulate sleep of controls and narcoleptics without introducing further constraints such as the circadian rhythm; however we cannot exclude the possible role of a weaker circadian modulation in narcoleptics in the genesis of SOREMPs. Indeed this aspect emerged clearly during the analysis of the 32-hour protocol of Bed Rest condition and will be taken into account in a subsequent simulation work.

In the experimental condition we have analyzed, narcoleptics were not allowed daytime sleep, thus the level of Process S at the beginning of sleep was increased compared with their habitual conditions. This would reduce the relative influence of the RemOn oscillator at the beginning of sleep and prevent the SOREMP, but the increased strength of the RemOn oscillator in narcoleptics was sufficiently high to counterbalance this increase in Process S. Despite the good capability in explaining the possibility of occurrence of SOREMPs in narcoleptics, further modifications, including probabilistic components, should be added in order to explain why narcoleptics do not always exhibit SOREMPs.

Our model might also explain the bimodal distribution of REM sleep latency in depressed patients. Indeed, the reduction of the level of Process S suggested in this population may allow not only a SOREMP but also a reduced latency of the second REM sleep episode.

Sleep onset REM periods occurring at the beginning of a night sleep associated most commonly with narcolepsy. However, they have been shown in subjects with other sleep and neurological disorders such as sleep apnea syndrome, Parkinson disease, and depression. Shorter REM latencies have also been reported in normal subjects due to various conditions: in case of an acute reversal of the sleep waking cycle, after sleep interruption in young

Figure 3a—Plot of the model obtained by the optimization procedure in 2800 iterations, computing 3973 functions, using the mean time series of SWA of 9 narcoleptics as reference. On the right the patterns at sleep onset are magnified: the black arrow at the beginning of sleep indicates the case of narcoleptic patients an augmented imbalance between RemOn and RemOff functions. On the Y-axis, the theoretical values relevant to each function are reported with an arbitrary scale.

Figure 3b—Superimposed optimized model and empirical data series of SWA in case of narcoleptic patients.
short sleepers, in free running condition, or in ultradian schedules. In these conditions the circadian process might have played a significant role.

In our model, we fixed sleep onset at the maximum value of RemOn pulse with Process S close to its maximum, attributing to REM sleep the ability to trigger the beginning of sleep episodes, thus linking REM sleep to stage 1. This approach can explain the possibility of sporadic SOREMPs at the beginning of a night’s sleep or a daytime sleep cycle; their increased presence in narcoleptics and might also serve as an explanation for the so-called skipped REM.

Similarities in electrophysiological features of drowsiness (stage 1) and REM sleep were pointed out by Borbely in the first version of the 2-process model. An increase of RemOn activity has also been described as a characteristic of sleep onset in the reciprocal interaction model by McCarley. Moreover, numerous works support the notion of covert REM sleep processes active at sleep onset. In the covert REM sleep hypothesis of dreaming, it is suggested that elements of REM sleep emerge during sleep onset. Recently, using intracranial EEG recording techniques, an increase of a 1.5–3.0 Hz activity within the parahippocampal region during REM sleep has been described; such an increase has been also found during the wake–sleep transition, supporting the hypothesis of covert REM sleep processes at sleep onset.

The transition from NREM to REM sleep is usually preceded by a progressive decline in SWA. It is not unusual to find REM EEG and polygraphic features (muscle atonia, slow eye movement activity, highly activated respiration, theta waves, sawtooth waves) during stage 2 sleep preceding the occurrence of a well defined REM sleep episode. Moreover, REM EEG features can appear without being followed by a REM sleep episode (skipped REM). This seems to indicate that REM sleep processes are active, even if covert, before the occurrence of a polygraphically “scored” REM sleep episode, and may also be active if a polygraphically “scored” REM sleep does not emerge. Indeed, electrophysiological studies have emphasized that REM sleep is preceded by specific events in the brain; changes in the firing rate of dorsal raphe neurons, in pontogeniculo-occipital (PGO) waves, and in the cortical EEG have been observed prior to REMs. To account for these aspects, Achermann and Borbely forced the REM trigger to begin a few minutes before the occurrence of a REM episode.

Conversely, these features are a direct consequence of the characteristics of our model. Our model shows that, before entering into REM sleep, the REM oscillator progressively increases; the mutual interaction between the REM oscillator and Process S induces a progressive decay of SWA that reaches its minimum in REM sleep.

Finally, the features of our model may also explain the distribution during the night of some EEG and microstructural events. The dominance of delta bursts, spindle, k complexes, and SWA during the build-up of NREM sleep is predicted in our model by a reduced activity of cholinergic RemOn neurons and the consequent activation of aminergic RemOff neurons. The prevalence of arousals and fast EEG activities before and during REM sleep is determined by the activation of cholinergic RemOn neurons that fire during the last part of NREM.

We are well aware that the nature of the homeostatic and circadian influence on REM sleep regulation and of the interplay between REM and NREM sleep is complex. It has been proposed that the need for REM increases exclusively during NREM, thus suggesting a somehow subservient function of REM. Other authors have postulated long-term and short-term homeostatic regulation of REM independent of NREM sleep with an accumulation in the absence of REM during both wakefulness and NREM sleep. However, the question of how REM sleep is regulated, and by what, and the role of awakenings in the resetting of sleep regulation are still matters of debate.

Our model implies a simplified regulation of REM sleep that is assumed to follow a uniform distribution during sleep, based on the Lotka-Volterra model. Even if the model appears simplified with regard to the mechanisms of NREM-REM regulation, it is able to predict complex pathological conditions such as the sleep features of narcoleptics. The model has been successfully applied to an uncommon sleep condition for narcoleptic patients (enforced daytime wake 16 hours prior to study). The SWA analysis during the whole time span (32 hours) of the Bed Rest protocol emphasized this aspect: the daytime sleep deprivation determined an augmented sleep pressure in narcoleptic subjects, thus allowing a sleep distribution pattern similar to that of control subjects in the first part of the experiment (the one used as reference to test our model); in the second part (daytime and second night), as the homeostatic influences diminished, and the differences became more evident with a prevalence of the ultradian distribution of sleep in narcoleptics.

During the last few years, experimental studies showed that animals with a loss of orexin or a dysfunction of the lateral hypothalamic hypocretin-orexin system have a phenotype very similar to the human narcoleptic disorder and a deficiency in orexin has been frequently observed in human narcolepsy.

In a valuable animal model of narcolepsy, transgenic rats in which orexin-containing neurons were destroyed postnatally showed REM dysregulation similar to that observed in humans. During the light period (rest phase), the rats did not show the gradual increase in REM sleep duration that was a hallmark of REM sleep in the wild-type rats, while the intervals between consecutive REM episodes were longer than in controls.

It has been found that the tuberomammillary nucleus (TMN), the locus coeruleus, and the raphe nuclei contain orexin receptors exerting an inhibitory effect on REM sleep. Consequently, the absence of excitatory orexin input would increase the strength of REM mechanisms, thus facilitating more frequent transitions to REM sleep. In our work, the results of the optimization procedure show that the only difference between the parameters of controls and narcoleptics relates to the strength of coupling between the RemOn and RemOff activity. In particular, the parameter variation controlling the RemOn/RemOff activity determines an increased pressure in the REM oscillator. This allows the appearance of REM sleep onset in narcoleptics, since the strength of the RemOn pulse is increased relative to those of the control subjects, while the homeostatic pressure remained unaltered.

In conclusion, our model is able to explain some peculiar features of sleep in narcolepsy by modifying a few parameters, enabling us to compare the sleep of narcoleptic subjects and normal controls. Our model also provides a new approach to the study of physiological sleep and its regulation. Further studies need to be carried out to assess its predictive power in other physiological and pathological conditions.
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