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MATHEMATICAL MODELS OF SLEEP REGULATION

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TABLE OF CONTENTS

1. ABSTRACT

The level of EEG slow-wave activity (SWA) is determined by the duration of prior sleep and waking. SWA is a marker of nonREM sleep intensity and may serve as an indicator of sleep homeostasis. The two-process model of sleep regulation posits the interaction of the homeostatic Process S and the circadian Process C. Also models of neurobehavioral functions (three-process model; interactive models of alertness and cognitive throughput) are based on the concept of an interaction between homeostatic and circadian factors. Whether the interaction is linear or non-linear is still unresolved. Models may serve as a guiding principle for specifying the relationship between processes occurring at the macroscopic and microscopic level of analysis.

2. INTRODUCTION

The processes underlying sleep regulation are illustrated in Figure 1. They consist of 1) a homeostatic process responsible for the rise of sleep propensity during waking and its dissipation during sleep; 2) a circadian process that is basically independent of prior sleep and waking, and is responsible for the alternation of periods with high and low sleep propensity; and 3) an ultradian process occurring within the sleep episode and representing the alternation of the two basic sleep states nonREM sleep and REM sleep. Models of sleep representing these three processes have been extensively reviewed (1-4).

By specifying the processes involved in the regulation of sleep, models offer a conceptual framework for the analysis of existing and new experimental data. Various models, in particular the two-process model of sleep regulation (5, 6), have inspired a considerable number of experiments that allowed to test specific predictions (for an overview see (1, 2)). Recent advances in relating regulatory processes to specific brain mechanisms increase the attractiveness of the modeling approach.

The two-process model of sleep regulation (5, 6) addresses the homeostatic and circadian aspects of sleep regulation. It assumes an interaction of its two constituent processes, the homeostatic Process S and the circadian Process C. The level of the sleep-wake-dependent Process S rises during waking and declines during sleep. Process C, which is independent of sleep and waking, modulates the thresholds H and L which determine the onset and termination of a sleep episode, respectively.

The time course of Process S was derived from the changes of EEG slow-wave activity (SWA, EEG power in the 0.75-4.5 Hz range) which exhibits a global declining trend during sleep and whose level in the first nonREMS episode increases as a function of prior waking (7-9). The declining trend of EEG slow waves (10) and of slow wave sleep (SWS) (11) as well as the rise of SWS after sleep deprivation (e.g. (12)) were observed already in early studies.

3. HOMEOSTATIC REGULATION OF SLEEP

3.1. EEG slow-wave activity: A physiological indicator of nonREM sleep homeostasis

The term "sleep homeostasis" (13) refers to the sleep-wake dependent aspect of sleep regulation, because homeostatic mechanisms counteract deviations from an average "reference level" of sleep. They augment sleep propensity when sleep is curtailed or absent, and reduce

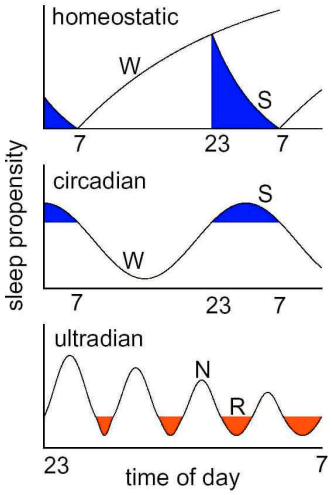

Figure 1. Schematic representation of the three major processes underlying sleep regulation. W, waking; S, sleep; N, nonREM sleep; R, REM sleep. The progressive decline of nonREM sleep intensity is represented both in the top and bottom diagrams (decline of ultradian amplitude). The increase in the duration of successive REM sleep episodes is indicated.

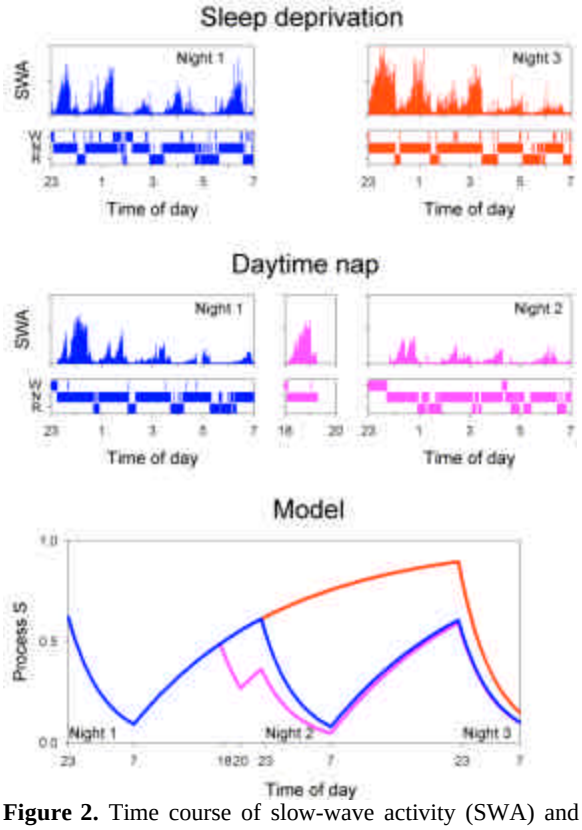

Figure 2. Time course of slow-wave activity (SWA) and sleep profiles (W: waking and movement time; N: nonREM sleep; R: REM sleep) in two baseline nights (Night 1), after 40 h of sleep deprivation (Night 3, upper right) and after a daytime nap (Night 2, middle right). Simulations of the homeostatic Process S are illustrated in the bottom panel. Blue: baseline with an 8-h sleep episode; red: sleep deprivation and recovery sleep; pink: 2-h nap at 18:00 h.

sleep propensity in response to excess sleep. The pioneering studies of Blake and Gerard revealed already in the 1930-ies that both the arousal threshold and the predominance of slow waves in the EEG are high in the initial part of sleep and then progressively decrease (10). Thus slow wave sleep, the high intensity portion of nonREM sleep, appears to be a valuable candidate to serve as a physiological indicator of sleep homeostasis. Indeed, the initial predominance of slow wave sleep in a sleep episode was confirmed in subsequent studies (11, 12, 14). The use of all-night spectral analysis of the sleep EEG made it possible to quantify SWA and to delineate its time course with more precision (8). Sleep intensity is a central part of the concept of sleep homeostasis. The compensation of a deficit occurs mainly by an increase in sleep intensity rather than by the prolongation of sleep duration.

Apart from exhibiting a global declining trend during sleep SWA is modulated by the nonREM-REM sleep cycle (Figure 2). The level of SWA in the first nonREM sleep episode is a function of the duration of prior waking (Figure 2, upper panels; (7-9)). Partial or total sleep deprivation gives rise to increased slow wave sleep in the recovery night. A quantitative analysis revealed that a night without sleep (i.e. 40 h of wakefulness) resulted in an enhancement of SWA during recovery sleep by approximately 40 % (Figure 2, top panels; (8)).

A daytime nap counteracts the rising trend of slow-wave propensity, and attenuates SWA in the subsequent nighttime sleep episode (Figure 2, middle panels; (15-17)). An opposite effect is induced by shortening nocturnal sleep which leads to an increased level of SWA in a morning sleep episode (18, 19).

Taken together, these studies have shown that SWA reliably reflects the prior history of sleep and waking. It appears to be an ideal marker to quantify the dynamics of nonREM sleep homeostasis.

3.2. Interaction of homeostatic and circadian processes

There is evidence that the homeostatic and circadian facets of sleep regulation are controlled by separate mechanisms. Thus in the course of a prolonged sleep deprivation period, subjective alertness showed a prominent circadian rhythm (20). Conversely, in a study in which the phase of the circadian process (as indexed by body temperature and plasma melatonin) was shifted by morning bright light, the time course of SWA remained unaffected (21). Furthermore, the homeostatic response to sleep deprivation persists even after circadian rhythmicity had been disrupted or abolished by lesioning the SCN (22-25).

Forced desynchrony is a useful paradigm for the separation of homeostatic and circadian facets of sleep regulation. In studies using this protocol, subjects were scheduled to 28-h sleep-waking cycles (26-28). During one third of each cycle the lights were turned off and the subjects were encouraged to sleep. Because the free-running circadian rhythm has a period of 24.1-24.2 h (29) and cannot be entrained to these experimental conditions,

the sleep episodes occurred at different circadian phases. The maximum of sleep propensity coincided closely with the minimum of rectal temperature. Sleep propensity declined on the rising limb of the rectal temperature rhythm and reached the minimum 16 hours after the temperature minimum. This circadian phase corresponds to the habitual bedtime under normal entrained conditions. When sleep was initiated at this phase, sleep continuity was high. In contrast, poor sleep continuity was observed when sleep was initiated after the temperature minimum.

The analysis of the data supported the notion that SWA is mainly determined by homeostatic factors. Furthermore a previously postulated sleep-related inhibition of REM sleep (5) was confirmed by the findings of the forced desynchrony study.

3.3. REM sleep homeostasis

While the regulation of nonREM sleep has been extensively modeled by comparing empirical and simulated data in various experimental schedules, this has not yet been the case for REM sleep (for an overview see (3)). One of the problems for modeling REM sleep regulation is the different response of the target variables (e.g. amount of REM sleep and number of interventions to prevent REM sleep) to experimental challenges (e.g. (30, 31)). Furthermore, there is no obvious marker of REM sleep intensity. If an intensity dimension of REM sleep is indeed not existent, then a rise in 'REM sleep pressure' must manifest itself exclusively in an increased duration of REM sleep. Recent data showed a correlate of REM sleep propensity in the sleep EEG. Thus repeated selective REM sleep deprivation gave rise to a reduction of alpha activity in REM sleep, an effect that dissipated over three recovery nights (30, 32). This EEG variable has not yet been used for modeling REM sleep regulation.

If REM sleep is homeostatically regulated it implies that REM sleep propensity accumulates in the absence of REM sleep, i.e. during both wakefulness and nonREM sleep. Benington and Heller (33) advanced the hypothesis that the homeostatic buildup of REM sleep propensity occurs solely during nonREM sleep. More recently, to resolve the contradiction, Franken (34) postulated that two processes underlie REM sleep regulation: a `long-term' process that homeostatically regulates the daily amounts of REM sleep and a `short-term' process that determines the nonREM-REM sleep cycles.

In future model approaches, interactions between nonREM sleep and REM sleep need to be also considered.

4. MODELS OF SLEEP REGULATION

Models help to delineate the processes involved in the regulation of sleep and offer a conceptual framework to interpret experimental data. Moreover, they stimulate new experiments to test the predictions of the model. Various mathematical models have been proposed to account for aspects of sleep regulation and circadian rhythms, both at the macroscopic (systemic) and microscopic (cellular) level. To investigate the possible role of different oscillations such as sleep spindles, computational models of neuronal networks were developed to simulate cellular activity in different sleep states (35). Also the generation of circadian rhythms was computationally modeled at the genetic level (36, 37) as well as on the basis of coupled oscillators (38, 38a). An attractiveness of the modeling approach is that it can serve to design and interpret studies at different levels.

A synopsis of the major models discussed in this chapter is provided in Table 1. Mathematical models of sleep regulation and circadian rhythms have been extensively reviewed (1-4). Here we focus on currently used models.

4.1 Two-process model of sleep regulation

The relationship of slow wave sleep and the duration of prior waking was investigated in early studies by Webb and Agnew (12) and placed into a theoretical framework by Feinberg (39). The two-process model, originally proposed to account for sleep regulation in the rat (13, 40), postulates that a homeostatic process (Process S) rises during waking and declines during sleep. It interacts with a circadian process (Process C) that is independent of sleep and waking (Table 1). The time course of the homeostatic variable S was derived from EEG SWA. The global decline of SWA during a sleep episode is essentially exponential (5, 8). Thus, Process S during sleep was modeled by an exponential function. A saturating exponential increase of sleep propensity was assumed to occur during waking (5, 6). The increase of S was first quantified on the basis of baseline data and recovery sleep after sleep deprivation (6). A saturating exponential function was fitted through 3 data points: relative SWA at the end of a normal night, at the end of a normal waking day, and after sleep deprivation. The analysis of daytime naps is useful for assessing the level of SWA after various durations of waking. It was shown that naps taken later in the day contain more slow wave sleep than naps taken early in the day (16, 41). Daytime naps scheduled at 2-h intervals throughout the day provided direct evidence for a monotonic rise of SWA (7, 42). A saturating exponential function corresponded well with the extrapolated initial values of S in the naps (7).

Various aspects of human sleep regulation were addressed in a qualitative version of the two-process model (5). An elaborated, quantitative version of the model was established later. In this version of the model Process S varied between an upper and a lower threshold that are both modulated by a single circadian process (6, 43). This model was able to account for various phenomena such as recovery from sleep deprivation, circadian phase-dependence of sleep duration, sleep during shift work, sleep fragmentation during continuous bedrest, and internal desynchronization in the absence of time cues (6).

In Figure 2 (bottom panel) the effects of sleep deprivation and napping on Process S as illustrated for empirical SWA data (Figure 2, upper panels) are simulated. If sleep is prevented S continues to rise until sleep occurs.

Table 1. Models of sleep regulation

Designation	Assumption	Description/Comment
TWO-PROCESS MODEL AND RELATED MODELS		
Two-process model (5, 6, 43)	Sleep propensity is determined by a homeostatic Process S and circadian Process C. The interaction of S and C determines the timing of sleep and waking.	Time course of S derived from EEG slow-wave activity; phase position and shape (skewed sine wave) of C derived from sleep duration data obtained at various times of the 24-h cycle.
Model of ultradian variation of slow-wave activity (46-48, 96)	Derived from the two-process model. The level of S determines the buildup rate and the saturation level of slow-wave activity within nonREM sleep episodes. Decline of S proportional to the amount of slow-wave activity.	In contrast to the original two-process model, the change of S, not the level of S, corresponds to slow-wave activity. A REM sleep oscillator triggers the decline of slow-wave activity prior to REM sleep.
Three-process model of the regulation of sleepiness/alertness (56-60)	Sleepiness/alertness are simulated by the combined action of a homeostatic process, a circadian process, and sleep inertia (Process W). Extension to include performance, sleep latency and sleep length.	Parameters derived from rated sleepiness during sleep/wake manipulations. Alertness normogram for sleep-related safety risks.
Interactive mathematical models of alertness and cognitive throughput (61)	Alertness and cognitive throughput are determined by a nonlinear interaction of a homeostatic (H) and a circadian process (C). In addition, sleep inertia is included. H falls in a sigmoidal manner during waking and rises in a saturating exponential manner at a rate determined by circadian phase during sleep.	Parameters derived from sleep inertia studies, sleep deprivation studies initiated across all circadian phases, and 28-h forced desynchrony studies.
MODELS OF THE NONREM-REM SLEEP CYCLE		
Reciprocal interaction model (63)	NonREM-REM sleep cycle generated by two coupled cell populations in the brainstem with self-excitatory and self-inhibitory connections according to the Lotka-Volterra model.	Simulation of data: Discharge rate of cholinergic FTG (or LDT/PPT) cells in cat. The role of postulated cell populations in the control of REM sleep, and their interactions have undergone revisions (67, 97).
Limit cycle reciprocal interaction model: Original version (64, 65)	NonREM-REM sleep cycle generated by the reciprocal interaction of two coupled cell populations (REM-on and REM-off).	Main features of previous model maintained, but assumption of a stable limit cycle oscillation that is independent of initial conditions. Introduction of a circadian term which determines mode of approach to limit cycle.
COMBINED MODELS		
Composite model of sleep regulation (68)	Combination of elaborated two-process model with ultradian dynamics (47), limit cycle reciprocal interaction model (64), model of the circadian pace maker (98), and sleep inertia.	Different models proposed to account for processes underlying the regulation of sleep and alertness are considered as "modules" have been integrated into a combined model.
Limit cycle reciprocal interaction model: Extended version (66)	As above; incorporation of sleep homeostasis and arousal events.	Assumption of first-order decay dynamics for the arousal system. Arousal as a stochastic process.

At sleep onset the level of S is above baseline indicating increased sleep pressure. In contrast, a daytime nap lowers the level of S at sleep onset of the following nocturnal sleep episode reflecting the reduced sleep propensity.

The two-process model triggered numerous experimental studies including the prediction of the response to sleep deprivation of habitual short and long sleepers (44). The results supported the hypothesis that short sleepers live under a higher 'nonREM sleep pressure' than long sleepers, and that the two groups do not differ with respect to the homeostatic regulatory mechanisms.

As proposed by Beersma *et al.* (7) and Dijk *et al.* (45) and formalized by Achermann and Borbély (46) the model was adapted so that it is the change of S, rather than its level, which is proportional to the momentary value of SWA. This elaborated model allowed to address also changes within nonREM sleep episodes. Thus the intranight rebound of SWA after selective slow wave sleep deprivation during the first 3 h of sleep was in accordance with the prediction by the model (46).

A further elaborated version of the model was subsequently developed (47) (Table 1). An optimization procedure was applied using the mean time course of empirical SWA from a large dataset (16 subjects, 26 nights) as a template (47). A sensitivity analysis revealed that the model is quite robust to small changes (± 5%) of the parameter values. In general, a close fit was obtained between simulated and empirical SWA data and their time course (Figure 3). In particular, the occurrence of late SWA peaks during extended sleep periods could be simulated ('resurgence of slow wave sleep'; Figure 3). The simulations demonstrated that the model can account in quantitative terms for empirical data and predict the changes induced by the prolongation of waking and sleep. This version of the model was recently used to simulate nocturnal SWA after an early evening nap (17) and the effect of changes in REM sleep latency on the time course of SWA (48).

Although the qualitative version of the two-process model had originated from animal data (13, 40), the quantitative version of the model was elaborated on the basis of findings from human studies. In the meantime, quantitative simulations of nonREM sleep homeostasis were also performed in rats (49-51) and mice (52, 53) (Figure 4). For example, SWA of consecutive 4-s epochs in a 24-h baseline period, a 6-h sleep deprivation period, and 18-h recovery period (52) served as the database for the simulation in mice (n = 8). As in the original human version of the model, Process S was assumed to decrease exponentially in nonREM sleep, and to increase according

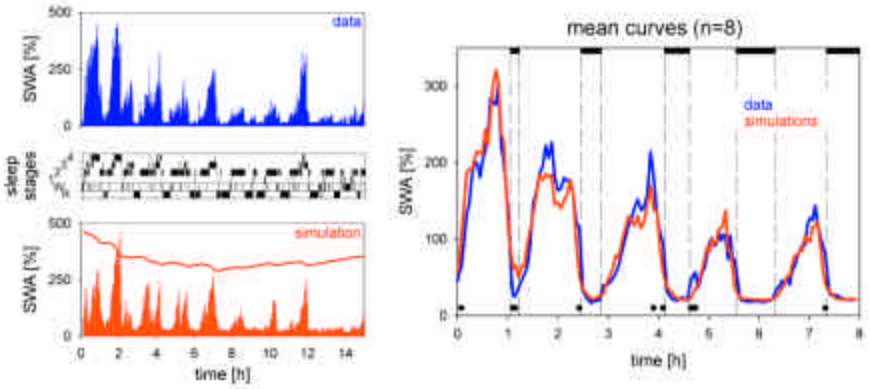

Figure 3. *Left:* Empirical SWA (top), sleep stages and simulation of SWA and Process S (bottom) of an individual extended baseline sleep episode starting at 00:00 h (prior waking: 17h). Empirical and simulated SWA were standardized with respect to the mean value of the first seven hours of sleep. Values are plotted for 1-min intervals. *Right:* Mean empirical (blue) and simulated SWA (red) (n=8) of an extended baseline experiment (95) (analysis of first 8 h). Significant differences are indicated by black dots (paired t-test; $p<0.05$). Bars on top and the interrupted vertical lines indicate REM sleep episodes (mean values). Modified from (47).

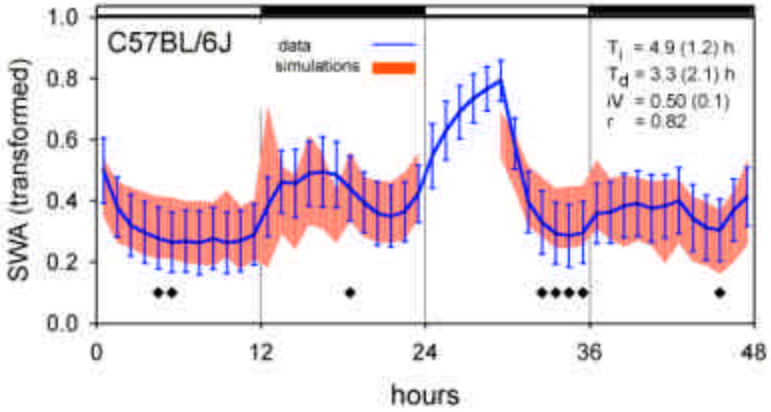

Figure 4. Time course of slow-wave activity (SWA) and simulation with the optimized time constants for the increase (T_i) and decrease (T_d) and initial value (iV) of Process S for C57BL/6J mice (n=8). Curves and shaded areas connect 1-h mean values (±SEM) for 24-h baseline, 6-h sleep deprivation and 18-h recovery. The close fit between the simulation of Process S (red areas) and time course of empirical SWA (blue line) indicates that the two-process model can predict SWA on the basis of the temporal organization of sleep in mice. Diamonds indicate differences between simulation and data ($p<0.05$; two-tailed paired t-test). For the comparison between SWA and S, SWA was transformed according to a linear regression. Inset: mean values of T_i, T_d and iV (SEM) and the mean r-value of the fit between SWA and S. Modified from (52).

to a saturating exponential function in waking. Unlike in the human model, an increase of S was assumed to occur also in REM sleep. After optimizing the initial value of S (iV) as well as its time constants (increase T_i; decrease T_d), a close fit was obtained between the hourly mean values of SWA in nonREM sleep and the prediction of Process S (Figure 4).

4.2. Models of neurobehavioral functions

Not only the timing of sleep, but also the time course of daytime vigilance could be accounted for by the interaction of homeostatic and circadian processes (Table 1). Levels of vigilance were simulated with the quantitative version of the two-process model (6). The rising homeostatic sleep pressure associated with waking appears to counteract the declining circadian sleep propensity (6, 25, 54, 55) thus allowing to maintain a constant level of vigilance throughout the waking period. Conversely, during sleep the rising circadian sleep propensity may serve to counteract the declining homeostatic sleep pressure, thereby ensuring the maintenance of sleep (28).

Based on a similar concept, the changes of subjective sleepiness/alertness ratings were simulated by a combined action of a homeostatic process (S), a circadian process (C), and a process representing sleep inertia (W) ("three-process model" (56-60); Table 1).

Jewett and Kronauer (61) proposed interactive mathematical models of subjective alertness and cognitive throughput in humans (Table 1). A homeostatic component (H) falls in a sigmoidal manner during waking and rises in a saturating exponential manner during sleep. The rise of H during sleep is determined by the circadian phase. H interacts with a circadian component (C; (62)) accounting for the effect of light on the circadian pacemaker. The

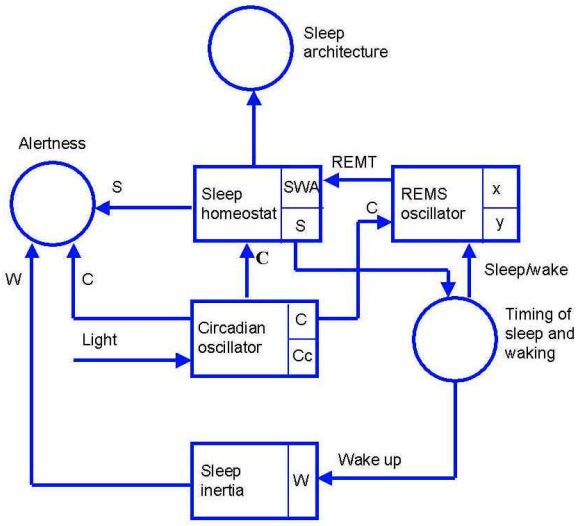

Figure 5. Outline of a combined model of sleep regulation. Rectangles: states of the system (substates are indicated by smaller rectangles); circles: state derived variables; arrows: direction of the connections (with respect to the states, not to the substates). A: alertness; SWA: slow-wave activity; S: Process S; x: REM-on activity; y: REM-off activity; C: basic circadian variable; Cc: complementary circadian variable; w: sleep inertia, wake up process; REMT: REM sleep trigger. Adapted from (68).

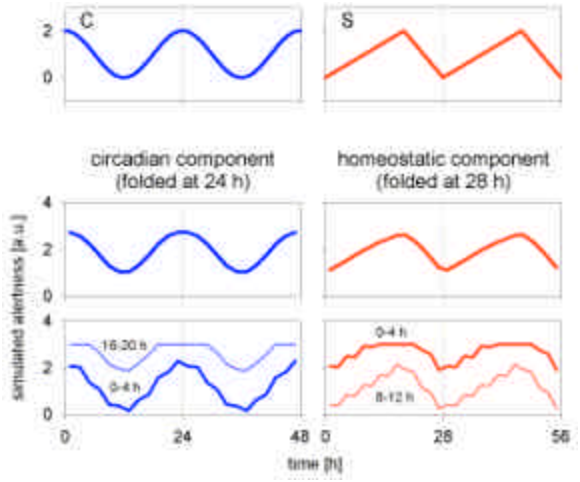

Figure 6. Additive interaction of a circadian (C, cosine, period 24 h) and a homeostatic component (S, saw-tooth, period 28 h) with saturation. Levels exceeding 3 were set to the threshold value of 3. Simulation of a forced desynchrony protocol over 28 days. *Left:* estimation of circadian component by folding at 24 h (middle: over entire simulation; bottom: for 2 different phases (4-h bins) of the homeostatic component). *Right:* estimation of homeostatic component by folding at 28 h (middle: over entire simulation; bottom: for 2 different circadian phases (4-h bins)). Both functions are double plotted.

amplitude of C depends on the level of H. In addition, a sleep inertia component (W) is included. In contrast to the two- and three-process models, a nonlinear interaction is assumed (see 4.5 for a discussion).

4.3. Reciprocal interaction models

These models account for the cyclic alternation of nonREM sleep and REM sleep (Table 1). A distinctive feature of this class of models is that they evolved from neurophysiological data obtained in animals (63). They postulate that the nonREM-REM sleep cycle is generated by the reciprocal interaction of two neuronal systems in the brain stem. The original proposition of a Lotka-Volterra type of interaction was later adapted to humans, and further elaborated into the limit cycle reciprocal interaction model (64-67).

4.4. Combined models

Attempts were made to integrate various concepts into a combined model (68). The models of various authors were considered as "modules" which were integrated to form a composite model (Figure 5). Initial simulations demonstrated the feasibility of incorporating homeostatic, circadian and ultradian factors regulating nighttime sleep and daytime sleep propensity in a single model. Homeostatic, circadian and ultradian processes were also integrated into a combined model by Massaquoi and McCarley (66).

4.5. Linear vs. nonlinear interaction

Although homeostatic and circadian processes are generated by separate mechanisms, their interaction must be specified. A linear interaction is the most straightforward option, which was adopted by different authors (6, 55, 60). In contrast, the model of Jewett and Kronauer (61) assumes that the interaction is nonlinear. Their assumption is based on evidence from forced desynchrony experiments in which the magnitude of the circadian amplitude changed with the level of the homeostatic sleep drive (69, 70). While the nonlinear interaction of the two processes can not be excluded, the non-linearity of the neurobehavioral metrics in the forced desynchrony experiments could be an alternative explanation (71).

To clarify this issue, simulations based on a forced desynchrony protocol were performed. For simplicity, the circadian component C was described by a cosine function (period 24 h; Figure 6) and the homeostatic component S by a saw-tooth function (period 28 h; linear increase during 2/3; linear decline during 1/3 of the cycle; Figure 6). Both variables varied between 0 and 2 (arbitrary units). In a first simulation a linear interaction was assumed by adding the two components. To mimic a nonlinear scale, a cutoff (saturation effect) was introduced, i.e. values exceeding a threshold value of 3 were set to the threshold level. Figure 6 illustrates that folding of the data at either 24 h or 28 h revealed the 2 constituent components (cosine and saw-tooth function) to a large extent. Performing the folding at 24 h for different phases of S showed that the amplitude of the circadian component depends on the phase

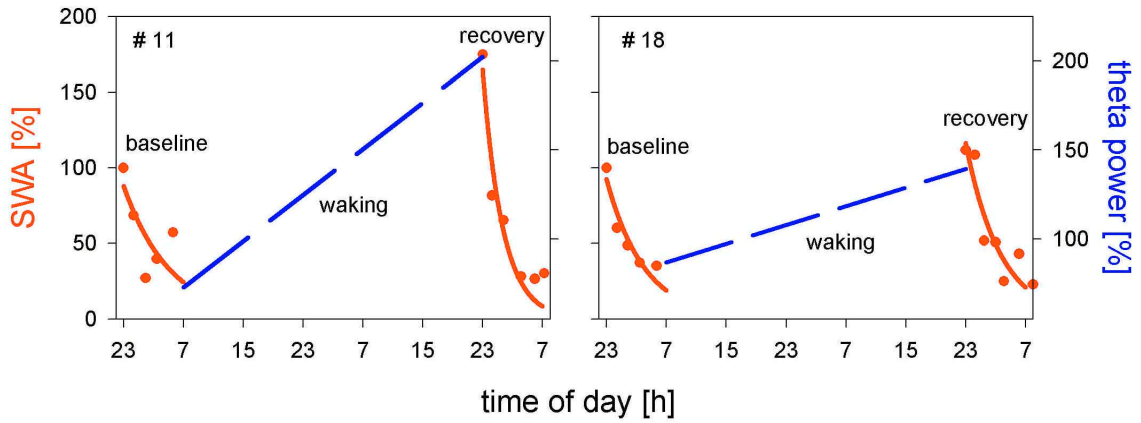

Figure 7. Association between rise of SWA in sleep and theta activity in waking illustrated for two subjects. Mean slow-wave activity (SWA) per nonREM sleep episode is plotted at the beginning of each episode, and expressed relative to the baseline value of the first nonREM sleep episode (100 %). Exponential functions were fitted through the data points (solid curves). The regression line represents theta power in waking (interrupted line). Adapted from (77).

of S. Similarly, folding at 28 h for different circadian phases resulted in a dependence of the amplitude of S on circadian phase.

In a further simulation (not shown), the homeostatic component S and the circadian component C whose amplitude was modulated by S, were added, to simulate one specific kind of nonlinear interaction. The analysis showed again that the two constituent components could be identified to considerable extent. However, assessing each component for different phases of the other component showed a mutual interdependence of both processes (71).

In conclusion, analyzing data of a forced desynchrony protocol allows to separate the constituent processes and to identify the presence of a nonlinear interaction. However, the specific type of interaction cannot be identified on the basis of such an analysis. In particular, it is impossible to determine which component modulates the other, and it can not be ruled out that the nonlinear interaction is the result of the nonlinearity of the metrics used. Therefore the linear action hypothesis has not been refuted.

5. DISCUSSION AND PERSPECTIVES

Already in 1987 Torsvall and Åkerstedt (72) reported that the waking EEG may serve as a quantitative measure of sleepiness. In recent studies, homeostatic and circadian processes could be characterized also for waking (see Tab. 2 in (2)). Power in the theta band of the waking EEG was shown to be determined by the duration of prior waking (73-76). Also an association between the waking and sleep EEG was observed. The rise rate of theta power in the waking EEG was correlated with the change in SWA in the first nonREM sleep episode (77). Figure 7 illustrates the rise rates of theta power in waking in those two subjects who showed the maximum and minimum SWA response to sleep deprivation. The line representing theta power in waking connects the two exponential functions that represent the decline of SWA during sleep. The results suggested that a common regulatory process controls specific parts of the waking and sleep EEG.

The two-process model was successful in predicting alertness and sleepiness for experimental manipulations that were within a physiological range. This does not apply to the modeling of cumulative effects of chronic sleep restriction (78-80). A discrepancy was observed between the predictions of the two-process model and data of a psychomotor vigilance test (PVT) in subjects whose sleep was restricted to 4 h for 14 consecutive days (79, 80). The level of Process S saturated quickly during sleep restriction in accordance with SWA data while PVT lapses continued to increase. These findings raise the question whether an additional process has to be assumed. A novel process that increases linearly over the days of sleep restriction was postulated (79, 80).

Recently, the question arose whether sleep represents a global or a local brain process. The observations that dolphins do not exhibit deep slow wave sleep in both hemispheres simultaneously and that selective deprivation of unihemispheric sleep gives rise to a unihemispheric slow wave sleep rebound (81) shows that sleep is not equally manifested in the entire brain. In addition, there is evidence from studies in monkeys that the process of falling asleep may not occur synchronously in the entire brain (82). Two hypotheses were advanced which both imply that regional increase of neuronal activity and metabolic demand during wakefulness may result in selective changes in EEG synchronization of these neuronal populations in nonREM sleep (83, 84). Benington and Heller (84) proposed that adenosine, which is released upon increased metabolic demand via facilitated transport by neurons and glia cells throughout the CNS, promotes slow EEG potentials. Thus a use-dependent, local mechanism would underlie the sleep-deprivation induced changes in the sleep EEG. There is evidence from microdialysis studies in animals that the adenosine level in the brain rises during waking and declines during sleep (85).

The tenet of a local, use-dependent increase of sleep intensity was tested by investigating whether the local activation of a particular brain region during wakefulness affected the EEG recorded from the same site during sleep (86). An intermittent vibratory stimulus was applied to the left or right hand during the 6-h period prior to sleep to activate the contralateral somatosensory cortex. Stimulation of the right (dominant) hand resulted in a shift of power in the nonREM sleep EEG towards the left hemisphere. This effect was most prominent in the delta range, was limited to the first hour of sleep and restricted to the central derivation located over the somatosensory cortex.

In a topographical study a sleep-dependent hyperfrontality of SWA was observed which varied in the course of sleep (87, 88). Thus in the initial two nonREM sleep episodes, the power in the 2-Hz band was dominant at the frontal derivation, whereas in the second part of sleep the antero-posterior gradient vanished. A recent topographical EEG analysis revealed that prolonged waking induced an increase in power in the low-frequency range (1-10.75 Hz) which was largest over the frontal region (89, 90). The topographic pattern of the recovery/baseline power ratio was similar to the power ratio between the first and second half of the baseline night. These results indicate that changes in sleep propensity are reflected by specific regional differences in EEG power. The predominant increase of low-frequency power in frontal areas may be due to a high 'recovery need' of the frontal, heteromodal association areas of the cortex. Recent experiments have shown that a sleep deficit impairs primarily high-level cognitive skills, which depend on frontal lobe function (91, 92). Patients with lesions of the prefrontal cortex suffer from deficits, which include distraction by irrelevant stimuli, diminished word fluency, flat intonation of speech, impaired divergent thinking, apathy and childish humor (93). Subjects foregoing sleep may exhibit similar symptoms. Therefore, it may be more than a coincidence that the prevalence of slow waves is maximal at frontal EEG derivations in the initial part of sleep. This finding is consistent with the notion that the sleep process may occur in a topographically graded manner by involving preferentially those neuronal populations that have been most activated during waking.

The expectation that the brain mechanisms underlying sleep homeostasis will be elucidated at the cellular and molecular level, is reasonable in view of recent advances (94). Models may serve as a guiding principle to establish a link between processes identified at different levels of analysis.

6. ACKNOWLEDGEMENT

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