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REVIEW ARTICLE

Models of human sleep regulation

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Non-REM sleep deprivation and REM sleep deprivation both lead to specific rebounds, suggesting that these states fulfil physiological needs. In view of impaired performance after sleep deprivation, a recovery function of sleep seems likely. The timing of this recovery is restricted to a narrow time interval within the 24 hour day, i.e. the night. Generally, nocturnal sleep in humans is considered a consequence of the impact of the circadian pacemaker in the hypothalamus on sleep propensity. The interaction between the homeostatic recovery process and the circadian pacemaker has been modelled in the two-process model of sleep regulation. This model is used as a starting point in the present review. A series of refinements and several alternative models are discussed, both with respect to the quality of fit of theory and data, as well as with respect to the concepts behind the models.

Key words: Sleep, slow wave activity, circadian pacemaker, models

One of the reasons to assume that sleep serves important functions to an organism is the fact that timing and duration of sleep are strictly regulated. Specific rebounds occur both upon non-REM sleep deprivation as well as upon REM sleep deprivation, suggesting that the states constitute necessary physiological processes. It is, however, not yet clear what these necessary processes are. The physiological characteristics of non-REM sleep and REM sleep are very different. Apart from the absence or presence of rapid eye movements, there are differences in the electroencephalogram, in thermoregulation, in cardiovascular processes, and in breathing. Virtually every physiological process is involved. Each of the processes seems to be crucial for the functioning of the organism, and so each of them may provide the ultimate reason for the rebound responses which occur upon non-REM and REM sleep deprivation.

Although the question why we sleep is still not fully answered, much is known about how we sleep. The available knowledge is consistent with the hypothesis that sleep serves to recover from previous wakefulness or to prepare for proper functioning in the wakeful period to come [1–3]. This hypothesis predominantly rests on electrophysiological observations regarding non-REM sleep regulation [4–6], which covers 75–80% of total sleep time in healthy adults. The available knowledge about REM

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sleep regulatory mechanisms [7,8] is not inconsistent with a recovery function of sleep, but this work suggests that the function of REM sleep *per se* is related to non-REM sleep instead of being related to wakefulness. Similar notions have been formulated in the consolidation hypothesis by Meddis [9]. An indirect consequence of this view is that non-REM sleep would fulfill the primary functions of sleep, while REM sleep would serve to keep non-REM sleep going.

The wide variety of data on how we sleep can best be summarized in terms of models of sleep regulation, since models can integrate many observations. Models in turn help to formulate relevant questions for future experimentation.

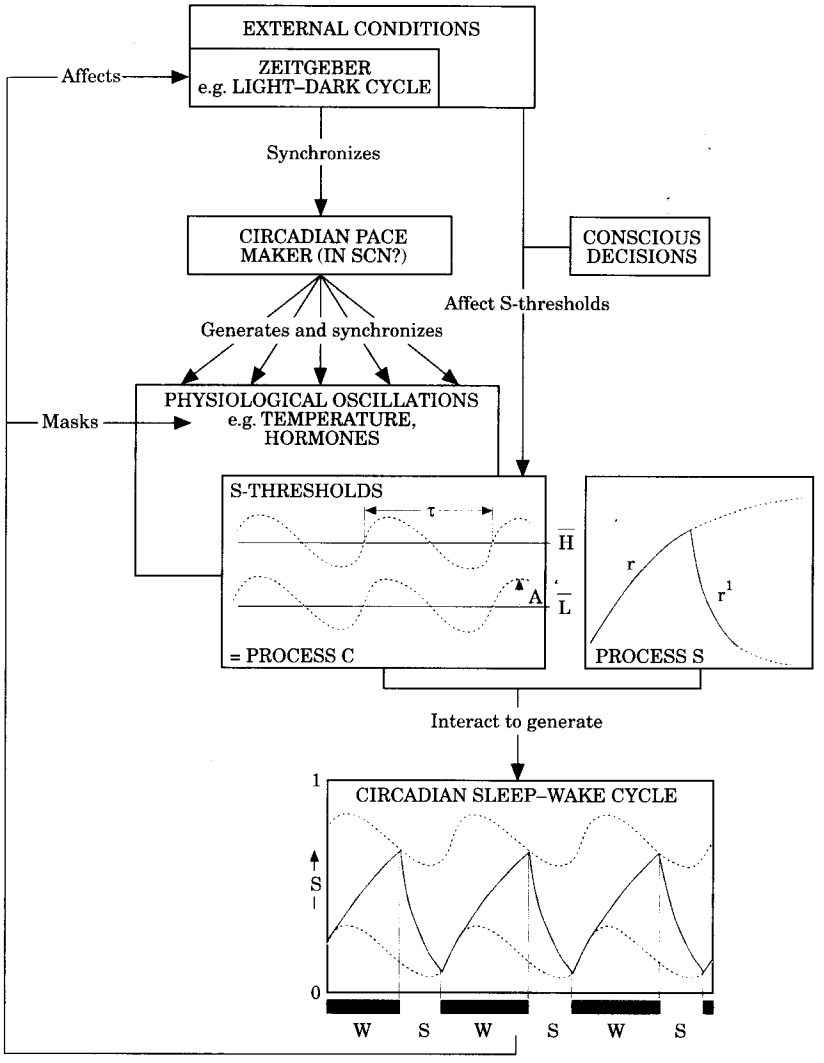
The present paper reviews currently available models of human sleep regulation, with an emphasis on models concerning electrophysiological processes. For that purpose, the two-process model of sleep regulation [2,3,10] will serve as a starting point. After having presented its concepts and merits, I will discuss alternative views which have arisen in the last 15 years. Subsequently, I will present various new findings and ideas which have modified or will probably soon modify our notions about sleep regulation. Previous reviews in this field were published by Borbély and Achermann [11], and by Borbély [12].

The two-process model of sleep regulation

In the early 1980s ideas on circadian and homeostatic regulation of behaviour were integrated, initially in global terms on the basis of both rat data [13,14] and human data [15]. Subsequently, two proposals for the detailed interaction between the processes in humans were presented at a meeting in Cape Cod in June 1981 [2,10]. Collaborative efforts culminated in a quantitative model of human sleep regulation, which became known as the two-process model of sleep regulation [3]. The model describes the timing of the alternation between human sleep and wakefulness as the result of the interaction of two processes: a homeostatic process keeping track of the instantaneous need for sleep, and a circadian process keeping track of environmental time. Figure 1 describes the model's structure.

The homeostatic process is called process S. This is the regulated variable in the model. It increases during wakefulness in an exponentially saturating way, and it declines exponentially during sleep. Originally it was suggested that the intensity of sleep, measured as the power density of the non-REM sleep EEG, would be proportional to S, because the power density of the non-REM sleep EEG decays in an approximately exponential way upon successive non-REM–REM cycles [4]. Due to the mathematical characteristics of exponential functions, however, it was not possible to distinguish between: (1) a proportionality of S and EEG power density; and (2) a proportionality of the rate of change of S and EEG power density [16]. Experimental suppression of non-REM EEG power density [17,18] demonstrated that non-REM sleep intensity (also called slow-wave activity, SWA) must be proportional to the momentary decrement of S.

In the model, the waxing and waning of process S is limited by two thresholds to the S process. One upper threshold determines the transition from the increase during wakefulness to the decrease during sleep. It thereby determines sleep onset and could be called the sleep threshold. The other, lower threshold determines the transition from decreasing towards increasing values of S, i.e. sleep termination. Therefore, this can be seen as the wake threshold. The two thresholds are supposedly under the control



re 1. Schematic representation of the two-process model of sleep regulation.

or the circadian pacemaker in the suprachiasmatic nuclei (SCN) of the hypothalamus. As a result, the thresholds vary systematically with time of day. The thresholds are presumed to run in parallel and together are called process C.

Apart from the processes S and C, there are many other influences on the alternation of sleep and wakefulness, such as conscious decisions, pain, stress, etc. It is assumed that these factors have an influence on the timing of sleep by modulating the levels of the sleep and wake thresholds, while leaving process S undisturbed.

Simulations demonstrated that with this model a wide variety of phenomena can be explained [3]. It was possible to simulate the characteristics of the sleep–wake patterns of subjects in temporal isolation, in particular upon spontaneous internal desynchronization [19]. Sleep fragmentation under conditions of continuous bed rest could be explained with the model as well as the duration of daytime sleep of shift workers. Attempts were made to extend the model to include measures of alertness

and predict their course under sleep deprivation conditions. For that purpose the distance between S and the sleep threshold was taken as a possible correlate of alertness. There was a reasonable correspondence between simulations and real data. However, later studies demonstrated that several modifications of the two-process model are required to make it a suitable model to describe and predict alertness data [20–24]. Recently, data collected by Dijk and Czeisler [25,26] revealed that alertness is determined by homeostatic and circadian influences in complex interaction. Even though the current models may be insufficient to explain the complex interaction between homeostatic and circadian processes underlying alertness, there is little doubt that such processes are involved in the regulation of alertness.

The two-process model was not primarily designed to simulate alertness data, but to integrate existing knowledge on sleep regulation. It was used to predict the outcome of new experiments and survived a series of critical tests [17,18,27–32]. It proved to be compatible with important new data sets, such as SWA data obtained in habitual long and short sleepers [33].

The interaction of process S and process C

The concept that sleep timing would be regulated by the interaction of one homeostatic process, S, keeping track of internal needs, and one circadian process, C, keeping track of environmental time was so appealing that it was rapidly accepted by the scientific community. This was not so much a consequence of the qualities of the simulations since a two-pacemaker model, developed by Kronauer *et al.* [34] had similar simulation qualities [35]. The attractiveness of the model was predominantly due to its physiological appeal, and its mathematical simplicity. The fact that only a single circadian pacemaker was detected in the mammalian brain [36,37] remained a stumbling block for the two-pacemaker approach. By now there is evidence for the existence of two other pacemakers, one in the mammalian eye [38], and one related to learning temporal patterns of food availability ("Food Entrainable Oscillator" [39]). However, these pacemakers do not seem to be involved in the regulation of the timing of sleep.

Despite the general acceptance of the concept of the two-process model, several publications have proposed alternative kinds of interactions between the two processes. Putilov [40], for instance, suggested to modify the two-process model in such a way that process S, like all processes in the body, is, to some extent, modulated by the circadian pacemaker. By doing so he could demonstrate that process C could be taken to be sinusoidal, which approximates the circadian variation of firing rate in the SCN [41], and the influence of the SCN on core temperature [42,43]. Putilov also demonstrated that some simulations of SWA with the adjusted model were slightly better than with the original two-process model. Yet, a large range of original simulations were not repeated with the adjusted model, and it remains to be seen whether the benefits of the adjustment outweigh the loss of simplicity of the concept.

Edgar *et al.* [44], on the basis of lesion studies in squirrel monkeys, concluded that one of the functions of the SCN is to consolidate vigilance states, which consolidation occurs in a circadian phase dependent manner. They suggested that sleep timing is the result of the interaction of two opponent processes. SCN-dependent processes would actively facilitate the initiation and maintenance of wakefulness, and oppose homeostatic sleep tendency during the subjective day. Along similar lines, Dijk and Czeisler [25,26] suggested that the circadian pacemaker has a function in consolidating

wakefulness as well as sleep. This conclusion was based on so-called "forced desynchrony" studies. In these studies sleep and wakefulness are scheduled to alternate at a period distinctly different from 24 hours. This leads to a desynchronization between the sleep–wake cycle and the circadian pacemaker. Plotting the values of several variables (alertness data, wakefulness during sleep, total sleep time, sleep latency) as a function of the time after scheduled wake-up and as a function of circadian phase, revealed that the circadian drive for sleep is maximal near habitual wake-up time. Similarly, the circadian drive for wakefulness is maximal near habitual bedtime (this interval of time is sometimes called the "dead zone" for sleep onset [35,45]). The data demonstrated that the circadian pacemaker serves to consolidate wakefulness at the end of the day, where alertness would otherwise decrease due to the long duration of prior wakefulness. The pacemaker, likewise, serves to consolidate sleep at the end of the night, where the increase of arousal in response to the long duration of prior sleep would otherwise induce wakefulness. In the two-process model of sleep regulation the circadian drive for wakefulness is modelled in the shape of the wake threshold and the circadian drive for sleep is modelled in the shape of the sleep threshold: high levels of the thresholds represent a low drive for sleep. As a consequence, the data by Dijk and Czeisler [26] suggest that the shape of the wake threshold is qualitatively correct, but that this does not hold for the sleep threshold. In contrast to the shape presented in Figure 1, the sleep threshold should increase in the course of habitual wakefulness and sharply decline at the beginning of habitual sleep time, just like Achermann and Borbély [20] proposed on the basis of simulations of alertness data. It must be noted that the shape of the sleep threshold in the original model was not derived from direct experimental results but, in the absence of such data, was simply postulated to run in parallel to the wake threshold. It is obvious that experiments aiming at assessing the shape of the sleep threshold are urgently needed.

Forced desynchrony studies further revealed that SWA is largely independent of circadian phase [26] which is consistent with the assumption of two independent processes underlying human sleep regulation. REM sleep, in contrast, was shown to vary with circadian phase and also with the time since sleep onset. The inhibition of REM sleep at high pressure for non-REM sleep, as proposed by Borbély [2], is consistent with this latter relationship.

Several other models of sleep regulation exist in the literature [46–48]. These models simultaneously take into account a wide variety of variables which influence sleep regulation. As a consequence, these models are physiologically and mathematically complex and beyond the scope of the present review.

In the following I will focus on several details of the model and review a series of relevant refinements and alternatives.

Process S

In general, the output of a process can be modulated by modulation of either its intensity or its duration. For non-REM sleep it is clear that it responds to experimental manipulations mainly by changing its intensity [4,16–18,49,50]. The two-process model of sleep regulation in its original formulation did not distinguish between REM and non-REM sleep. The non-REM–REM sleep cycle was simply taken as the unit of analysis of sleep intensity. Sleep intensity was defined on the basis of non-REM sleep EEG features only, by calculating the power of the electroencephalogram in the delta

frequency range (0.5–4 Hz) by Fourier analysis, or by calculating the amplitude of EEG half-waves with relatively long half-wave durations. It has been shown that the power densities of EEG signals correlate highly with the squares of the half-wave amplitudes [51].

Achermann *et al.* [5] have refined the two-process model, in particular with respect to the details of process S during sleep. For that purpose, they developed a sub-model or module which specifically addressed the time course of SWA in the course of a non-REM–REM sleep cycle. This fine structure was analysed in earlier studies [52,53]. The module receives as inputs information about both the timing of REM sleep as well as the timing of arousals and intermittent wake time. It then produces a SWA profile which almost perfectly mimics the actually observed SWA profile. Apparently, the dynamics of SWA are very well known now. A subtle but important difference with the original formulation of the two-process model is that Achermann had to assume that process S during sleep has two dynamic components. One is the decline which is proportional to SWA, and the other is an increment of S which is presumed to be always present, i.e. both during wakefulness and during sleep. Although the reason to incorporate the latter term in the model was to improve the quality of fit between simulations and data, the term suggests that the activity of cells under all conditions leads to a need for recovery. The recovery occurs during sleep and is superimposed on and outweighs the ongoing activity which creates the need for sleep.

With respect to the module presented by Achermann *et al.*, it is important to note that the timing of the intrusions of wakefulness and of the transitions to and from REM sleep are as yet difficult to predict. For the intrusion of arousals no models are available, and the existing models of the alternation between REM and non-REM sleep are based on the assumption of the existence of an ultradian pacemaker in the human brain [7,54], which remains to be demonstrated. Modelling is hampered by the fact that the functions of REM sleep are not known. Benington and Heller [8] recently revived the discussion regarding the function of REM sleep. They suggested on the basis of various data sets that REM sleep does not serve to recover from some wastage of wakefulness, but that it could serve to recover from the preceding non-REM sleep. (This is a more generalized form of the hypothesis proposed earlier by Wehr [55] that REM sleep serves to counteract the brain cooling in prior non-REM.) If this hypothesis survives critical experimentation it could serve as a basis for further modelling. It would then also substantiate the notion that the main function of sleep is fulfilled during the delta waves of non-REM sleep.

Intrusions of wakefulness into sleep as well as intervals of REM sleep have their impact on SWA, e.g. because it takes time before SWA resumes maximum values after interruptions. Experimental studies using SWA as outcome variables are advised to integrate SWA values over sufficiently long time intervals of accumulated non-REM sleep [56].

The work of Steriade *et al.* [6] has revealed that the delta waves in the EEG originate from cortico-thalamic feedback loops which bring subsets of neurons in mutually synchronous firing and pausing states. The greater the number of neurons participating in a synchronous sample, the larger the amplitude of the delta wave in the EEG. This notion has brought Mourtazaev *et al.* [57] to propose a "model-based" analysis of the sleep EEG. They model the interactions between the neurons with a feedback system which receives a white noise signal as an input, and produces the EEG signal as its output. The feedback strength of the model required to mimic the actually observed EEG is calculated as a function of time during sleep. The strength of the feedback is

hypothesized to represent the intensity of the non-REM sleep process. One of the advantages of the method is that the feedback strength is a relative measure, not dependent on the absolute level of the EEG signal. Differences in EEG power density between individuals, which, for instance, may be due to anatomical differences, are automatically set aside with this model-based method of analysis. Another advantage over classical Fourier analysis is that, by its nature, the model-based method discriminates waves in the EEG from transients with other characteristics, such as movement artifacts. An obvious disadvantage is that the results of the analysis depend on the characteristics of the model on which it is based.

The work of Steriade has stimulated other new developments. The electrophysiological findings have triggered research aiming at the biochemical origin of SWA, which may provide clues for the understanding of the fundamental function of sleep itself. Porkka-Heiskanen *et al.* [58] showed that extra-cellular adenosine has a temporal course over the sleep–wake cycle which is similar to process S. Benington and Heller [59] also indicated adenosine as being related to the generation of delta waves. In addition they suggested that the replenishment of astrocytic glycogen represents the ultimate need for sleep. They hypothesized that slow waves are required for the restoration of the glycogen that is depleted during wakefulness. These are highly interesting developments which deserve much attention in the near future.

Merica and Blois [60] also extended on the work by Steriade. They presented a simple model which could explain some of the changes in the composition of the frequency spectrum of the EEG in the course of the non-REM episode [61]. They estimated the electrical consequences when a population of neurons went from the polarized state during waking to the hyperpolarized state during deep SWA. As was shown by Steriade *et al.* [6], the thalamocortical neurons are capable of generating spindle activity at intermediate levels of polarization. Merica and Blois [60] could show that the temporal distributions of energy of the non-REM sleep EEG signal in the spindle range and in the delta range can be simulated with such a simple model.

Another new development concerning process S during sleep is the work by Werth *et al.* [62,63]. They showed that in the early work by Bos *et al.* [64] on the spatial distribution of electrical activity over the scalp, one important phenomenon had been overlooked: maximum SWA gradually shifts from occipital to frontal regions in the course of each non-REM episode. Such fine structure of the processes involved in sleep regulation is not yet incorporated in any model. It suggests that the recovery processes occur at specific locations, as was already demonstrated for some aquatic mammals [65] and also for humans [66]. It shows that a non-REM episode is not just containing a bulk of SWA, but that the process develops in a carefully controlled topographical way. Perhaps, this is associated with the dependence of non-REM–REM cycle durations on the brain size of an animal [67]: in larger brains it takes longer to complete a "wave" of recovery processes from occipital to frontal areas.

Against the background of these new developments in our knowledge of process S during non-REM sleep, it is remarkable that virtually nothing is known about the kind of stimuli to which SWA responds. Few experiments have been performed to test whether different activities during the day lead to differences in SWA during sleep [66,68–70]. SWA does seem to increase in response to heat load. Intense physical activity can lead to increased SWA, but such changes are not observed when physical activity is combined with cooling of the brain [71]. There are detectable increases in SWA in response to long sessions of finger tapping [66], but the effects are small. It is as if the wear and tear of the neurons in the brain only depend on their level of

operation, which is modulated by brain temperature, and that these cells otherwise operate at a similar average rate, independent from the stimuli they have to deal with. However, it is not sure whether similar statements can be made regarding other types of activity. Aggressive confrontations between rats lead to systematic changes in their subsequent sleep [70]. Obviously, such confrontations entail various changes in emotional, cognitive and somatic states, such as increased anxiety, alertness, energy metabolism, etc. It is not clear which of these changes is responsible for the changes observed during sleep. In humans, no systematic data on the impact of mental processes on SWA are available.

REM sleep received little attention within the context of the two-process model. One of the reasons is the fact that the non-REM–REM cycle was originally taken as the unit of analysis. However, there are some other reasons contributing to this fact. Concerning the homeostatic regulation of REM sleep the situation is not very clear. No obvious REM sleep intensity measure is available. REM density cannot be a measure of REM sleep intensity because it predominantly responds to changes in non-REM sleep intensity [72–74]. There are data suggesting that certain frequency characteristics of the REM sleep EEG can serve as a measure of REM sleep intensity [75,76], but this needs independent validation. In contrast to non-REM sleep, it is evident, however, that REM sleep responds to deprivation by a partial rebound REM sleep duration [77,75,76].

Process C

Much less progress than in our knowledge of process S and its underlying physiology has been made with respect to process C. There is not much more than the assumption that process C is driven by the circadian pacemaker. Insight into the physiology and biochemistry of the circadian pacemaker, however, has progressed spectacularly. It is known that the primary circadian pacemaker in mammals is located in the supra-chiasmatic nucleus of the hypothalamus [36,37]. The period of the circadian pacemaker can be transplanted by transplanting the SCN [78]. Much is known about the anatomical connections between the pacemaker and other structures in the brain [79,80]. It is clear that the light–dark cycle is the most important stimulus to entrain the circadian pacemaker [81–84]. Much effort is being given to unravel the pathways which transfer the light–dark information to the SCN [85]. Amir and Stewart [86] noted that phase responses of the circadian pacemaker are not solely dependent on light, but that such phase responses can be conditioned and also occur when the conditioning stimulus is presented alone.

There is considerable progress in the knowledge of the circadian pacemaker on the microscopical level. Welsh *et al.* [87] reported that individual SCN cells, cultured in a dish are capable of generating circadian rhythmicity in the production of action potentials. Apparently, single SCN cells in culture are as capable of sustaining circadian rhythmicity as are unicellular algae [88]. This notion was anticipated long ago, and incorporated in a model of the circadian pacemaker by Enright [89]. In this model a series of individual self-sustained "pacers" are thought to be coupled to each other on the basis of their integrated output. The coupling can explain many characteristics of circadian pacemakers. Shinohara *et al.* [90] reported the simultaneous presence of independent circadian rhythms in neurotransmitter production in the isolated SCN.

Despite all these exciting developments in the field of circadian pacemaker research,

it must be concluded that the physiology of process C remains largely obscure. Some data indicate that it is unlikely that the two thresholds run in parallel. Experiments aimed at the shape of the sleep threshold are urgently needed.

Conclusions

In this review I have tried to discuss a series of modelling approaches to the mechanisms of sleep regulation. Admittedly, the review is limited. There is a clear focus on electrophysiological models, with an emphasis on models describing aspects of the human non-REM sleep EEG. I have tried to emphasize the functional aspects of the models and the functional concepts behind them, more than the mathematical details. The two-process model of sleep regulation was taken as the background for this discussion. The reason for this is that the two-process model conceptually sorts out two major influences on sleep regulation: the circadian pacemaker and homeostatic needs. This approach enables modular modelling: Recognition of the separate influences makes it possible to perform experiments and develop models for each influence separately, which reduces the complexity of the problem [91]. Prospects for a more detailed theoretical understanding of sleep regulation will heavily depend on experimental progress in particular with respect to two questions: what controls the onset of sleep and what controls the timing of REM episodes within sleep.

A remaining issue is whether the modelling approach has consequences for clinical practice. Models of sleep regulation are fundamental to the development of theories about how and why we sleep. The models specify those theories in quantitative detail, which allows critical testing and improvement of the theories. Since the theories about how and why we sleep should form the basis for understanding the nature and the consequences of sleep disorders, there is no doubt that models of sleep regulation are very relevant for diagnosis and treatment.

The clinical problems for which knowledge of sleep regulation could be relevant include all kinds of "pure" sleep disorders and disorders in which disregulation of sleep is a prominent feature. In this way, models of sleep regulation have, for instance, contributed to the development of therapies for delayed sleep phase syndrome and for jet lag, and large-scale investigations are underway to see whether adjustments of the circadian pacemaker by light can reduce the sleep problems of shift workers.

In the field of psychiatric disorders, models have been applied in the study of the pathogenesis and therapy of seasonal and non-seasonal mood disorders [92,93]. In view of these developments it is more than justified to expect increasing impact of models of sleep regulation on clinical practice in the future.

Research Agenda

1. Simulations with Putilov's model should be performed of the data sets which have been used to test the two-process model of sleep regulation. A comparison of the results should be performed to test whether the assumption of a modulation of process S by process C improves the quality of fit.
2. Experiments to quantify the shape of the sleep threshold of the two-process model of sleep regulation are urgently needed.
3. The impact of mental work load on subsequent sleep should systematically be investigated.

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