Modeling the Effects of Sleep Debt: On the Relevance of Inter-Individual Differences

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Modern society is increasingly driven to take advantage of the full 24 hours of the day. Therefore, despite large-scale automation efforts, the demand and desire for wakefulness at all hours of the day steadily increases. However, two fundamental neurobiological processes do not readily adapt to this situation. On the one hand, there is an imperative need for sleep, the fulfillment of which may be postponed but eventually cannot be ignored. On the other hand, the biological clock is driving wakefulness during the day, but not during the night. Thus, living in a society running 24/7 presents considerable challenges for sleep and wake neurophysiology. Nevertheless, the 24-hour society offers unique opportunities for those who have little need for sleep, for those who have low vulnerability for the functional impairment associated with sleep loss, and for those whose circadian phase position or rate of adjustment allows them to be awake at night naturally or to rapidly adapt. Inter-individual differences in sleep need, vulnerability to sleep loss and circadian adaptation remain understudied scientifically and are rarely considered theoretically (e.g., in mathematical models) or practically (e.g., in interventions for sleepiness and fatigue in the workplace). Here we present evidence that inter-individual differences in sleep need and in vulnerability to the effects of sleep loss need to be taken into account when modeling the waking neurobehavioral response to sleep deprivation.

The temporal dynamics of neurobehavioral functioning

To describe and understand the temporal profile of neurobehavioral functioning, researchers have applied the two-process model of sleep–wake regulation [3,4,6]. This model, which was designed to predict the timing and duration of sleep, consists of a *homeostatic* process (process S) and a *circadian* process (process C), which are combined to estimate the timing of the onset and offset of sleep. The homeostatic process represents the drive for sleep that increases progressively during wakefulness, and decreases during sleep (symbolizing the physiological recovery obtained from sleep). Sleep is triggered when the homeostatic drive increases above a certain threshold (unless wakefulness is deliberately maintained). Wakefulness is spontaneously invoked when the homeostatic drive has decreased sufficiently during sleep to fall below another threshold. The circadian process represents the daily oscillatory component in the drive for sleep and wakefulness, which is modeled as circadian variation in the threshold values. It has been suggested that the circadian system actively promotes wakefulness more so than sleep. The circadian drive for wakefulness can be observed as, for instance, the spontaneously enhanced alertness that occurs during the day following a sleepless night. From this perspective, the homeostatic and circadian systems can be viewed as opponent processes [15].

The homeostatic and circadian components of the two-process model can also be utilized to predict waking neurobehavioral alertness [16,17,19]. In this conceptualization, the circadian and homeostatic processes influence neurobehavioral functioning simultaneously. The interaction of the two processes appears to be oppositional during natural diurnal wake periods, such that a relatively stable level of alertness and performance can be maintained throughout the day [7]. At night, however, a rapid breakdown of alertness and performance capability is predicted and observed, as the two processes are now both permissive of sleep. During prolonged sleep deprivation, neurobehavioral deficits occur in response to increasing homeostatic sleep drive as well as circadian-modulated withdrawal of waking drive, making the impairment progressively worse during biological night [29].

A model-based understanding of the interaction of the homeostatic and circadian regulation of sleep and wakefulness can be helpful to elucidate the consequences of stress on the homeostatic and circadian regulatory systems. Obvious stressors on these systems include extension of wakefulness (i.e., sleep deprivation; e.g., [10]), sleep–wake cycle displacement (e.g., shift work; [22]), and circadian displacement (e.g., transmeridian flights; [31]). Under such circumstances, the circadian and homeostatic systems can be found to interact in a way that decreases neurobehavioral function. Alertness and performance may decline considerably, enhancing the probability of accidents in the workplace [8] and on the road [21,25]. However, the predicted magnitude of the performance decline depends on the precise values of at least three independent model parameters:

– the timing and/or rate of adjustment of the circadian process (*circadian phase*);
– the amount of sleep needed per day (*sleep need*);
– the rate of impairment per hour of sleep loss (*vulnerability*).

The *vulnerability* parameter is an often overlooked dimension of the waking neurobehavioral response to sleep deprivation, that is distinct from the *sleep need* parameter. For example, two individuals could each have the same *sleep need* of, say, 8 hours per day, but when they both receive only 4 hours of sleep on a given day, the magnitude of their performance impairment due to the ensuing sleep loss could still be substantially different—thus, the rate of impairment per hour of sleep loss (i.e., *vulnerability*) would be different for the two individuals in this example. The *vulnerability* parameter has thus far not been considered explicitly in models of sleep–wake regulation.

There is evidence for substantial inter-individual differences in the values of each of the three model parameters *circadian phase*, *sleep need* and *vulnerability.* Historically only the variability in *sleep need* has been broadly recognized and focused upon.

Inter-individual differences in circadian phase, sleep need and vulnerability

Considerable variation has been observed among humans in the timing of circadian rhythmicity (i.e., *circadian phase*). This variation finds expression in morningness/ eveningness [14,20]. By means of constant routine experiments, it was shown that the phase positions of the endogenous circadian rhythms of extreme morning-types and evening-types, as measured by core body temperature, differ by more than 2 hours. Possibly due to the interaction with the homeostatic drive for sleep, this results in a difference of at least 4 hours in the timing of peak alertness between morning-types and evening-types [20]. This may explain the finding that evening-types are more tolerant to permanent night work than morning-types [26]. Similarly, in shift work, morning-types appear to have a relative advantage on morning shifts and a disadvantage on night shifts, and vice versa for evening-types (e.g., [2,5]). Furthermore, evening-types appear to adapt more easily to rotating shift work [24].

Inter-individual differences in *sleep need* have been carefully studied in the context of the two-process model of sleep–wake regulation. Using the waking electroencephalogram (EEG) as a physiological marker of sleep homeostasis, it was found that naturally short sleepers tolerate a higher homeostatic pressure for sleep than naturally long sleepers [1]. There may be a genetic basis for this variability in natural *sleep need* [18]. Not everybody who reports to be a naturally short sleeper actually is one, though [23]; many can sustain living on a short sleep schedule for a while but eventually build up a sleep debt (resulting in the need to extend sleep on the weekend, for instance).

Individuals who sleep comparable amounts each night, who have comparable circadian phases, and who are comparable neurobehaviorally when not sleep-deprived, are observed to be differentially affected—by as much as an order of magnitude—in their neurobehavioral functioning when exposed to loss of sleep [11]. These inter-individual differences in *vulnerability* are consistent, as was evident in the three studies that have been done on repeated exposure to sleep loss in the same subjects [28,30,32]. The studies of Wilkinson [32] and Webb and Levy [30] both reported substantial inter-individual differences in the effects of sleep deprivation, that appeared to reliably reflect greater sensitivity of some subjects to deprivation. Neither study actually quantified the stability of inter-individual differences in response to sleep loss, but this issue was addressed in the third study [28]. This study sleep-deprived 10 healthy adults (who were comparable in *sleep need*) on two separate occasions, and found that a significant portion of the variance in vigilance performance deficits (58% of total variance) was stable. This finding indicated that some individuals were consistently more vulnerable to neurobehavioral deficits due to sleep loss than others (i.e., *trait vulnerability*).

Inter-individual differences in the response to chronic sleep loss

Chronic sleep restriction causes cumulative sleep debt, which results in increasing neurobehavioral performance deficits [12]. The magnitude of these deficits depends on the cumulative amount of sleep loss. When fixing time in bed, the actual amount of sleep loss depends on *sleep need*. The magnitude of performance deficits, therefore, depends on *sleep need* as well. It also depends, however, on the *vulnerability* to the effects of a given amount of sleep loss. Thus, there are at least two factors for which inter-individual differences affect the waking neurobehavioral response to chronic sleep restriction (i.e., *differential sleep need* and *differential vulnerability)*. In a laboratory experiment, we studied the effects of chronic sleep restriction in a group of subjects who had a sleep–wake history indicative of equivalence in circadian timing. Using the data obtained for neurobehavioral functioning in this study, we evaluated an additive (i.e., linear) model of sleep debt postulating that, for a given individual, each hour of sleep loss is equally important in determining the performance deficits resulting from chronic sleep restriction. We explicitly estimated inter-individual variability in *sleep need* and *vulnerability* as part of the model.

Data from n=24 subjects (ages 22–36; 5 females) who spent 20 days inside a controlled laboratory environment were used. After 3 baseline days (time in bed 23:30–07:30), subjects were partially sleep deprived for 14 days. Time in bed was restricted to 4h (03:30–07:30; n=9), 6h (01:30–07:30; n=8), or 8h (23:30–07:30; n=7) per day. Neurobehavioral performance was tested every 2h during wakefulness, and included a 10-minute psychomotor vigilance test (PVT). The daily average (09:30–23:30) of PVT lapses (reaction times ? 500 ms) per test bout was used to measure neurobehavioral impairment (IMP), relative to baseline. Sleep was recorded polysomnographically on all baseline nights and on 2 out of every 3 nights throughout the 14-day restriction period, and total sleep time (TST) was assessed using conventional sleep scoring criteria. For the 4 days with no sleep recordings, TST was estimated by linear regression interpolation over the other days of sleep restriction. Finally, cumulative TST (CTST) was computed for each day of restriction.

The additive model of sleep debt

The additive model of sleep debt was formulated as:

$$IMP_D \sim \alpha .(\gamma . D - CTST_D)$$

where D is the day of sleep restriction (1–14), $CTST_D$ is the cumulative total sleep time (in hours) on day D, IMP_D is the neurobehavioral impairment (in PVT lapses) on day D, α is the *vulnerability* parameter (in PVT lapses per hour of sleep loss), and γ is the *sleep need* parameter (in hours). Between-subjects variances for α and γ were estimated in the model by incorporating random effects for these parameters, assuming a bivariate normal distribution. The model was fit to the data using mixed-model regression, for which we applied the SAS procedure NLMIXED [27].

We found that the model had good predictive potential. The residual error variance was only 17.4% of the overall variance in the data. Thus, 82.6% of the variance was explainable by the model assuming that subject-specific values for *sleep need* and *vulnerability* were known. Without subject-specific knowledge, the explained variance dropped dramatically to 21.9%. Considerable variability in both *sleep need* as well as *vulnerability* contributed to the additional variance explained when inter-individual differences were taken into account. These results highlight the importance of inter-individual differences in modeling the effects of

cumulative sleep debt [9]. In this experiment, the estimated *sleep need* was 8.2 hours, and the estimated standard deviation for inter-individual differences in *sleep need* was 2.6 hours. As the subjects in the study were similar in circadian timing, we did not as yet incorporate inter-individual variability for the *circadian phase* parameter in the model.

Conclusion

Despite the success of the two-process model of sleep–wake regulation to describe and predict group data in a variety of experimental protocols, it has proven to be difficult to apply the model to individual subjects reliably. There is mounting evidence that inter-individual differences in variables affecting the model are consistent and substantial. Conceivably, the parameters of the two-process model could be adjusted to match each individual's characteristics. The challenge will be, however, to find objective behavioral or physiological markers of these parameters. For *circadian phase*, core body temperature or melatonin profiles can provide reliable markers. To date, there is no consensus about what biological markers should be used for *sleep need*, or for *vulnerability* to neurobehavioral impairment from sleep loss. When probed with a psychomotor vigilance test, *vulnerability* to neurobehavioral impairment from sleep loss is observed as "wake state instability" [13]. This is the term we use for the mixture of normal performance with lapses and false responses, increasing in frequency with time on task, observed to be a consequence of sleep loss. A quantitative measure of wake state instability (e.g., performance lapses) may serve as a marker of *vulnerability*. It is becoming increasingly clear that inter-individual differences in *vulnerability*, as well as *sleep need* and *circadian phase*, should be taken into account explicitly when studying the waking neurobehavioral consequences of sleep deprivation or circadian misalignment [9]. These stressors do not have the same effects for everyone.

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CLUB HYPNOS EVENTS HELD IN SAN DIEGO & PHILADELPHIA

Club Hypnos at the Association for the Advancement of Behavior Therapy

by Kathy Sexton-Radek, Ph.D.

A Club Hynos reception was held at the Association for the Advancement of Behavior Therapy conference in Philadelphia November 17, 2001. The event followed their special interest group on Insomnia meeting that is coordinated by Kenny Lichstein of Memphis State. Approximately 25 were in attendance. Although the event got off to a few minutes late start because of the length of the meeting, all sleep researchers in attendance seemed to enjoy the time to socialize and snack on some treats. The SRS membership forms were passed out to everyone and many conveyed their thanks for the SRS hosting of a social at the AABT conference. A word of note to all future Club Hypnos coordinators, read through the helpful information sent by Jodi Mindell to make sure all the details of hosting the event are in order-it is all there in the attachment that is sent to you and really helps to identify the steps necessary for a success! Furthermore, many of the sleep researchers at the event knew each other and the new people were readily introduced to members in attendance at the social-it proved to be a wonderful opportunity for networking.

Club Hypnos at Society for Neuroscience 2001

This last November's Club Hypnos reception at the Society for Neuroscience meeting in San Diego again proved to be a great success. This year marked the seventh time this SRS-sponsored social event has been held. The original idea for such an event, conceived by Dr. Adrian Morrison, was to publicize opportunities in sleep research and attract students to the field. Since the Society for Neuroscience meeting held in New Orleans in 1997, Club Hypnos has met sequentially in time with the National Center for Sleep Disorders Research (NCSDR)-sponsored "Neuroscience in Sleep and Circadian Biology Data-Blitz". This cooperation has resulted in increased publicity and visibility for the SRS and Club Hypnos.

I am pleased to report that this year there were 150 visitors to Club Hypnos in San Diego. Not only did several SRS Executive Committee members attend, but Dr. Carl Hunt; the recently appointed Director of the NCSDR also paid a visit. The food provided proved to be a big hit once again and since all the SRS membership brochures I brought were picked up, I am hoping that our central office will soon report that some new members were recruited. In closing I would like to encourage all of you to think about the other scientific meetings you attend and consider if a Club Hypnos social would enhance your meeting experience. As many of you know, the Society for Neuroscience annual meeting is huge and often overwhelming. Through hosting Club Hypnos I have a gained a renewed interest and enthusiasm for this meeting and believe that by providing this SRS "home away from home" we are promoting the field of sleep research.

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