

Investigating the interaction between the homeostatic and circadian processes of sleep–wake regulation for the prediction of waking neurobehavioural performance

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SUMMARY The two-process model of sleep regulation has been applied successfully to describe, predict, and understand sleep–wake regulation in a variety of experimental protocols such as sleep deprivation and forced desynchrony. A non-linear interaction between the homeostatic and circadian processes was reported when the model was applied to describe alertness and performance data obtained during forced desynchrony. This non-linear interaction could also be due to intrinsic non-linearity in the metrics used to measure alertness and performance, however. Distinguishing these possibilities would be of theoretical interest, but could also have important implications for the design and interpretation of experiments placing sleep at different circadian phases or varying the duration of sleep and/or wakefulness. Although to date no resolution to this controversy has been found, here we show that the issue can be addressed with existing data sets. The interaction between the homeostatic and circadian processes of sleep–wake regulation was investigated using neurobehavioural performance data from a laboratory experiment involving total sleep deprivation. The results provided evidence of an actual non-linear interaction between the homeostatic and circadian processes of sleep–wake regulation for the prediction of waking neurobehavioural performance.

KEYWORDS circadian process, homeostatic process, non-linear interaction, non-linear metric, sleep deprivation, two-process model of sleep regulation

INTRODUCTION

One of the major advances in the understanding of the regulation of sleep was the development of the two-process model of sleep regulation (Borbély, 1982; Borbély and Achermann, 2000; Daan *et al.*, 1984). The model consists of a homeostatic process termed ‘process *S*’ and a circadian process termed ‘process *C*’. Process *S* represents a putative drive for sleep that increases progressively during wakefulness, and decreases progressively during (non-REM) sleep. Process *C* represents a (nearly) 24-h oscillatory variation in the propensity for sleep. These two processes were demonstrated to

predict the timing and duration of sleep and the intensity of non-REM sleep (e.g. Achermann *et al.*, 1993; Borbély, 1982). When applied in an additive (i.e. linear) manner, the two processes were also shown to predict measures of alertness and performance during wakefulness (Achermann and Borbély, 1994; Åkerstedt and Folkard, 1997), although the degree of accuracy of these predictions is an area of continuing research (Van Dongen, 2003). A review and update of the two-process model, including the mathematical formulation used in the present research, was recently presented by Borbély and Achermann (1999).

The two-process model has been applied successfully to describe, predict and understand sleep–wake regulation in a variety of experimental protocols, including total sleep deprivation followed by recovery sleep (e.g. Daan *et al.*, 1984), and constant routine and forced desynchrony paradigms (e.g. Dijk *et al.*, 1992). The forced desynchrony paradigm is of particular

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interest because its design permits the systematic scanning of many combinations of different states of the processes S and C . It was found that application of the two processes in an additive manner did not suffice to predict subjective alertness and cognitive performance during forced desynchrony, leading investigators to hypothesize a non-linear interaction between the two processes¹ (Dijk *et al.*, 1992; Jewett and Kronauer, 1999). Establishing the existence of a non-linear interaction between process S and process C is important for the reliability of the model's predictions, especially under extreme circumstances such as long-duration total sleep deprivation. It is also of theoretical interest, and has implications for the design and interpretation of experiments placing sleep and wakefulness at different circadian phases or varying the duration of sleep and/or wakefulness.

Achermann (1999) pointed out that an apparent non-linear interaction could be entirely due to an intrinsic non-linearity in the mapping of the predictions of the two-process model onto the measurement variable in the experiment, that is, a non-linearity in the metric used to measure alertness or performance. For instance, if the inclusion of a non-linear interaction between processes S and C is found to improve the model's predictions for a given measure of subjective alertness, then assuming that the metric used to measure subjective alertness may be intrinsically non-linear could have equal potential to improve the model's predictions. Thus, it seemed that the hypothesis of a non-linear interaction between processes S and C would not be testable. This issue was further discussed by Dijk *et al.* (1999), but to date no resolution has been found.

Here we show that the issue of whether or not there is an inherent non-linearity in the interaction of processes S and C , regardless of the metric used to measure waking neurobehavioural function, can in fact be addressed with existing data sets. The idea is to select different combinations of the states of the processes S and C that predict *similar* outcomes if the two processes are strictly additive. The corresponding measurements of alertness or performance should then also be similar, regardless of any non-linearity in the metric, as the *same* portion of the metric scale is involved. If the measurements are statistically significantly dissimilar, then the assumption that the processes S and C are strictly additive in predicting alertness and performance can be rejected. Consequently, the existence of an actual non-linear interaction between the homeostatic and circadian processes of sleep-wake regulation can be inferred, independently of the characteristics of the metric at hand. In the present paper, the nature of the interaction between the two processes is investigated using neurobehavioural performance data from a laboratory experiment involving total sleep deprivation.

METHODS AND RESULTS

Empirical data and model predictions

Data were taken from a laboratory experiment involving 88 h (3.7 days) of total sleep deprivation (see Doran *et al.*, 2001;

Van Dongen *et al.*, 2001). The experiment involved a pharmacological and a placebo condition; for the present purposes, only data from $n = 13$ healthy subjects in the placebo condition were used. After three baseline days with sleep scheduled from 23:30 until 07:30 hours, subjects were kept awake for 88 h continuously.

Starting 30 min into the sleep deprivation period (at 08:00 hours), subjects' neurobehavioural performance was tested at 2-h intervals on a computerized assessment battery. This battery included a 10-min high-load psychomotor vigilance task (Dinges and Powell, 1985) documented to be sensitive to the effects of sleep loss and circadian rhythmicity (e.g. Dinges *et al.*, 1987; Doran *et al.*, 2001). The psychomotor vigilance task is devoid of practice effects (Van Dongen *et al.*, 2003a), which is a critical property with regard to the investigation of the interaction between the homeostatic and circadian processes of sleep-wake regulation. For each assessment on the task, the average of the reciprocals of the 10% slowest reaction times was computed as a measure of performance impairment. These experimental data y are shown in Fig. 1 (top panel) for up to 64 h of continuous wakefulness. The last 24 h of the 88-h sleep deprivation period were not used because of negligible predicted homeostatic variability during that period (i.e. < 1% of the total range for process S during the experiment).

Predictions for processes S and C were made (see Borbély and Achermann, 1999) for the three baseline days and across the subsequent total sleep deprivation period. Stable circadian rhythmicity with an effective period of $\tau = 24.0$ h was assumed throughout the experiment. Empirical evidence has shown this to be a reasonable approximation (Van Dongen *et al.*, 1998). The predictions for processes S and C across the first 64 h of sleep deprivation are shown in Fig. 1 (middle panel).

Predictions assuming strictly additive processes

We considered the null hypothesis that the processes S and C are strictly additive (linear) in modelling the data y :

$$y \sim f(S - \gamma \cdot C), \quad (1)$$

where γ represents the contribution of the circadian process relative to the homeostatic process, and f is a monotonic function mapping the predictions of the two-process model onto the measurement variable y . Initially, all data analyses were performed under the null hypothesis. Later in this paper, we will investigate whether maintaining the null hypothesis led to a contradiction that would prove the hypothesis wrong.

In order to determine the relative contributions of the homeostatic and circadian processes to psychomotor vigilance as measured by y , we needed to estimate the value of γ . To accomplish this, it was necessary to also assess the nature of the monotonic mapping function f . The mapping function can be expressed in terms of a finite number of parameters $\Theta_m = \{\theta_1, \theta_2, \dots, \theta_m\}$. In the face of ever-present noise in the data, the number of parameters m required to properly specify the mapping function had to be estimated from the data, using

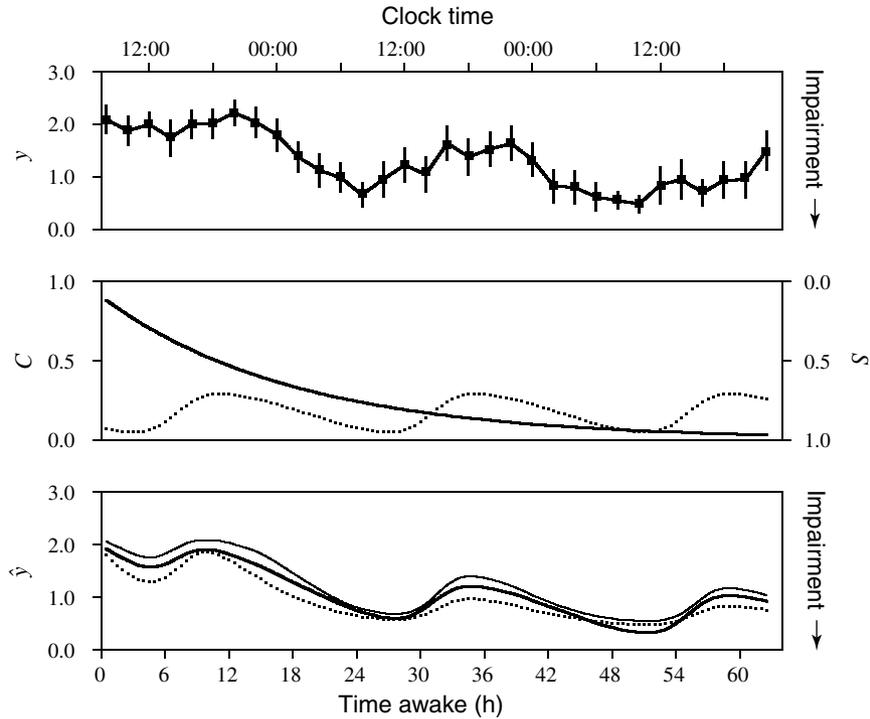


Figure 1. Empirical waking neurobehavioural performance data y (top panel), two-process model predictions for processes S and C (middle panel) and performance predictions \hat{y} (bottom panel) for 64 h of total sleep deprivation in a laboratory experiment. The top panel shows observations y for the average of the reciprocals of the 10% slowest reaction times (1/RT; in 1/s units) on a 10-min psychomotor vigilance task. The task was presented at 2-h intervals; data are shown as mean \pm standard error for $n = 13$ subjects. Performance decrements (i.e. impairments) are associated with lower values on the ordinate. The middle panel shows the two-process model predictions for process S (solid curve; right-hand ordinate) and process C (dotted curve; left-hand ordinate) during the 64 h of total sleep deprivation. Process S is reversed (see right-hand ordinate) to facilitate comparison with the empirical data. The bottom panel shows the two-process model predictions \hat{y} for the data in the top panel, under the null hypothesis of eqn 1, after estimation of the parameter γ in eqn 6. The curves in the bottom panel display the results using three different functions mapping the predictions P of eqn 6 onto the measurements y : f_2 (thick line), f_3 (dotted line) and f_4 (thin line). Using Akaike's Information Criterion (AIC; Akaike, 1973), f_2 (thick line) was selected as the most suitable mapping function. Goodness of fit for f_2 was similar to that for f_3 and f_4 , but f_2 required the least (i.e. $m = 2$) parameters to be estimated.

an appropriate statistical criterion such as Akaike's Information Criterion (AIC; Akaike, 1973). In the simplest possible case, the mapping function would be linear, which means that $m = 2$ and f is given by:

$$f_2(x) = \theta_1 + \theta_2 x. \tag{2}$$

Commonly used metrics have floor and/or ceiling effects, however, which could require mapping functions with more than two parameters. Generic *monotonic* functions with $m = 3$ parameters (either a floor or a ceiling effect; exponential) or $m = 4$ parameters (both a floor and a ceiling effect; sigmoidal) can be formulated as:

$$f_3(x) = \theta_1 + \theta_3 e^{\theta_2 x}, \tag{3}$$

$$f_4(x) = \theta_1 + \frac{\theta_4}{1 + \theta_3 e^{\theta_2 x}}. \tag{4}$$

We estimated γ , taking into account any inter-individual differences therein, to assess the relative contributions of the homeostatic and circadian processes for predicting psychomotor vigilance. Simultaneously, we estimated m and Θ_m , allowing for inter-individual differences in baseline performance levels, to identify the most suitable function mapping the

predictions of the two-process model onto the psychomotor vigilance measurements. Under the null hypothesis of eqn 1, we therefore considered the following set of mixed-effects regression models (Davidian and Gallant, 1993) for $m = 2,3,4$ (assuming independent, normally distributed noise in the data):

$$y \sim f_m(P) + \beta_i, \tag{5}$$

where P represents the two-process model predictions:

$$P = S - \gamma_i \cdot C. \tag{6}$$

Here γ_i (for $i = 1, \dots, 13$) is the subject-specific contribution of the circadian process relative to the homeostatic process, implemented as a normally distributed random effect with mean γ and standard deviation σ ; and β_i represents inter-individual variability in performance levels, implemented as a log-normally distributed random effect with mean zero and standard deviation ω . The covariance between these two random effects was assumed to be zero, as it is usually not estimable for small populations. Note that the results of this analysis do not critically depend on *a priori* assumptions about the distributions of the random effects (Olofsen *et al.*, 2003).

The computer algorithm Proc NLMIXED in SAS release 8.2 (Wolfinger, 2000) was employed to estimate the parameters Θ_m , γ , σ and ω of the mixed-effects models in eqn 5. To choose the mapping function f_m , the AIC was used; smaller AIC values correspond to better mapping functions in terms of both goodness of fit and parsimony. We found that for $m = 2$, AIC = 776.3; for $m = 3$, AIC = 805.9; and for $m = 4$, AIC = 777.6. Thus, under the null hypothesis of eqn 1, the linear function f_2 (i.e. $m = 2$) was identified to best describe the relationship between the predictions of the two-process model and the psychomotor vigilance data; see Fig. 1 (bottom panel). The contribution of the circadian process relative to the homeostatic process, for $m = 2$, was $\gamma = 1.6 \pm 0.3$ with standard deviation $\sigma = 0.6 \pm 0.4$ (estimates \pm standard error).

These analyses were repeated leaving out the first measurement during the sleep deprivation period, taken 30 min after awakening (at 08:00 hours). The reason for leaving out this data point is that it might have been confounded by sleep inertia – the transient performance impairment frequently observed immediately after awakening (Dinges *et al.*, 1981) – which falls outside the predictive capability of the two-process model. Sleep inertia may take up to approximately 2 h to dissipate (Achermann *et al.*, 1995; Jewett *et al.*, 1999); leaving out the first data point for each subject should therefore remove any sleep inertia effects from the data set. Nevertheless, we found essentially the same results with or without the first data point. The linear function f_2 was again the most suitable mapping function (i.e. it had the lowest AIC value). Also, the parameter estimates were again $\gamma = 1.6 \pm 0.3$ and $\sigma = 0.6 \pm 0.4$.

Null hypothesis testing

Under the null hypothesis of eqn 1, which states that the processes S and C are strictly additive in modelling the data y , the relationship between the predictions P of eqn 6 and the measurements y should be independent of the separate values of S and C . If there is a non-linear interaction between the two processes, however, we should expect that the relationship between the predictions P and the measurements y is modulated by the underlying values of S and C . Thus, after having assessed the relative contributions of the homeostatic and circadian processes by estimating γ , different combinations of values for S and C can be selected that yield the *same* values for P in eqn 6. As these P values would be affected in the *same* manner by any metric non-linearity – if the null hypothesis holds true – they should map to the *same* values of y (aside from random measurement noise). This consequence of the null hypothesis can be tested to examine if the null hypothesis is to be rejected.

Fig. 2 shows the subject-specific values of $\gamma_i \cdot C$ plotted against the values of S for all times of measurement during the 64 h of sleep deprivation. We wrote an optimization computer program to identify two *different* sets A and B of S values and associated $\gamma_i \cdot C$ values – with all subjects contributing multiple data points to each set – that yielded *similar* P values

in a moderately restricted range. The core steps of the computer program were as follows (in symbolic language):

Scan a range of different sizes d for possible sets A and B (in small steps):

Scan a range of different lowest boundaries s for process

S (in small steps):

Scan a range of different lowest boundaries c for $\gamma_i \cdot C$

(in small steps):

For each subject i compute the number of data points a_i in

set A, counting only $s < S < s + d/2$ and $c < \gamma_i \cdot C < c + d/2$;

For each subject i compute the number of data points b_i

in set B, counting only $s + d/2 < S < s + d$ and

$c + d/2 < \gamma_i \cdot C < c + d$;

Compute the product q of the a_i and b_i values across all subjects i .

Let Q be the greatest q value among all different combinations of d , s and c .

The values of d , s and c corresponding with Q define the selected sets A and B.

The two sets A and B thus identified are shown in Fig. 2 as shaded areas. The lower left shaded area (set A) is described by $0.70 < S < 0.85$ and $0.03 < \gamma_i \cdot C < 0.18$; using eqn 6, this yields $0.52 < P < 0.82$. The upper right shaded area (set B) is described by $0.85 < S < 1.00$ and $0.18 < \gamma_i \cdot C < 0.33$; this also yields $0.52 < P < 0.82$.

The similarity of the ranges of P values in sets A and B ($F_{1,101} = 0.11$, $p = 0.74$) was crucial for testing the existence of a non-linear interaction term, because it followed that – under the null hypothesis – the corresponding data y were affected in the same manner by any metric non-linearity. Thus, although sets A and B comprised only 115 (56 in set A and 59 in set B)

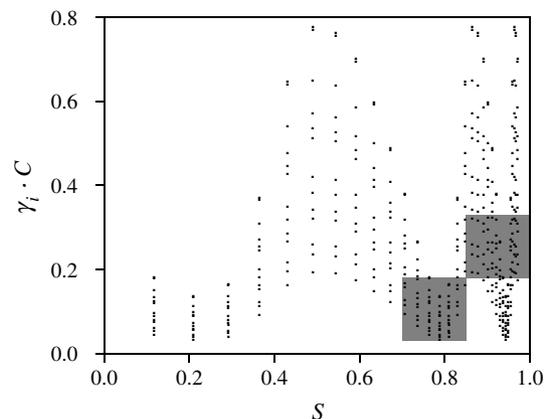


Figure 2. Subject-specific $\gamma_i \cdot C$ values plotted against S values, with S and C predicted by the two-process model for the 32 time points associated with empirical data during the 64 h of sleep deprivation. Thus, each of the $n = 13$ subjects contributed 32 points to the figure, with each point corresponding to a different time in the experiment; these points are plotted at the predicted S (abscissa) and $\gamma_i \cdot C$ (ordinate) values for those times. The two shaded areas contain different sets of predictions for S and $\gamma_i \cdot C$, yielding similar ranges of P values in eqn 6. Each subject contributed multiple points to the lower left shaded area, which is referred to here as set A, and the upper right shaded area, which is referred to here as set B.

of a total of 416 data points (i.e. 28% of the whole data set), they constituted a selected subset of data suitable² for testing the null hypothesis that the processes *S* and *C* are strictly additive in modelling the data *y*. Note that data points potentially affected by sleep inertia (see above) were not included in sets A and B.

Under the null hypothesis, the relationship between the predictions *P* and the measurements *y* should be independent of the underlying values of *S* and *C*. As the range of *P* values in sets A and B was similar (by design), this implies that the range of corresponding *y* values should also be similar. Fig. 3 shows the *P* values and associated *y* values in sets A and B. Direct statistical comparison of the (subject-specific) *y* values in sets A and B did not conclusively demonstrate if the *y* values in the two sets were indeed similar ($F_{1,101} = 3.45, p = 0.066$). It is difficult to interpret the result of this comparison anyway, however, as the values for *P* were not *exactly* the same for

sets A and B; thus, we should not expect the corresponding values for *y* to be *exactly* the same for the two sets either, whether the null hypothesis is true or not. At the least, though, the relationship between *P* and *y*, which we had found to be well described by a linear function f_2 , should be identical for both sets if the null hypothesis is true. We tested this with the following mixed-effects regression model, which was derived from eqn 5 with $m = 2$:

$$y \sim I_A \cdot f_A(P) + I_B \cdot f_B(P) + \beta_i, \quad (7)$$

where I_A and I_B are indicator variables that equal unity if the data *y* are from sets A and B, respectively, and zero otherwise; and β_i represents inter-individual variability as in eqn 5. The functions f_A and f_B were mapping functions f_2 with newly estimated parameters Θ_A and Θ_B representing the relationship between *P* and *y* for sets A and B, respectively. Examining the null hypothesis that the processes *S* and *C* are strictly additive in modelling the data *y* was thus reduced to considering the following null and alternative hypotheses:

$$\begin{aligned} H_0: & \Theta_A = \Theta_B, \\ H_a: & \Theta_A \neq \Theta_B. \end{aligned}$$

The computer algorithm Proc. NL MIXED in SAS release 8.2 was again used to estimate the parameters of the model, and to statistically test H_0 . The parameter estimates for θ_1 and θ_2 constituting Θ_A and Θ_B are shown in Table 1; statistical testing revealed differences for set A vs. set B in both parameters. The overall statistical test for Θ_A vs. Θ_B corroborated this finding ($F_{2,12} = 4.55, p = 0.034$). Thus, H_0 was rejected in favour of H_a . This directly implied the existence of an actual non-linear interaction between processes *S* and *C* for the prediction of waking neurobehavioural performance, irrespective of the characteristics of the metric we used to examine this.

DISCUSSION

The two-process model was originally developed as a model of sleep regulation, but its use has gradually been expanded to include prediction of human waking alertness and performance (Borbély and Achermann, 1999). This has typically been performed by (linear) addition of the homeostatic process *S* and the circadian process *C* (Achermann and Borbély, 1994), but in data from a forced desynchrony study evidence was found of the need for a non-linear interaction term (Dijk *et al.* 1992). A debate ensued about whether this apparent non-linear interaction was merely an artefact resulting from non-linearity

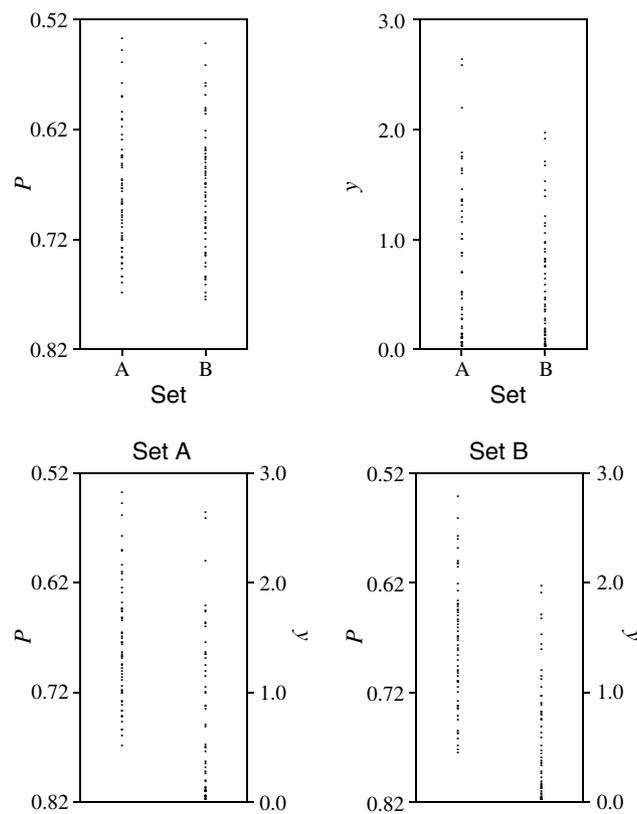


Figure 3. Two-process model predictions *P* under the null hypothesis of strict additivity between processes *S* and *C* as in eqn 6 (top left-hand panel), and observations *y* for the average of the reciprocals of the 10% slowest reaction times ($1/RT$; in $1/s$ units) on a 10 minute psychomotor vigilance task (top right-hand panel), in sets A and B. These two sets were selected to have similar *P* values but different underlying values for processes *S* and *C*; each subject contributed multiple data points to sets A and B. The relationship between *P* and *y* values should be identical for set A, and for set B if the null hypothesis is true. The *P* and *y* values are juxtaposed in the bottom panels (set A: bottom left-hand panel; set B: bottom right-hand panel), with *P* values on the left and *y* values on the right in both panels. All *P* ordinates are reversed to facilitate comparison with the *y* ordinates (lesser *P* values should correspond to greater *y* values).

Table 1 Estimates \pm standard errors of eqn 2 parameters θ_1 (offset) and θ_2 (slope) for sets A and B (i.e. constituting Θ_A and Θ_B), and *F* statistics and *p* values comparing sets A and B to test the null hypothesis that the processes *S* and *C* are strictly additive in modelling the data *y*

	Θ_A	Θ_B	$F_{1,12}$	<i>p</i>
θ_1	0.39 ± 0.77	2.60 ± 0.76	4.82	0.049
θ_2	0.86 ± 1.08	-2.63 ± 1.07	5.56	0.036

in the metrics used to measure alertness or performance, or constituted an actual non-linear interaction between the homeostatic and circadian processes (Achermann, 1999; Dijk *et al.*, 1999).

To investigate this controversy, we studied psychomotor vigilance measurements collected during a laboratory experiment involving 64 h of total sleep deprivation. We considered the null hypothesis of a strictly additive (linear) interaction between process *S* and process *C*, and identified time points at which the addition of the two processes led to similar predictions for psychomotor vigilance while the separate underlying values of *S* and *C* were different. By means of within-subject statistical testing (allowing for inter-individual differences), we then showed that the similarity of the predictions was not consistent with the observations, indicating that there was an actual non-linear interaction between the two processes *S* and *C* when used to predict waking neurobehavioural performance. This result is in line with recent findings in hamsters (Antle *et al.*, 2001) and mice (Sigworth and Rea, 2003) that adenosine (a putative sleep homeostatic signal) may affect the suprachiasmatic nuclei (site of the circadian pacemaker), which could well result in a non-linear interaction between the homeostatic and circadian processes. Whether or not our finding of non-linear interaction is dependent on the specific metric *y* we used (Dijk *et al.*, 1999), or conditional to the experimental context (i.e. total sleep deprivation in a laboratory), remains to be determined.

Further research is needed to assess the precise mathematical form of the non-linear interaction term exposed in the study. This may reveal whether process *S* modulates process *C*, or vice versa, or both (see Achermann, 1999), and whether or not the mode and duration of waking activity (e.g. cognitive testing in a laboratory) are contributing factors. It is important to recognize, however, that misspecification of the model presently used to predict waking function may have resulted in the rejection of the null hypothesis; that is, the current evidence of a non-linear interaction between processes *S* and *C* could also point to an incorrect formulation of the two-process model with regard to prediction of waking function. Such model misspecification could stem from an inaccurate definition of the shape of the circadian process, for instance, which is an issue that has been revisited from time to time (e.g. Achermann and Borbély, 1994). There could also be an additional, as yet unidentified regulatory process for waking neurobehavioural function accumulating over time, which may result in the mere appearance of a non-linear interaction term during total sleep deprivation (irrespective of the non-linear metric debate). Results from a laboratory experiment involving 14 days of chronic sleep restriction have suggested the existence of such a novel process (Van Dongen and Dinges, 2002; Van Dongen *et al.*, 2003b).

In the total sleep deprivation experiment of the present paper, although the variable time was not directly involved in the data analyses, a non-linear interaction between processes *S* and *C* cannot be unequivocally distinguished from any additional regulatory process for waking function varying

with time, because process *S* also built up continuously over time. Data from forced desynchrony or ultradian sleep–wake cycle paradigms, which provide a systematic scanning across many combinations of different states of the processes *S* and *C* – neither of which varies monotonically over time in these paradigms – will be useful to resolve this matter. New studies employing these paradigms with neurobehavioural measurements scheduled at predetermined times *a priori* predicted to yield identical *P* values (rather than nearly identical *P* values as in the present study) with different underlying values of *S* and *C* could enhance the precision of such inquiries. Whether using existing or newly acquired data, though, those investigations will inform the further development of biomathematical models for the prediction of temporal changes in alertness and performance (Van Dongen, 2003). This may ultimately result in reliable tools for anticipating neurobehavioural incapacitation as a result of sleep loss and/or circadian misalignment.

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¹ The term ‘non-linear interaction’ refers to a non-additive combination of the two processes (e.g. multiplicative). From a statistical perspective, it is sufficient to call this an ‘interaction’; the adjective ‘non-linear’ specifies a particular type of interaction which is not necessarily what is meant here. Nevertheless, we used ‘non-linear interaction’ in this paper, because it is commonly used terminology in the context of the two-process model of sleep regulation.

² Statistical tests in the framework of mixed-effects regression models derive statistical power primarily from the number of subjects ($n = 13$) rather than the number of data points per subject.