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Original Article

ORIGINAL ARTICLE

Response to chronic sleep restriction, extension, and subsequent total sleep deprivation in humans: adaptation or preserved sleep homeostasis?

Jelena Skorucak[1,2,3,†], Emma L. Arbon[4,†], Derk-Jan Dijk[4,‡] and Peter Achermann[1,2,3,‡,*]

[1]Institute of Pharmacology and Toxicology, University of Zurich, Zurich, Switzerland, [2]Neuroscience Center Zurich, University of Zurich and ETH Zurich, Zurich, Switzerland, [3]Zurich Center for Interdisciplinary Sleep Research, University of Zurich, Zurich, Switzerland and [4]Surrey Sleep Research Centre, University of Surrey, Guildford, United Kingdom

*Corresponding author. Peter Achermann, Institute of Pharmacology and Toxicology, University of Zurich, Winterthurerstrasse 190, 8057 Zurich, Switzerland. Email: acherman@pharma.uzh.ch.
†These authors contributed equally to this work.
‡Shared last authorship.

Abstract

Sleep is regulated by a homeostatic process which in the two-process model of human sleep regulation is represented by electroencephalogram slow-wave activity (SWA). Many studies of acute manipulation of wake duration have confirmed the precise homeostatic regulation of SWA in rodents and humans. However, some chronic sleep restriction studies in rodents show that the sleep homeostatic response, as indexed by SWA, is absent or diminishes suggesting adaptation occurs. Here, we investigate the response to 7 days of sleep restriction (6 hr time in bed) and extension (10 hr time in bed) as well as the response to subsequent total sleep deprivation in 35 healthy participants in a cross-over design. The homeostatic response was quantified by analyzing sleep structure and SWA measures. Sleep restriction resulted primarily in a reduction of rapid eye movement (REM) sleep. SWA and accumulated SWA (slow-wave energy, SWE) were not much affected by sleep extension/restriction. The SWA responses did not diminish significantly in the course of the intervention and did not deviate significantly from the predictions of the two-process model. The response to total sleep deprivation consisted of an increase in SWA and rise rate of SWA and SWE and did not differ between the two conditions. The data show that changes in sleep duration within an ecologically relevant range have a marked effect on REM sleep and that SWA responds in accordance with predictions based on a saturating exponential increase during wake and an exponential decline in sleep of homeostatic sleep pressure during both chronic sleep restriction and extension.

Statement of Significance

Both chronic short and long sleep are associated with negative health consequences. It is therefore important to understand sleep regulation during sleep restriction and extension. Sleep homeostasis refers to the sleep–wake dependent aspect of sleep regulation and slow-wave sleep is often considered of particular importance. We observed that 1 week of sleep restriction primarily leads to deficits in rapid eye movement sleep while slow-wave activity is little affected throughout the week long sleep restriction and sleep extension in accordance with predictions of the two-process model. The data imply that there is no significant adaptation to insufficient or excessive sleep.

Key words: chronic sleep restriction; chronic sleep extension; sleep deprivation; homeostasis; allostasis; Process S; simulations; adaptation

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Introduction

Altered sleep patterns such as short, long, irregular, and mistimed sleep are all implicated in a variety of adverse health conditions [1, 2]. Chronically restricted sleep is probably the most widely cited condition associated with negative health consequences, but long self-reported sleep duration also increases the risk of conditions such as type 2 diabetes, cardiovascular disease, and increased risk of all-cause mortality [2–4]. In addition, laboratory studies of altered sleep duration have documented changes in waking performance, primarily in response to sleep restriction [5, 6]. It is therefore relevant to investigate how sleep is affected and regulated under such conditions. A question of particular interest is whether sleep regulatory processes adapt to restricted or extended sleep opportunities. According to the two-process model of sleep regulation, sleep is regulated by a circadian process and a homeostatic process, and slow-wave sleep (SWS) or slow-wave activity (SWA) is thought to be reflecting the homeostatic process. This process depends on the duration of waking and sleep. The homeostatic process has been described by a saturating exponential increase during wakefulness and exponential decrease during sleep. The parameters of the exponential functions were estimated from electroencephalogram (EEG) SWA, defined as the EEG power between 0.75 and 4.5 Hz in nonrapid eye movement (NREM) sleep at baseline and after total sleep deprivation [7–10]. Many studies of acute manipulation of wake duration have confirmed the precise homeostatic regulation of SWA in accordance with the saturation exponential increase and exponential decrease of sleep pressure during wakefulness and sleep, respectively, in rodents and humans [11–13]. It is assumed that the parameters of these exponential functions are invariant to the history of sleep and wakefulness, i.e. adaptation to chronically restricted or extended sleep does not occur and the effects of acute sleep deprivation do not depend on prior sleep history [7–9].

In humans, the effects of repeated sleep restriction on SWA has been investigated for restriction periods ranging from 2 to 14 days [5, 14–17]. In these studies, sleep opportunity was 4 hr per night [14–16], 5 hr per night [17], and 4, 6, or 8 hr per night [5], and in most of these experiments, a homeostatic response in SWA was observed. The response to sleep restriction stabilizes quickly [5, 18], which is in accordance with the exponential parameters of the homeostatic process in the two-process model. In fact, in 2 to 4 day restriction experiments in which the sleep opportunity was 4 hr, the SWA response to sleep restriction did not deviate significantly from the predictions from the two-process model of sleep regulation [14, 15]. It is however unknown how the homeostatic responses develop during longer sleep restriction and quantitative analyses of the time course of SWA in various EEG derivations, and comparisons with the predictions of the two-process model during chronic sleep extension are not available.

Sleep restriction studies in animals have yielded heterogeneous results. In a study by Leemburg et al. in which rats were sleep restricted for 5 days (4 hr sleep opportunity and 20 hr sleep restriction during the day), SWA increased above baseline levels throughout the restriction period [19]. This is in agreement with the homeostatic regulation of NREM sleep during sleep restriction. However, in this study, it was also shown that the SWA response is derivation dependent (no increase in the occipital derivation). In another study of Deurveilher et al., rats were chronically sleep restricted (4 days of 3 hr of sleep deprivation followed by 1 hr of sleep opportunity repeated over 24 hr) [20]. SWA increased initially, but then gradually declined during the following protocol days while staying above baseline values during the entire protocol. This time course was interpreted as evidence for homeostatic regulation and adaptation or allostasis. Within this context, allostasis refers to an adaptive response to a change in an environment, which maintains stability through physiological or behavioral changes [21]. Other animal studies reported an initial increase in SWA after which SWA values were maintained at or fell below baseline [22, 23]. This attenuated or missing homeostatic response to sleep restriction was implicitly assumed to reflect an allostatic response [20, 22, 23]. Whether this interpretation is in line with the original definition of allostasis can be discussed (see Discussion) [21, 24]. These animal studies and the paucity of quantitative comparisons of data and model predictions in human studies led us to revisit sleep homeostasis during chronic changes in sleep opportunity. We not only investigated sleep restriction but also sleep extension.

Sleep extension studies in humans have been reported to lead to an increase in sleep latency, an increase in total sleep time (TST), and a reduction in sleep efficiency, as well as to increased waking towards the end of the night [25, 26]. In these studies, SWS and SWA appear to follow a homeostatic response but quantitative comparisons with predictions of the two-process model of sleep regulation have not been reported. Comparable animal studies on the effect of sleep extension on sleep structure are not available although variations in TST per 24 hr can be induced by varying access to a running wheel [27, 28].

One other aspect of sleep homeostasis which is rarely investigated is how the response to acute total sleep deprivation depends on initial conditions, i.e. prior sleep history. Studies investigating the effects of acute total sleep deprivation on cognitive performance have indicated that the sleep loss–related deterioration of cognitive performance during acute total sleep loss depends on prior sleep history. Thus, prior sleep extension (sleep banking) attenuates the negative effects of sleep loss on performance [29], whereas sleep restriction exacerbates these effects [6, 30, 31]. However, how and whether prior sleep history affects the changes in sleep structure and SWA induced by total sleep deprivation has not been studied extensively.

Discussions about sleep homeostasis and accuracy of model predictions, etc., are marred by the use of various markers/measures for sleep homeostasis. Thus, discrepancies in the data and divergent interpretations of the data may be related to the measure used for quantifying the homeostatic process and the homeostatic response. SWS is a measure of time in deep sleep. SWA is an intensity (or density) measure describing slow waves (amplitude squared) per time unit. Slow-wave energy (SWE) is the product of time in NREM sleep and SWA (cumulative SWA, i.e. how much SWA was obtained in a sleep period). One additional measure that has been used to describe changes in the homeostatic (NREM) process is the rise rate of SWA in the initial part of NREM episodes. All these measures describe slightly different aspects of the homeostatic process but are rarely all presented and their interpretation within the context of sleep homeostasis is sometimes opaque. Although sleep homeostasis in the two-process model is often related to SWA, other aspects of sleep, such as REM sleep and sleep continuity, are also affected by sleep restriction or extension [15, 32], and we therefore report some of these measures as well. Sample

sizes in many of the published human and animal sleep restriction studies were rather small which may also contribute to the reported discrepancies.

In this study, we investigated sleep regulation in humans undergoing 7 days of sleep restriction and 7 days of sleep extension in 35 participants. Both conditions were followed by total sleep deprivation. Several markers of sleep homeostasis were quantified, some of which were compared with predictions of the two-process model of sleep regulation [11, 12, 14, 16, 33, 34]. We aimed to test whether adaptation to the imposed conditions occurred and whether this resulted in deviations from predictions based on a sleep homeostasis model. Thus, to facilitate the interpretation, empirical data were compared with model predictions of the homeostatic process.

Methods

Study protocol

The study was conducted at the Surrey Sleep Research Centre of the University of Surrey. The study protocol was approved by the Institutional Review Board of the Air Force Research Laboratory, United Kingdom and was also reviewed by the University of Surrey Ethics Committee.

The study was conducted according to a single-center, two-way crossover design with two laboratory sessions: sleep restriction and extension. Each participant took part in both laboratory sessions in randomized order, and each session was separated by a minimum of 10 days. Each laboratory session lasted 11 days and consisted of a habituation night (8 hr), a baseline night (8 hr), seven condition nights of either restricted (6 hr) or extended (10 hr) sleep opportunities, followed by a ~40 hr total sleep deprivation period under constant routine conditions (Figure 1), and ended with recovery sleep (12 hr sleep opportunity). At night, participants slept in windowless, sound attenuated, temperature controlled rooms and during the day participants remained within the unit.

A total of 36 individuals were selected to participate in the laboratory study (see Supplementary Table S1 for demographics), out of which one participant withdrew from the restriction condition session and was excluded from the analysis, resulting in 35 participants. Depending on artifacts and sleep measures (see below), 25–35 participants contributed to the results presented here, and the number of participants contributing to a particular analysis is provided in figure and table legends and in Supplementary Table S3.

Participants were in good health, were not taking any medication (except oral contraceptives), were nonsmokers, did not consume more than five caffeinated beverages per day (< approximately 500 mg of caffeine), did not consume more than 14 units of alcohol per week, did not suffer from any self-reported sleep disorders or sleep complaints such as apnea or insomnia, were not shift workers, and had not travelled across more than one time zone in the 2 months preceding the laboratory phase.

For 3 weeks prior to the laboratory phase and for the duration of the study, participants were asked to refrain from all medications and recreational drugs. For 3 days prior to each laboratory session, participants were asked to refrain from alcohol, chocolate, food supplements, and strenuous exercise. Medical screening was carried out approximately 1 week before admission to the center and on the day of admission in order to assess general physical health and to perform toxicological screening of blood and urine samples. A pregnancy test was also required for female participants.

Participants were asked to wear an actiwatch (Actiwatch-L or Actiwatch 4, Cambridge Neurotechnology Ltd., Cambridge, UK) on their wrist for 2 weeks prior to the first admission to the center. The first week of actigraphy data was used to determine an average habitual sleep–wake schedule for each participant.

During the second week of actigraphy, participants were requested to maintain their calculated average sleep–wake schedule and a deviation of more than 30 min twice in the week preceding the laboratory session would result in that participant being replaced with a reserve. Participants were required to wear the actiwatch for 1 week prior to the second admission to the center and were required to sleep at their calculated average sleep–wake schedule, unless there was a particularly long time period between the two visits (>4 weeks), in which case participants' habitual sleep–wake schedule was reassessed, and therefore, two full weeks of actigraphy were required. Participants were also asked to complete the Karolinska Sleep Diary [35] on a daily basis for approximately 2 weeks prior to each admission to the center.

A buccal swab was obtained from each participant to determine their PER3 genotype. The buccal swabs were processed by extracting the cells from the swabs, performing a polymerase chain reaction (PCR) protocol to extract the DNA and then running the DNA in an electrophoresis gel, the exact procedures are those previously described variants of the genotype including homozygosity for the 4-repeat allele ($PER3^{4/4}$), homozygosity for the 5-repeat allele ($PER3^{5/5}$), or a heterozygous genotype ($PER3^{4/5}$). For details, see Ref. 6.

Sleep schedule and polysomnographic recordings

The individual sleep–wake schedule was calculated by taking each participant's habitual sleep time midpoint and calculating 4 hr either side to determine the individual 8 hr sleep opportunity. Sleep was restricted by removing 1 hr from either side of their calculated sleep period and extended by adding 1 hr either

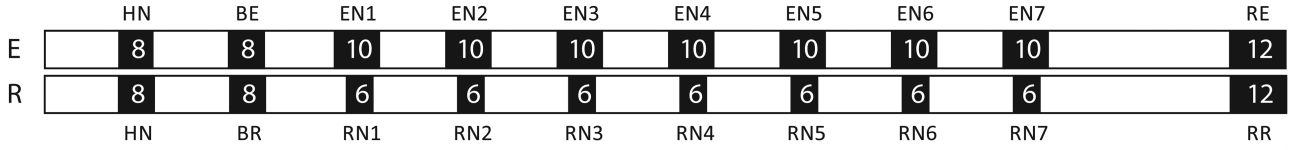

Figure 1. Study protocol. Each subject participated in two laboratory sessions: sleep restriction and extension, in randomized order. Each session consisted of habituation night (HN, 8 hr of sleep opportunity), baseline night (BE or BR, 8 hr of sleep opportunity), 7 condition nights (sleep extension EN1–EN7 with 10 hr of sleep opportunity; sleep restriction RN1–RN7 with 6 hr of sleep opportunity), followed by ~ 40 hr of total sleep deprivation during a constant routine, and a recovery night (RE or RR; 12 hr of sleep opportunity). EN1–EN7 or RN1–RN7 are numbered 1–7 in the figures.

side of their calculated sleep periods. The timing of the midpoint of extended and restricted sleep opportunities was scheduled according to the participants' habitual sleep schedule. Following the week of sleep restriction and sleep extension, participants underwent total sleep deprivation under constant routine conditions (see Ref. 6). Total sleep deprivation lasted 39 hr after sleep extension, and 41 hr following sleep restriction. Total sleep deprivation was followed by 12 hr recovery sleep, starting at participants' habitual time (same clock time as in baseline). During all wake episodes, participants completed a battery of performance tests and these results have been reported elsewhere [6].

Polysomnographic (PSG) measures comprising the EEG (frontal, central, parietal, and occipital derivations referenced to contralateral mastoids), electromyogram (EMG), electrooculogram (EOG), and electrocardiogram (ECG) were recorded. EEG electrodes were placed according to the internationally standardized 10–20 electrode placement system [36]. Impedance values were at or below 5 kΩ at the beginning of the recordings. PSG data were recorded using Siesta 802 devices (Compumedics Ltd., Abbotsford, Victoria, Australia). The sampling and storage rates were 256 Hz. The following filters were applied: a high-pass filter at 0.3 Hz, a low-pass filter at 70 Hz, and a notch filter at 50 Hz.

Data processing and signal analysis

Sleep EEG data were visually scored by experienced scorers in 30 s epochs according to the standard criteria. Artifacts within the EEG derivations were manually highlighted. If there was an artifact in a 30 s epoch, this epoch was excluded from the quantitative analysis of the corresponding derivation. In the case when less than 67 per cent of the data were available for one night (arbitrary threshold), that night was excluded from our analysis. The amount of available data was calculated as the number of epochs without artifacts from lights off until lights on, relative to the expected number of epochs for the corresponding study night. In case a baseline night had to be excluded, all other nights of this condition and derivation were also excluded. See Supplementary Table S3 for the number of participants included in the analyses.

All recordings were exported in European Data Format (EDF) and further analyzed in Matlab (The Math Works Inc., Natick, MA, USA).

Sleep latency and efficiency

Sleep latency was measured as the time from lights off until the first occurrence of stage 2 sleep. In two restriction nights, sleep onset REM sleep episodes occurred, and in these nights latency was measured until the first occurrence of REM sleep. In case the first occurrence of stage 2 lasting less than 6 min was followed by a wakefulness and stage 1 period longer than 30 min, the next occurrence of stage 2 was selected as sleep onset (occurred in 2 nights). Sleep efficiency was calculated as the number of epochs spent in sleep (NREM sleep: stages 1–4 and REM sleep) in the period from lights off until lights on, relative to the total number of epochs in that period.

Sleep structure, and cumulative curves, quantifying deficits, and rebounds

TST, time spent in sleep stages 1, 2, SWS, and REM sleep were calculated, as well as time spent awake after sleep onset (WASO). To quantify the deficit or surplus resulting from the restriction and extension protocol and the influence of prior sleep history on acute total sleep deprivation, cumulative differences from baseline of TST, SWS, and REM sleep were determined. These measures were obtained by cumulating the differences from baseline over the entire protocol. Missing values were interpolated by the average of the night prior to and the one following the missing night for condition nights (N1–N7). Recovery nights were not interpolated. A night of sleep that was skipped during total sleep deprivation was considered as a loss corresponding to the amount present during baseline (i.e. subtracting the baseline value).

Slow-wave activity, rise rate of slow-wave activity, and slow-wave energy

Spectral analysis of EEG channels was performed on consecutive 30 s epochs (FFT, Tukey window [r = 0.5], average of ten 4 s epochs overlapping by 1 s; matched with sleep stages), resulting in a 0.25 Hz frequency resolution.

SWA (power in the 0.75–4.5 Hz range) was determined for 30 s epochs. Average SWA is assumed to reflect the level of sleep pressure, but since SWA decreased during sleep, a unbiased comparison of sleep pressure between different conditions requires that the same number of NREM sleep epochs per night is included for the calculation of average SWA as a measure of NREM sleep pressure (i.e. the maximal number of NREM sleep epochs common to all nights, 331 epochs—2.8 hr [14, 16]). The data obtained from the left and right hemisphere were averaged. To obtain a standardized measure, SWA of each night was normalized with SWA of the corresponding baseline night.

Another possible measure reflecting the homeostatic process underlying SWS is the rate of the buildup of SWA (SWA rise rate) in the first NREM sleep episode [11, 37]. The SWA buildup was determined by measuring the rise rate of the smoothed SWA in the first NREM sleep episode (see Supplementary Methods and Supplementary Figure S1 for details). The rise rate was normalized to the rise rate of the corresponding baseline night.

To quantify the dissipation of sleep pressure during a night and to obtain a measure of total SWA produced, SWE was calculated as cumulative SWA [12, 38–40]. SWE was obtained by cumulating mean SWA of artifact-free NREM sleep epochs in 30 min segments multiplied by the number of NREM sleep epochs in that segment [34]. The values of SWE at the end of sleep are indicators of the level of dissipated sleep pressure during the night. The data obtained from the left and right hemisphere were averaged. They were normalized to the corresponding level at the baseline night.

Cumulative differences from baseline were calculated for SWE (relative data) in order to estimate the SWE deficit or excess at the end of the restriction and extension protocol, as well as after recovery sleep following total sleep deprivation. This was calculated by cumulating the difference from baseline (in baseline equivalents) over the protocol nights. Missing values were interpolated as described before. A night of sleep that was skipped during total sleep deprivation was considered to correspond to the baseline value (i.e. 1 was subtracted).

Simulations

To compare empirical data with predictions of two-process model of sleep regulation, we simulated Process S using the

average timing of sleep and average sleep duration across individuals of the extension and restriction conditions as well as of recovery sleep following total sleep deprivation (Figure 2). We applied the time constants and asymptotes estimated for C3A2 according to Rusterholz et al.: time constant of increase τ_i 19.9 hr, time constant of decrease τ_d 2.16 hr, upper asymptote *UA* 371%, and lower asymptote *LA* 40%.

SWA and SWE were also calculated from the simulations: SWE as the area under the curve (Process S) from sleep onset to sleep end, and SWA as the mean of Process S over the first 331 30 s epochs of sleep (Supplementary Figure S2). They were normalized to the corresponding values at baseline.

Statistical analysis

We applied five different models for statistical analysis, denoted as "large model," "small model," "simulation model," "derivation model," and "adaptation model." All five models were linear mixed-effect models, they were fitted by restricted maximum likelihood method, and type III sum of squares tests were used to estimate significance of the effects (procedure MIXED, IBM SPSS, version 23). The models included intercepts. The only random factor was "subject." An autoregressive first-order covariance matrix was used for repeated effects. Large and small models were also used for sleep variables derived from visual scoring. Scaled identity matrix was used for random effects. In all models, the effects of extension and restriction were evaluated separately from the effects of total sleep deprivation at the end of the protocol. All power values were log10 transformed, as were sleep latency, TST, and time in REM sleep. Cumulative differences from baseline in TST, time in SWS, time in REM sleep, and SWE were not transformed. In case *p*-values are not presented in the tables, they are indicated in the text. Mean values, standard errors of the mean, and 95% confidence intervals provided in the text, tables, and figures were calculated from the data (not from statistical models below).

Large model

Differences between conditions were assessed with this model (relative data). Repeated factors were condition (extension or restriction) and night (baseline nights, and either condition nights or recovery nights), whereas fixed factors were night, condition, order (first extension or restriction), and interactions condition*night and condition*order. The effects of order and condition*order interaction were assessed with this model, and since they were not significant, they were not considered in the reduced model ("small model").

Small model

The small model was constructed to evaluate extension and restriction condition separately (relative data) to test for differences to baseline. Night (baseline nights, and either condition nights or recovery nights) was a repeated and fixed factor. Post hoc analysis for the comparison of all condition nights with corresponding baseline nights was performed using Sidak correction for multiple comparisons. For the cumulative curves, post hoc tests were only performed for condition nights N7 and recovery nights.

Simulation model

Comparisons between empirical data and simulations (SWA and SWE) were performed by analyzing the difference of the relative values (normalized to baseline) between each subject's empirical value and the averaged simulated one (deviation from 0). This was

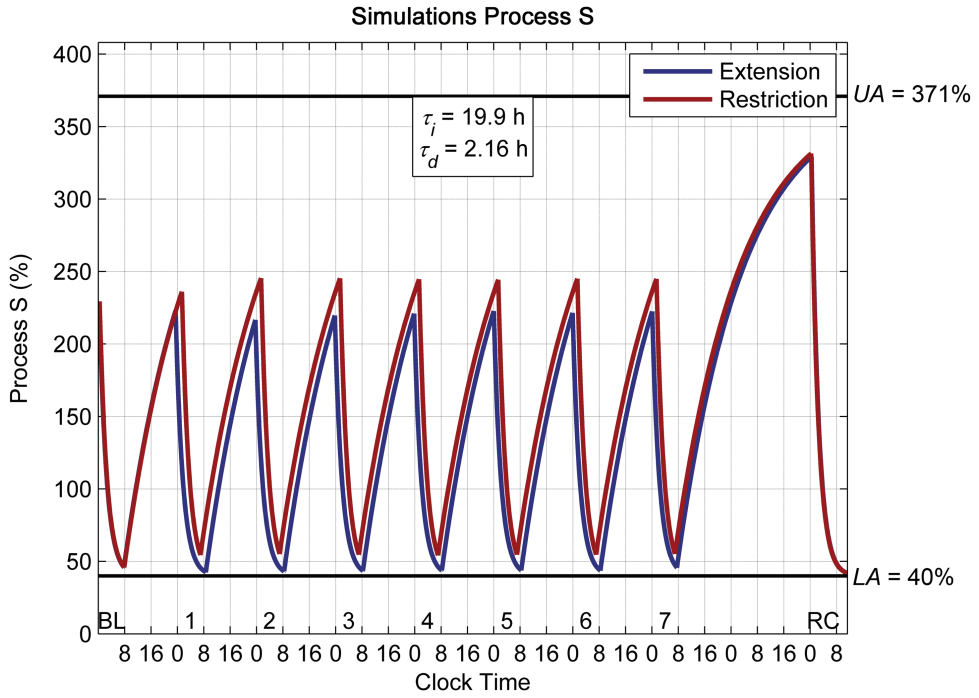

Figure 2. Simulation of Process S for baseline (BL: BE or BR), sleep extension (blue; EN1-EN7) and restriction (red; RN1-RN7) and recovery from total sleep deprivation (RC: RE or RR). Simulations were performed with average timing derived from the data: average time of falling asleep (lights off plus latency to fall asleep) and average duration of sleep for extension, restriction, and recovery sleep. Parameters for the simulation: time constant of increase τ_i 19.9 hr, time constant of decline τ_d 2.16 hr, upper asymptote *UA* 371%, and lower asymptote *LA* 40% [10]. Process S is scaled as in Rusterholz et al. [10].

first tested with a linear mixed model with the repeated and fixed factor night. If the effect of night was significant, a post hoc test was performed for each night (two-tailed *t*-test; difference data-simulations). For the cumulative curves (SWE), post hoc tests were only performed for condition nights N7 and recovery nights.

Derivation model

Differences between derivations were assessed separately for extension and restriction conditions (relative data). Repeated factors were night and derivation, and subject was a random factor. Fixed factors were derivation (frontal, central, and occipital), night, order (first extension or restriction session), and the interaction derivation*night. Post hoc analysis was performed with Sidak correction for multiple comparisons between different derivations.

Adaptation model

With this model, we tested deviations from the expected homeostatic response in three ways: (1) whether empirical data and predictions differ ("simulation model"); (2) whether deviations from the model predictions showed a consistent temporal evolution, i.e. increasing deviations with time ("simulation model" with experimental nights 2 to 7, post hoc testing); (3) whether the temporal evolution of the empirical homeostatic variables (SWA, SWE) showed a trend in their response to the challenge, i.e. a decreasing response over experimental nights ("small model" with experimental nights 2 to 7, post hoc testing). We excluded the baseline from the analyses as we were interested in the temporal change of the response and restricted the analyses to experimental nights 2 to 7 as the first night does not show a full response to the manipulation.

Results

Sleep variables derived from visual scoring

Sleep latency and sleep efficiency are depicted in Figure 3; TST, time in SWS (hr), and REM sleep (hr) in Figure 4; and further sleep variables derived from visual scoring in Table 1.

The employed protocol was effective as TST was different from baseline in both conditions in all extension and restriction nights, as well as during recovery nights, except for the last night of the extension condition (EN7; Figure 4 and Table 1). TST was increased in the extension protocol from 7.46 ± 0.1 hr in baseline to, e.g., 8.40 ± 0.1 hr in EN4 and decreased during sleep restriction from 7.48 ± 0.1 hr at baseline to, e.g., 5.76 ± 0.0 hr (RN4; Figure 4 and Table 1). The cumulative difference from baseline in TST after the last condition night (N7) differed between extension and restriction ($p < 0.001$) and reached a surplus of +6.75 hr during sleep extension ($p < 0.001$) and a deficit of −12.60 hr during sleep restriction ($p < 0.001$) which equates to +0.90 and −1.69 baseline equivalents, respectively. After recovery sleep following total sleep deprivation, the cumulative difference from baseline in TST differed between the two conditions ($p < 0.001$) and showed a deficit of −16.56 hr after RR (−2.21 baseline equivalents, $p < 0.001$), whereas it was close to baseline levels after RE.

During the extension protocol, sleep latency gradually increased from baseline (16.73 ± 1.9 min) to EN7 (61.25 ± 6.3 min), and reverted to baseline in recovery sleep (RE) (Figure 3; Table 1). During sleep restriction, sleep latency stayed at baseline levels (14.91 ± 2.1 min) and was below baseline in recovery sleep (RR, 9.60 ± 1.3 min).

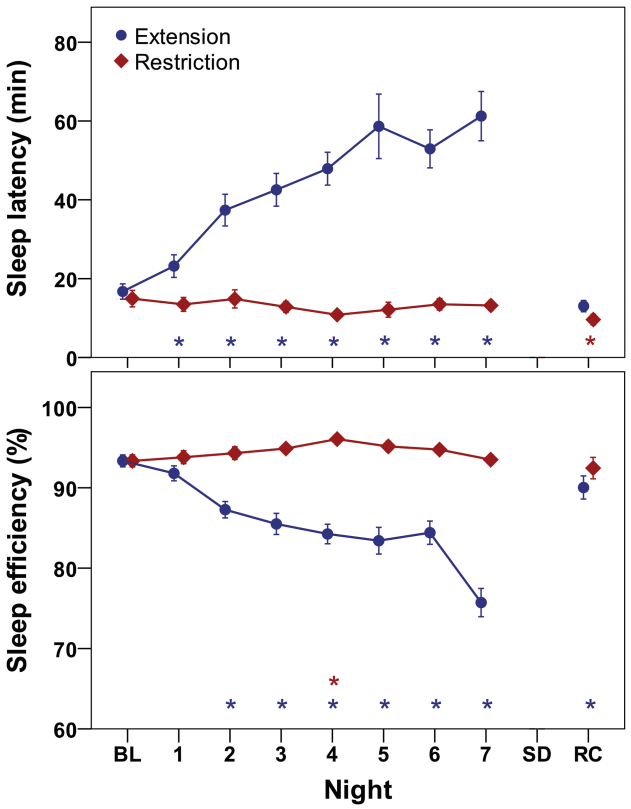

Figure 3. Sleep latency and sleep efficiency for sleep restriction (red) and extension (blue). Mean values ± SEM are shown (n = 32–35). Asterisks mark significant differences to the baseline (linear mixed model, post hoc comparison to baseline with Sidak correction for multiple comparisons, $p < 0.05$). n = 32–35 (E); n = 34–35 (R). BL = baseline; 1–7 = experimental conditions (extension or restriction); SD = total sleep deprivation; RC = recovery after 39 (E) and 41 hr (R) of prolonged wakefulness.

WASO was increased in the extension condition (EN2-EN7); it increased from 15.07 ± 2.9 min at baseline to 83.38 ± 10.0 min in EN7 (Table 1). During sleep restriction, WASO was decreased during RN2-RN6 (17.01 ± 3.0 min at baseline and 3.37 ± 0.5 min in RN4). During recovery nights after total sleep deprivation, WASO was increased in both conditions compared with baseline. However, one has to keep in mind that the sleep opportunity differed between the nights (BE, BR, EN, RN, RE, RR).

Sleep efficiency was decreased during sleep extension in EN2–EN7, decreasing from 93.35 ± 0.7% at baseline to 75.72 ± 1.8% in EN7 and remained below baseline at recovery (RE) (Figure 3; Table 1). In the restriction condition, sleep efficiency stayed at a similar level as at baseline (93.36 ± 0.7%) and increased only in RN4 (96.06 ± 0.3%), also remaining at baseline levels during recovery sleep (RR).

The percentage of time spent in sleep stage 1 (%TST) was increased during sleep extension in EN2, EN4, EN6 and decreased in RE. It was reduced during sleep restriction in RN2–RN7 and RR (Table 1). During sleep extension, the percentage of time spent in sleep stage 2 remained at baseline level (40.15 ± 1.0%) in all nights (EN1–EN7, RE). However, during sleep restriction stage 2 was reduced in RN1, RN3–RN6 (e.g. to 32.67 ± 1.3% in RN4) compared with 38.98 ± 1.2% at baseline, returning to baseline levels in RN7 and RR.

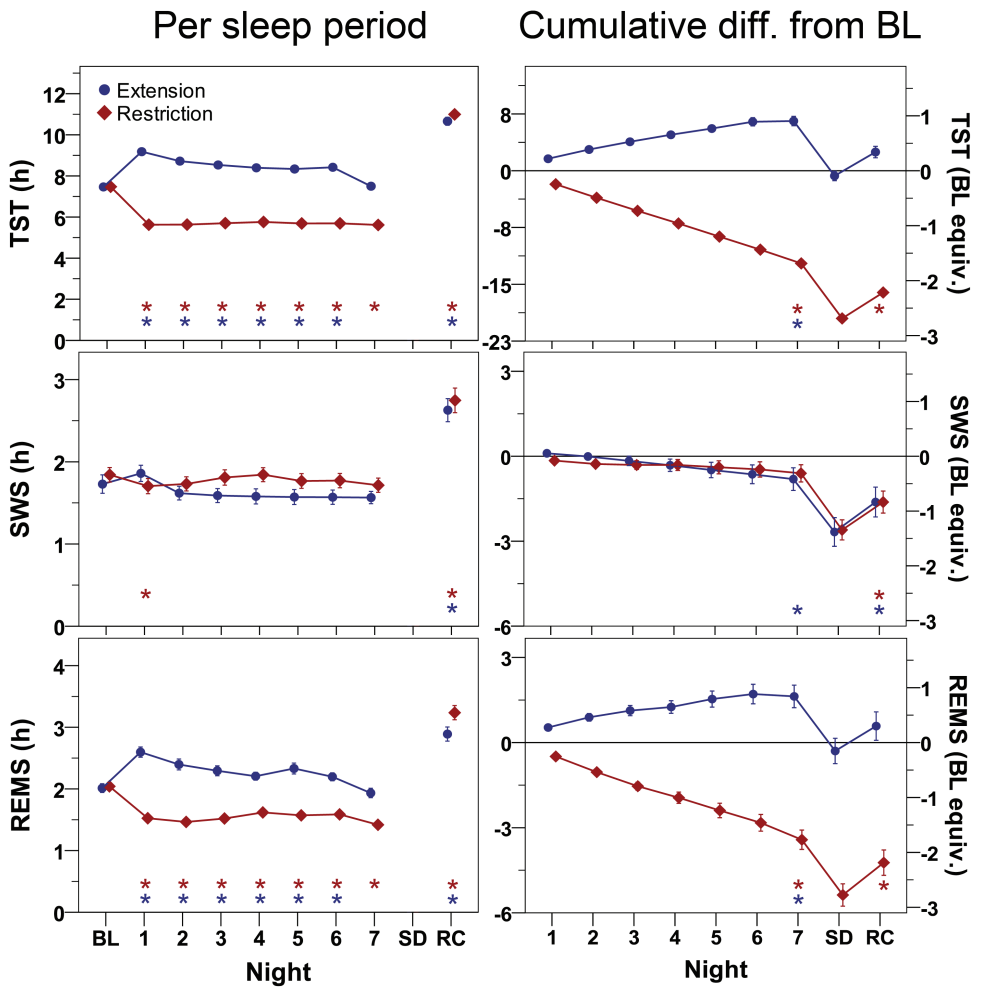

Figure 4. TST, time spent in SWS, and time spent in REM sleep (REMS) during the sleep period (left column), and cumulative difference from baseline (right column) for sleep restriction (red) and extension (blue). Mean values ± SEM (n = 32–35). The cumulative curves are displayed on two y-axes: as absolute values (h, left axis) and as relative values (right axis, baseline equivalent, i.e. –3 means a reduction of 3 times the baseline value). SEM relates to absolute values (left axis). Asterisks mark significant differences to the baseline (linear mixed model, post hoc comparison to baseline with Sidak correction for multiple comparisons, $p < 0.05$). n = 32–35 (E) and n = 34–35 (R) for TST, SWS, and REMS in hours; n = 33–35 (E) and n = 35 (R) for cumulative TST, SWS, and REMS. BL = baseline; 1–7 = experimental conditions (extension or restriction); SD = total sleep deprivation; RC = recovery after 39 (E) and 41 hr (R) of prolonged wakefulness.

The percentage of time spent in REM sleep (%TST) did not differ between the two conditions and did not differ from the baseline except for being increased in the recovery night of the restriction condition (RR, Table 1). However, total time spent in REM sleep differed from baseline; it was increased during sleep extension (EN1–EN6), from 2.01 ± 0.1 hr at baseline to, e.g., 2.21 ± 0.1 hr (EN4) and reduced during sleep restriction (RN1–RN7) from 2.04 ± 0.1 hr at baseline to, e.g., 1.62 ± 0.1 hr in RN4 (Figure 4). The cumulative difference from baseline in REM sleep was different between extension and restriction ($p < 0.001$), reaching an excess of +1.71 hr in extension (EN7, +0.85 baseline equivalents, $p = 0.003$) and a deficit of –3.59 hr in restriction (RN7, –1.76 baseline equivalents, $p < 0.001$). Total sleep deprivation resulted in increased REM sleep in both conditions. The cumulative difference from baseline in REM sleep after recovery sleep remained different between the conditions ($p < 0.001$), reaching baseline levels in extension, and a deficit of –4.43 hr (equivalent to a loss of –2.17 baseline equivalents) in restriction ($p < 0.001$, Figure 4).

The time spent in SWS as a percentage of TST decreased during sleep extension (EN1–EN6) from 23.09 ± 1.4% at baseline to a stable level of, e.g., 18.77 ± 1.0% in EN4, and it increased during sleep restriction (RN1–RN7), from 24.64 ± 1.2% in baseline to 31.95 ± 1.4% (RN4). It returned to baseline values in RR after total sleep deprivation and was elevated in RE (Table 1). A similar picture emerged when SWS was expressed as percentage of the first 331 epochs of NREM sleep with lower values in extension than restriction (Supplementary Table S2). Absolute time in SWS (hr) was different between extension and restriction with slightly lower values in extension and did not deviate from baseline during condition nights (except for being decreased in RN1) and was increased in recovery sleep during both conditions (not different between conditions). The cumulative difference from baseline in SWS did not differ between conditions, and there was a loss in SWS in both conditions (deficit of –0.74 hr, –0.43 baseline equivalents, $p = 0.014$, extension; –0.56 hr, –0.30 baseline equivalents, n.s., restriction; Figure 4, right column). After recovery sleep, the accumulated deficit in SWS was –1.49 hr in both extension (–0.86 baseline equivalents, $p = 0.001$) and restriction (–0.81 baseline equivalents, $p < 0.001$).

Table 1. Sleep variables derived from visual scoring (mean ± SEM; *n* = 32–35)

											Large model cond. nights			Large model RC		Small model	
		BL	1	2	3	4	5	6	7	RC	C	N	C*N	RC C	RC N	N	RC N
total sleep time (h)	E	7.46 ± 0.1	**9.18 ± 0.1**	**8.72 ± 0.1**	**8.53 ± 0.1**	**8.40 ± 0.1**	**8.34 ± 0.2**	**8.42 ± 0.1**	7.50 ± 0.2	**10.66 ± 0.2**	<0.001	<0.001	<0.001	n.s.	<0.001	<0.001	<0.001
	R	7.48 ± 0.1	**5.63 ± 0.0**	**5.63 ± 0.1**	**5.70 ± 0.0**	**5.76 ± 0.0**	**5.69 ± 0.0**	**5.69 ± 0.0**	**5.61 ± 0.0**	**11.00 ± 0.2**						<0.001	<0.001
sleep latency (min)	E	16.73 ± 1.9	**23.18 ± 2.9**	**37.39 ± 4.0**	**42.54 ± 4.2**	**47.89 ± 4.2**	**58.66 ± 8.2**	**52.94 ± 4.8**	**61.25 ± 6.3**	13.02 ± 1.4	<0.001	<0.001	<0.001	0.005	0.003	<0.001	n.s.
	R	14.91 ± 2.1	13.46 ± 1.8	14.84 ± 2.3	12.81 ± 1.4	10.81 ± 1.0	12.10 ± 1.9	13.49 ± 1.5	13.19 ± 1.3	**9.60 ± 1.3**						n.s.	0.006
WASO (min)	E	15.07 ± 2.9	26.02 ± 4.3	**38.43 ± 6.0**	**45.27 ± 7.9**	**46.05 ± 6.6**	**40.69 ± 8.0**	**40.30 ± 7.5**	**83.38 ± 10.0**	**57.97 ± 10.2**	<0.001	<0.001	<0.001	n.s.	<0.001	<0.001	<0.001
	R	17.01 ± 3.0	**8.60 ± 2.3**	**6.14 ± 1.7**	**5.61 ± 1.1**	**3.37 ± 0.5**	**5.31 ± 1.2**	**5.40 ± 0.9**	10.21 ± 1.7	**43.87 ± 9.3**						<0.001	0.005
sleep efficiency (%)	E	93.35 ± 0.7	91.80 ± 0.9	**87.28 ± 1.0**	**85.50 ± 1.3**	**84.25 ± 1.2**	**83.41 ± 1.7**	**84.42 ± 1.4**	**75.72 ± 1.8**	**90.04 ± 1.4**	<0.001	<0.001	<0.001	n.s.	n.s.	<0.001	0.017
	R	93.36 ± 0.7	93.81 ± 0.8	94.32 ± 0.8	94.89 ± 0.5	**96.06 ± 0.3**	95.15 ± 0.6	94.76 ± 0.5	93.50 ± 0.6	92.45 ± 1.3						0.006	n.s.
stage 1 (%TST)	E	9.92 ± 0.8	10.79 ± 0.7	**12.20 ± 0.6**	**12.09 ± 0.7**	**12.60 ± 0.7**	**11.89 ± 0.6**	**12.50 ± 0.7**	**11.86 ± 0.6**	**7.52 ± 0.4**	<0.001	n.s.	<0.001	n.s.	<0.001	0.002	0.004
	R	9.11 ± 0.6	8.33 ± 0.6	**7.49 ± 0.5**	**7.00 ± 0.4**	**7.25 ± 0.5**	**7.57 ± 0.5**	**7.00 ± 0.5**	**7.34 ± 0.5**	**6.32 ± 0.4**						<0.001	<0.001
stage2 (%TST)	E	40.15 ± 1.0	40.81 ± 1.1	41.97 ± 0.9	42.46 ± 0.9	42.38 ± 1.0	41.31 ± 1.0	42.77 ± 1.0	41.42 ± 0.9	40.92 ± 1.1	<0.001	n.s.	<0.001	n.s.	n.s.	n.s.	n.s.
	R	38.98 ± 1.2	**34.56 ± 1.2**	35.83 ± 1.5	**34.62 ± 1.6**	**32.67 ± 1.3**	**33.86 ± 1.3**	**34.10 ± 1.4**	36.90 ± 1.6	39.31 ± 1.3						<0.001	n.s.
SWS (%TST)	E	23.09 ± 1.4	**20.19 ± 1.0**	**18.46 ± 0.9**	**18.52 ± 0.9**	**18.77 ± 1.0**	**18.78 ± 1.0**	**18.61 ± 1.0**	**20.98 ± 1.0**	**24.60 ± 1.2**	<0.001	n.s.	<0.001	n.s.	n.s.	<0.001	0.047
	R	24.64 ± 1.2	**30.06 ± 1.5**	**30.64 ± 1.5**	**31.71 ± 1.6**	**31.95 ± 1.4**	**30.98 ± 1.5**	**31.04 ± 1.5**	**30.50 ± 1.5**	24.98 ± 1.3						<0.001	n.s.
REMS (%TST)	E	26.83 ± 0.8	28.21 ± 0.8	27.37 ± 0.9	26.93 ± 0.9	26.25 ± 0.6	28.02 ± 1.0	26.11 ± 0.7	25.74 ± 0.8	26.95 ± 0.8	n.s.	0.022	n.s.	0.040	0.046	0.040	n.s.
	R	27.28 ± 0.8	27.05 ± 0.8	26.04 ± 0.9	26.67 ± 1.0	28.13 ± 0.9	27.59 ± 0.8	27.86 ± 0.8	25.26 ± 0.9	**29.39 ± 0.9**						n.s.	0.015

TST, sleep latency (first occurrence of stage 2), WASO, sleep efficiency, percentage of time spent in sleep stages 1 and 2, SWS (stages 3 and 4), and REM sleep (REMS) for extension (E) and restriction (R) conditions.

BL = baseline; RC = recovery. Linear mixed model (“***large model***”, see Methods) performed with factors: condition (E, R), night (BL, EN1–EN7 or RN1–RN7), order and interactions condition*night, and condition*order. C = condition (E, R); N = night (BL, EN1–EN7 or RN1–RN7); C*N = interaction condition*night; RC C = condition for recovery night (E, R); RC N = recovery night (BL, RE, or RR), RC.

Effect of order as well as the interaction condition*order was not significant for condition as well as for the recovery nights, except for condition*order during condition nights for stage 1 (%TST) and during recovery nights for stage 2 (%TST) and REM sleep (%TST). Linear mixed model (“*small model*”, see Methods) performed separately for sleep extension and restriction with factor night (N: BL, EN1-EN7 or RN1-RN7, or RC N: BL, RE or RR). n.s. not significant. Bold values indicate significant difference to baseline (Sidak correction).

Markers of sleep homeostasis predicted by the two-process model

We performed simulations of Process S based on the average timing of sleep and average sleep duration of the entire protocol (Figure 2) and extracted the homeostatic variables from the simulation (SWA and SWE, see Supplementary Figure S2 and Methods). As expected, the simulations revealed lower initial levels of Process S during sleep extension and higher ones during restriction although, due to the exponential nature of Process S, these changes were small (Figure 2) compared with the large change in TST (approximately +1 hr in extension, –1.8 hr in restriction) induced by the protocol.

Predicted SWA in EN1 was 97.6 per cent of the baseline level, remaining below baseline in EN2–EN7 at, e.g., 96.8 per cent in E4 (Figure 5). Sleep restriction resulted in a predicted increase of SWA to 102.6 per cent compared with baseline (=100%) in RN1, remaining increased at a stable level in RN2–RN7 (e.g. 105.9% in R4).

For SWE, the predicted pattern was opposite to the pattern predicted for SWA (Figure 5). In sleep extension, predictions were higher than baseline at 108.9 per cent of the baseline level in the EN1, being stable in EN2–EN6 (e.g. 103.5% in EN4), and 98.1 per cent in E7. Predictions of SWE for sleep restriction were at 88.8 per cent of the baseline in RN1 and remaining at a stable level below baseline in RN2–RN7 (e.g. at 92.4% of the baseline in RN4). The predicted cumulative difference from baseline in SWE showed an excess of +0.26 baseline equivalents in extension (EN7) and a deficit of –0.60 baseline equivalents in restriction (RN7).

Increased SWA and SWE were predicted for recovery sleep after total sleep deprivation in both conditions (Figure 5). SWA was 138.4 and 139.3 per cent of the baseline, and SWE 150.6 and 153.2 per cent of the baseline in RE and RR, respectively. The predicted cumulative difference from baseline in SWE after recovery sleep was a deficit of –0.23 baseline equivalents in extension, and of –1.07 in restriction.

SWA in the first 331 epochs of NREM sleep

To obtain a fair comparison between different conditions [16, 17], SWA was averaged over the first 331 30 s epochs of NREM sleep (2.8 hr, i.e. the maximum number of NREM sleep epochs

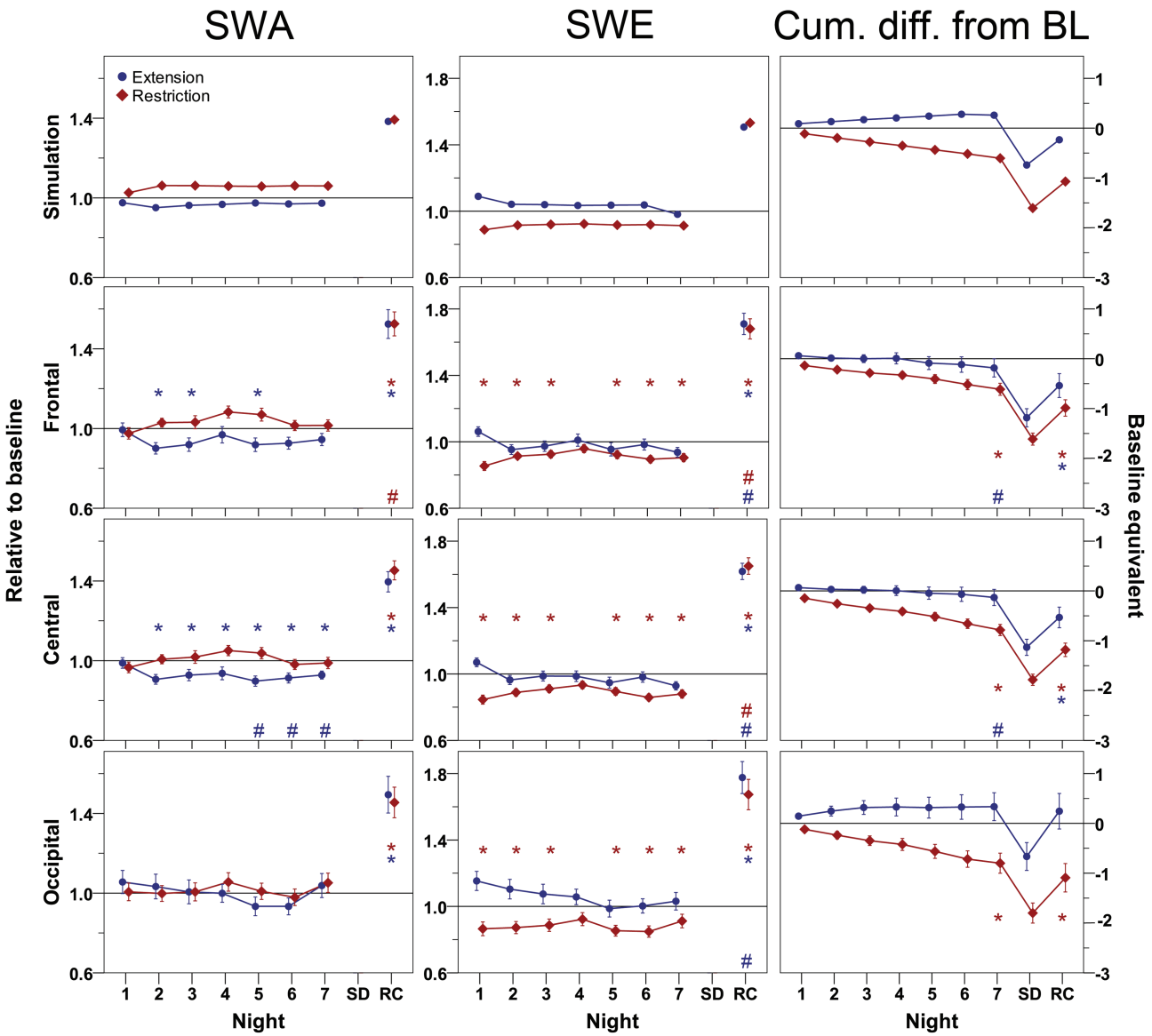

Figure 5. SWA, SWE, and cumulative difference from baseline in SWE derived from simulations and empirical data (frontal, central, and occipital derivations). Simulations of Process S based on the average sleep timing derived from the data; average SWA (EEG power in 0.75–4.5 Hz range) during first 331 30 s epochs of NREM sleep, SWE (cumulative SWA across the entire night), and cumulative difference from baseline in SWE relative to baseline (in baseline equivalent, i.e. −3 means a reduction of 3 times the baseline value). All values are expressed as mean and standard error of the mean, relative to the baseline (represented as 1). Data of left and right derivations were averaged (e.g. C3A2 and C4A1). *$p < 0.05$, significant differences from baseline (linear mixed model repeated measures, post hoc comparison to baseline). #$p < 0.05$, significant differences between data and simulations (linear mixed model, post hoc *t*-test). $n = 27–33$ (E) and $n = 32–34$ (R) for SWA and SWE; $n = 27–34$ (E) and $n = 30–33$ (R) for cumulative difference from baseline in SWE.

common to all nights; see Methods). The composition of these 331 epochs differed between the two conditions, with a higher percentage of SWS in restriction (Supplementary Table S2). After total sleep deprivation, the percentage of SWS was increased in both conditions.

SWA in the first condition nights (EN1 and RN1) did not differ from baseline in any of the EEG derivations (Figure 5, Table 2). In sleep extension, SWA was below baseline in EN2, EN3, and EN5 (e.g. 91.9 ± 3.4% of the baseline in EN3) of frontal derivations, in EN2–EN7 (e.g. 93.7 ± 3.2% of the baseline in EN4) of central derivations, whereas no difference to baseline was observed in occipital derivations. The adaptation model did not reveal any effect for sleep extension, i.e. temporal trend was not observed.

Mixed-model analysis of sleep restriction revealed significant differences from baseline in frontal and central derivations, and no difference in occipital derivations. Post hoc tests showed no deviation from baseline in the two derivations, despite increased SWA in some nights (e.g. 105.1 ± 2.6% in RN4 of central derivations). The adaptation model revealed a significant effect of night in central derivations (Table 2), which might point to a temporal trend. However, none of the experimental nights deviated significantly from baseline. Also, baseline nights of sleep extension and restriction did not differ.

After ~40 hr of total sleep deprivation, SWA in the recovery nights was increased in all derivations in both conditions and did not differ between the two conditions (Table 2). In RE, SWA was at 152.4 ± 7.2% in frontal, 139.6 ± 5.1% in central, and

Table 2. Markers of sleep homeostasis: SWA, rise rate of SWA and SWE (mean ± SEM) for extension (E) and restriction (R) conditions, for frontal, central, and occipital derivations (average of left and right hemisphere)

											Large model cond. nights and RC					Small model		All. m.
		BL	1	2	3	4	5	6	7	RC	C	N	C*N	RC C	RC N	N	RC N	N
SWA frontal (μV^2)	**E**	936.5	940.8	**831.9**	**844.5**	865.7	**858.3**	830.5	824.7	**1407.6**	<0.001	0.028	0.014	n.s.	<0.001	0.001	<0.001	n.s.
		± 110.1	± 103.5	**± 88.7**	**± 96.0**	± 98.9	**± 109.2**	± 100.6	± 107.0	**± 178.4**								
	R	904.3	869.6	889.6	938.4	977.0	988.7	916.8	941.4	**1388.2**						0.011	<0.001	n.s.
		± 97.2	± 94.6	± 91.3	± 99.9	± 99.4	± 109.0	± 94.6	± 105.3	**± 172.4**								
SWA central (μV^2)	**E**	641.9	638.3	**571.0**	**588.4**	**577.2**	**564.6**	**558.9**	**569.1**	**899.9**	<0.001	0.010	0.003	n.s.	<0.001	<0.001	<0.001	n.s.
		± 67.9	± 64.5	**± 55.2**	**± 62.1**	**± 61.9**	**± 62.4**	**± 63.4**	**± 68.1**	**± 108.9**								
	R	649.8	621.0	622.6	647.6	665.4	679.5	627.7	635.1	**933.2**						0.024	<0.001	0.039
		± 67.6	± 62.7	± 61.1	± 65.2	± 62.7	± 71.1	± 63.2	± 64.0	**± 102.4**								
SWA occipital (μV^2)	**E**	315.0	328.9	335.0	289.0	309.3	287.8	285.0	303.3	**444.8**	n.s.	n.s.	n.s.	n.s.	<0.001	n.s.	<0.001	n.s.
		± 34.5	± 39.0	± 46.5	± 32.9	± 39.2	± 35.3	± 39.4	± 36.7	**± 52.2**								
	R	323.6	329.4	305.7	325.6	335.1	326.4	322.3	339.0	**445.1**						n.s.	<0.001	n.s.
		± 31.8	± 35.6	± 31.2	± 33.9	± 33.1	± 36.8	± 35.8	± 40.4	**± 45.9**								
rise rate of SWA frontal (μV^2/30s)	**E**	59.6	66.6	61.4	62.8	59.7	62.4	57.8	57.5	**87.6**	n.s.	n.s.	n.s.	n.s.	<0.001	n.s.	<0.001	n.s.
		± 8.2	± 7.8	± 8.4	± 8.7	± 8.1	± 13.0	± 8.0	± 9.0	**± 12.1**								
	R	58.3	56.6	57.7	62.2	58.8	65.5	59.3	61.7	**90.6**						n.s.	<0.001	n.s.
		± 7.0	± 7.1	± 7.1	± 8.2	± 6.5	± 10.0	± 8.5	± 9.3	**± 11.0**								
rise rate of SWA central (μV^2/30s)	**E**	40.8	41.1	40.1	41.3	40.1	40.2	39.4	40.0	**57.2**	n.s.	n.s.	n.s.	n.s.	<0.001	n.s.	<0.001	n.s.
		± 4.7	± 4.9	± 5.1	± 5.5	± 5.0	± 6.9	± 4.9	± 5.8	**± 5.9**								
	R	40.8	40.7	38.2	40.9	41.3	43.0	38.8	38.1	**61.1**						n.s.	<0.001	0.049
		± 4.9	± 4.5	± 4.1	± 5.3	± 4.1	± 5.9	± 5.6	± 4.9	**± 6.7**								
rise rate of SWA occipital (μV^2/30s)	**E**	21.7	21.3	24.0	21.4	20.0	21.0	22.1	19.7	**29.4**	n.s.	n.s.	n.s.	n.s.	<0.001	n.s.	<0.001	n.s.
		± 2.7	± 2.6	± 4.0	± 2.5	± 2.2	± 3.4	± 3.7	± 2.6	**± 3.6**								
	R	20.7	21.3	18.3	20.2	21.1	18.9	19.6	21.5	**30.7**						n.s.	<0.001	n.s.
		± 2.2	± 2.5	± 2.0	± 2.7	± 2.3	± 2.7	± 2.9	± 3.6	**± 3.7**								
SWE frontal ($x10^3$; μV^2*30s)	**E**	400.9	432.6	378.9	388.0	386.1	385.1	380.9	353.3	**689.9**	<0.001	<0.001	<0.001	n.s.	<0.001	<0.001	<0.001	n.s.
		± 47.3	± 47.0	± 41.7	± 45.2	± 43.8	± 50.3	± 46.4	± 46.2	**± 90.0**								
	R	386.4	**336.3**	**348.5**	**369.8**	380.5	**374.2**	**351.5**	**364.2**	**662.0**						<0.001	<0.001	n.s.
		± 39.1	**± 38.3**	**± 38.2**	**± 41.2**	± 40.2	**± 42.7**	**± 36.8**	**± 41.0**	**± 80.7**								
SWE central ($x10^3$; μV^2*30s)	**E**	281.1	300.9	265.4	277.0	263.6	260.9	263.0	251.4	**462.7**	<0.001	<0.001	<0.001	n.s.	<0.001	<0.001	<0.001	n.s.
		± 30.3	± 30.1	± 26.2	± 30.5	± 27.7	± 29.6	± 29.9	± 31.4	**± 57.9**								
	R	282.2	**243.6**	**246.3**	**257.9**	263.6	**260.8**	**242.8**	**248.1**	**463.9**						<0.001	<0.001	0.043
		± 27.8	**± 25.8**	**± 26.1**	**± 27.3**	± 26.0	**± 28.4**	**± 24.8**	**± 25.0**	**± 50.5**								
SWE occipital ($x10^3$; μV^2*30s)	**E**	138.7	156.9	155.6	137.9	140.3	134.2	134.3	134.5	**237.5**	<0.001	n.s.	0.002	n.s.	<0.001	n.s.	<0.001	n.s.
		± 15.5	± 18.3	± 20.9	± 16.1	± 16.0	± 16.5	± 17.6	± 16.6	**± 29.1**								
	R	143.0	**128.5**	**121.2**	**129.0**	131.8	**125.0**	**125.5**	**131.6**	**226.5**						<0.001	<0.001	n.s.
		± 13.6	**± 14.3**	**± 13.0**	**± 14.1**	± 13.5	**± 14.5**	**± 14.3**	**± 15.4**	**± 22.6**								

Statistical evaluation of experimental nights and recovery nights was performed separately. Linear mixed model ("*large model*", relative values, see Methods) with factors condition C (E, R), night N (BL, EN1-EN7 or RN1-RN7; or BL, RE or RR), order (first extension or restriction), and interactions condition*night and condition*order. Factor order and the interaction condition*order are not significant, except for the rise rate of SWA in occipital derivations. Linear mixed model ("*small model*", relative values, see Methods) performed separately for the two conditions (E, R), with factor night N (BL, EN1-EN7 or RN1-RN7; or BL, RE or RR). RC: recovery night. Linear mixed model ("*adaptation model*" (All. m.), see Methods) performed separately for the two conditions (E, R), with factor night N (EN2-EN7 or RN2-RN7). n=27–34 (SWA and SWE), n=25–32 (rise rate). n.s. not significant. Significant differences to the baseline (post hoc tests) are indicated in bold.

149.4 ± 9.2% in occipital derivations, and in RR at 152.5 ± 6.0%, 145.3 ± 4.8%, and 145.5 ± 7.7%.

Individual data are provided in Supplementary Figure S5, and the number of subjects contributing to the analyses in each night is listed in Supplementary Table S3.

Slow-wave energy

With the purpose of quantifying the total of SWA produced during the night, SWE was calculated over the entire sleep opportunity (cumulative SWA in 30 min bins, see Methods).

In central and frontal derivations of sleep extension, a significant effect of night was obtained in the mixed-model analysis. No differences were present at occipital derivations (Table 2). However, post hoc tests did not reveal significant differences in SWE from baseline in any of the condition nights (EN1–EN7, Figure 5). The adaptation model did not reveal significances in any of the derivations.

In sleep restriction, SWE was lower than in baseline in all derivations in all condition nights except RN4, e.g. SWE in RN3 was at 92.5 ± 2.3% of the baseline in frontal, 91.1 ± 2.3% in central, and 88.7 ± 3.7% in occipital derivations (Figure 5, Table 2). The adaptation model revealed a significant effect of night in central derivations, although no systematic temporal evolution indicative of adaptation was observed.

SWE in recovery nights after total sleep deprivation was increased compared with baseline in all derivations and did not differ between the two conditions (Table 2). In RE, SWE was at 171.0 ± 6.4% of the baseline, 161.8 ± 4.9% and 177.6 ± 9.6%, and in RR at 168.0 ± 6.1%, 165.0 ± 5.0%, and 167.4 ± 9.1% in frontal, central, and occipital derivations, respectively.

Individual data are shown in Supplementary Figure S5, and the number of subjects contributing to the analyses of each night in Supplementary Table S3.

The cumulative difference from baseline in SWE did not differ from baseline in the last condition night (EN7) in the extension condition for any of the EEG derivations. In restriction (RN7), a deficit of –0.61 baseline equivalents in frontal ($p < 0.001$), –0.78 in central ($p < 0.001$), and –0.80 in occipital ($p < 0.001$) derivations was observed. The cumulative difference from baseline in SWE

was different between conditions in all derivations (Figure 5, $p = 0.030$ in frontal, $p = 0.001$ in central and occipital derivations).

In sleep extension, the cumulative difference from baseline in SWE after recovery sleep was –0.54 below baseline in frontal ($p = 0.015$) and –0.53 in central derivations ($p = 0.009$) and reached baseline levels in occipital derivations (Figure 5). In the restriction condition, the cumulative difference from baseline in SWE after recovery sleep revealed a deficit of –0.99 baseline equivalents in frontal ($p < 0.001$), of –1.18 ($p < 0.001$) in central, and of –1.09 in occipital ($p < 0.001$) derivations. The deficit in cumulative SWE at the end of the entire protocol differed between the two conditions in central ($p = 0.006$) and occipital ($p < 0.001$) derivations (Figure 5).

Rise rate of SWA after sleep onset

The rise rate of SWA after sleep onset was determined by calculating the median first derivative of the smoothed SWA time course after sleep onset (see Supplementary Figure S1 and Supplementary Methods for details). The rise rate of SWA in extension and restriction nights did not differ from baseline nights in any derivation (Supplementary Figure S3, Table 2). The adaptation model revealed a significant effect of night in central derivations (Table 2), but none of the experimental nights deviated from baseline.

In recovery sleep after ~40 hr of sustained wakefulness, the rise rate of SWA was increased to 169.3 ± 18.3%, 158.7 ± 14.9%, and 158.7 ± 14.2% of the baseline in RE and to 160.6 ± 10.7%, 162.5 ± 10.0%, and 158.2 ± 11.8% in RR in frontal, central, and occipital derivations, respectively (Supplementary Figure S3, Table 2).

Individual data are given in Supplementary Figure S5, and the number of subjects contributing to the analyses of each night in Supplementary Table S3.

Homeostatic response is derivation dependent

The homeostatic response to sleep extension and restriction was brain region specific. SWE differed between the derivations ("derivation model") both in response to sleep extension ($p = 0.006$) and restriction ($p = 0.002$). In sleep extension, the SWE response was stronger in occipital derivations (larger relative values) compared with frontal and central ones ($p = 0.023$, $p = 0.014$), and in sleep restriction the SWE response in occipital derivations was weaker (smaller relative values) than in frontal derivations ($p = 0.002$). The rise rate of SWA had a weaker response in occipital derivations compared with frontal ones during sleep restriction ($p = 0.035$). Although the factor derivation was significant for SWA in sleep extension (mixed model, $p = 0.045$), post hoc tests revealed no differences between derivations.

In recovery sleep after total sleep deprivation, there were no differences between derivations.

Comparison of model predictions and empirical data and tests for adaptation

Figure 5 illustrates both model predictions and empirical SWA and SWE of the entire protocol. Time periods over which empirical and model-derived homeostatic markers were calculated were identical. However, a direct comparison between predictions and empirical data is difficult. Thus, in Figure 6 a direct comparison is shown, empirical data with the corresponding 95% confidence interval are plotted against the predictions. The black line indicates equality of empirical data and predictions. Values above the line reflect that empirical data are larger than predictions (underestimation by the model), values below the line that they were lower (overestimation by the model).

In general, there was good agreement between predicted SWA and SWE and empirical data during both sleep extension and restriction (for linear mixed model and post hoc tests, see Table 3, Figures 5 and 6). Only during sleep extension, differences between predicted and empirical SWA were observed in the last 3 nights of central derivations (EN5–EN7, Figures 5 and 6), where empirical SWA was lower (e.g. 91.3% of baseline in EN6) than the values predicted by the model (e.g. 97.0% in EN6). No systematic temporal evolution indicative of adaptation was observed (Table 3, Figure 5).

In recovery sleep after total sleep deprivation, SWE was generally underestimated by the model (Figures 5 and 6). Empirical SWE was higher than predicted in all derivations of RE, with prediction of 150.6% of the baseline, and empirical SWE of 171.0 ± 6.4% of the baseline, 161.8 ± 4.9% and 177.6 ± 9.6% in frontal, central, and occipital derivations, respectively, and 168.0 ± 6.1% and 165.0 ± 5.0% in frontal and central derivations of RR. SWA was 9.5 per cent higher than predicted only in frontal derivations of RR. We investigated whether these underestimations were due to sex or PER3 polymorphisms (Supplementary Figure S4). Although data from PER3 polymorphism differed from predictions in some nights, it did not reveal systematic picture. However, discrepancies between data and model predictions were mainly found in males (Supplementary Figure S4).

Simulations predicted a surplus of SWE after 7 days of sleep extension and a deficit after sleep restriction. The cumulative difference from baseline in SWE at the end of sleep restriction (RN7) was significantly different from zero in all derivations and did not differ significantly from the predictions in any of the derivations (Figure 5). After sleep extension, no significant surplus was observed for any of the derivations. Only at the occipital derivation was a surplus observed, but this was not significantly different from baseline. Empirical data were significantly below the predicted values for frontal ($p = 0.021$) and central derivations ($p = 0.022$). After recovery sleep, the observed deficit in SWE did not differ from predictions in either of the conditions and any of the derivations (Figure 5).

Discussion

The data show that the response to extending or restricting the nocturnal sleep opportunity varies across sleep parameters and the different measures of sleep homeostasis. Only limited evidence for adaptation to the altered sleep opportunities emerged and the response to total sleep deprivation was not significantly different between the sleep history conditions.

Sleep structure

Measures of sleep duration confirmed that the protocol was successful in extending (increased TST) and restricting (decreased TST) sleep by altering participants' window of sleep opportunity. Following chronic sleep restriction, time spent in SWS (%TST) increased, and time spent in stages 1 and 2 (%TST) and WASO decreased, indicating that there was an increased

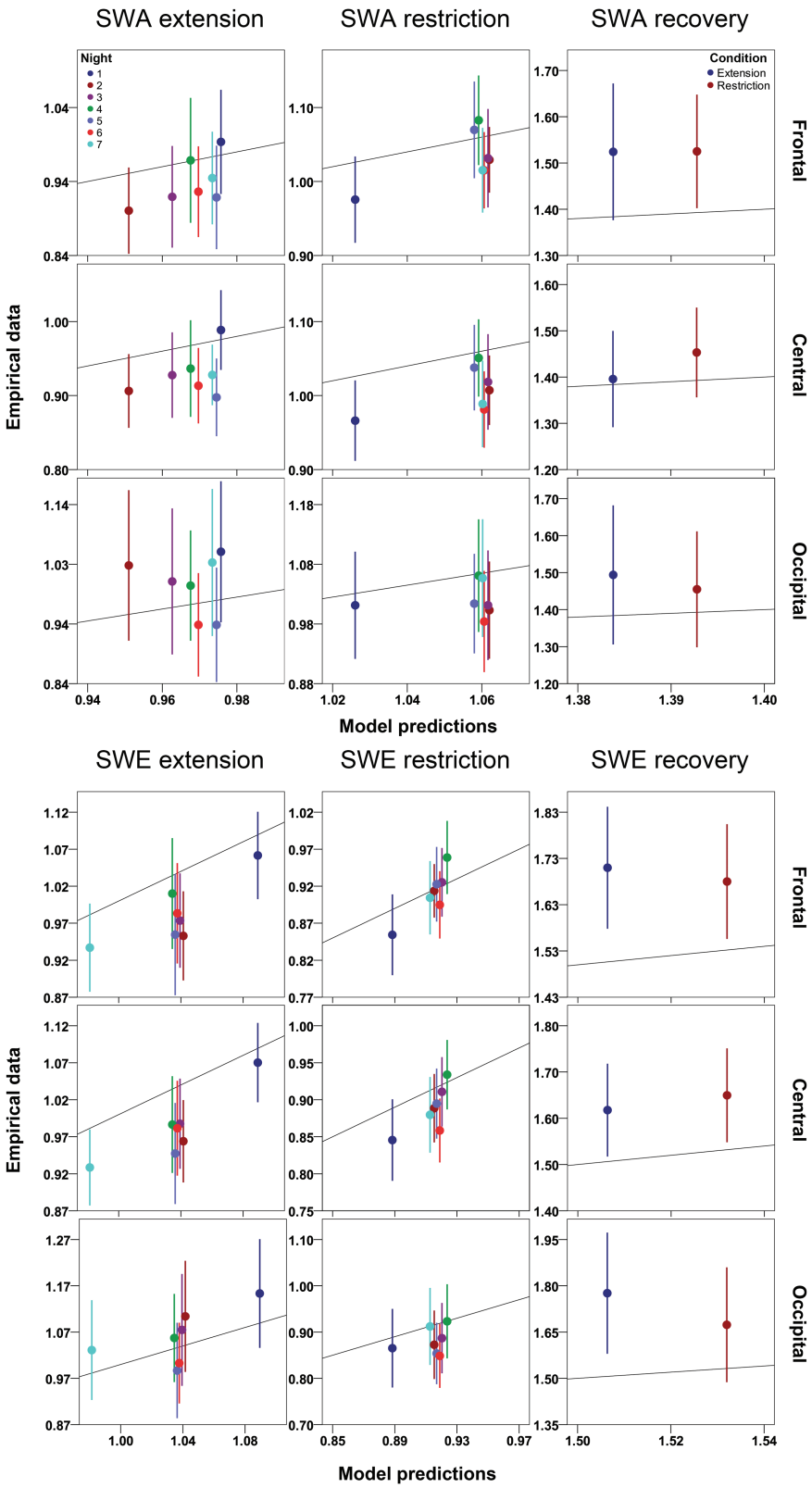

Figure 6. Comparison of model predictions and empirical SWA and SWE for extension, restriction, and recovery sleep after ~40 hr of sustained wakefulness (average data, normalized to baseline). Lines indicate the 45 degrees lines, i.e. empirical data = model predictions. Error bars depict 95% confidence interval of the mean.

homeostatic drive for sleep. During sleep extension, sleep latencies, WASO, and time in stage 1 increased, and sleep efficiency and time spent in SWS decreased, indicating that although more time was spent asleep, the sleep was lighter pointing to a reduced homeostatic sleep drive. These data are in general in accordance with previous studies [14, 16, 41, 42]. Computations

Table 3. Comparison of empirical and simulated data (SWA and SWE) of frontal, central, and occipital derivations for nights 1 to 7: night (EN1–EN7 or RN1–RN7) and for nights 2 to 7: night* (EN2-EN7 or RN2-RN7)

	SWA frontal		SWA central		SWA occipital	
Factor	E	R	E	R	E	R
Night	0.034	n.s.	0.036	n.s.	n.s.	n.s.
night*	n.s.	0.048	n.s.	0.033	n.s.	n.s.
	SWE frontal		SWE central		SWE occipital	
Factor	E	R	E	R	E	R
Night	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
night*	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

Linear mixed model ("*simulation model*", see Methods) with factor night.
n = 27–33 (E); n = 32–34 (R); n.s. = not significant.

of cumulative deficits/surpluses revealed that sleep extension, compared with the 8 hr baseline sleep opportunity, leads to a surplus in TST and REM sleep and, maybe surprisingly, also to a deficit in SWS, whereas sleep restriction leads to a large deficit in TST and REM sleep, no deficit in SWS and a deficit in accumulated SWE.

Effect of chronic sleep restriction and extension on homeostatic sleep measures

In this study, four different homeostatic measures were calculated: time spent in SWS (%TST; Table 1), SWA (mean SWA in the first 331 epochs of NREM sleep), rise rate of SWA after sleep onset, and SWE (cumulative SWA across entire night) (Figure 5 and Supplementary Figure S3). SWS, SWA, and the rise rate of SWA are supposed to reflect sleep pressure, and SWE is reflecting the dissipation of sleep pressure across the entire sleep episode [12, 40].

The time spent in SWS (%TST) was lower than baseline during sleep extension, and higher during sleep restriction, reflecting the change in homeostatic sleep drive induced by the experimental manipulation. This is in agreement with other restriction studies also showing increased amounts of SWS [14, 16, 41, 42].

SWA was lower than baseline during sleep extension in the last 3 nights in central derivations, and in one night in frontal derivations, while during sleep restriction no significant change from the baseline was observed in any derivation. The observed changes are in the expected direction (Figure 5) but did not reach significance. Other sleep restriction studies [14–16] reported an increase of SWA after sleep restriction (4 hr time in bed [TIB]). However, these subjects were exposed to a stronger challenge with 4 hr TIB.

The rise rate of SWA after sleep onset was not affected by sleep extension and restriction. Possibly, this measure is not sensitive enough to moderate changes in sleep pressure but might reflect adequately stronger challenges. Indeed, we observed a significant increase in the rise rate of SWA in recovery sleep after ~40 hr of sleep deprivation, both after sleep restriction and extension (Supplementary Figure S3). Brunner et al. [14] reported a faster buildup of SWA in the first NREM sleep episode after sleep restriction although they did not determine the rise rate; they reported the temporal evolution of SWA in the first 24 min. It seems, however, that the main change occurred within the first 2 min after sleep onset, i.e. higher SWA values than in baseline (see Figure 3 in Ref. 14).

SWE did not differ from baseline during sleep extension reflecting an adequate dissipation of the sleep drive with a prolonged sleep opportunity, while during sleep restriction SWE was lower than baseline in most nights and all derivations indicating an insufficient dissipation of sleep pressure during a shortened sleep opportunity. Please note that the deficit in SWE was only around 10 per cent. This is in agreement with previous findings by Brunner et al. [14] and Banks et al. [42] where the authors observed decreased levels of SWE compared with baseline during a 4 hr TIB protocol. Thus, from a sleep regulation perspective, SWE might be considered as the best measure reflecting the homeostatic response to sleep extension and restriction.

Few studies have investigated changes in sleep under sleep restriction over prolonged periods of time in humans. Previous studies with sleep restriction for 2–5 days typically report an increase above baseline levels of SWS and SWA in restriction nights [14–17]. Our protocol did not elicit an increase of SWA in sleep restriction; however, SWE was below baseline. In contrast, Plante et al. [17] performed a sleep restriction over 4 days with 5 hr TIB and did not observe a significant change in SWE. A further study did impose sleep restriction of 6 and 4 hr for 14 days and surprisingly did not observe any significant deviation of SWE from baseline [5]. However, they reported that chronic restriction of sleep to 6 hr or less per night resulted in cognitive performance deficits equivalent of up to 2 nights of total sleep deprivation. Belenky and colleagues [43] observed that cognitive deficits in chronic sleep restriction of 7 hr or less per night were not recovered even after 3 nights of recovery sleep. Outcomes from these two studies and the present results are implying that even relatively moderate sleep restriction which does not lead to large changes in SWA or SWE can seriously impair waking neurobehavioral functions in healthy adults. This is in agreement with the cognitive performance deficits elicited by sleep restriction in our participants [6]. However, looking at the cumulative deficit might be more revealing. Indeed, 7 days of sleep restriction led to a cumulative deficit in SWE corresponding to 0.6 to 0.8 baseline equivalents. This may explain the differences in cognitive performance observed during total sleep deprivation (constant routine) between the two conditions [6].

Two-process model of sleep regulation predicted response to sleep extension, restriction, and total sleep deprivation

Markers of sleep homeostasis were derived from frontal, central, and occipital brain regions throughout the protocol and compared with predictions from the two-process model of sleep regulation. In general, there was good agreement between model predictions and empirical data.

According to the two-process model [7, 8], sleep restriction leads to higher initial levels of Process S and lower ones during sleep extension (Figure 2). We simulated the Process S based on the average timing of sleep and average sleep duration of the entire protocol (Figure 2), and derived SWA and SWE from the simulations (see Supplementary Figure S2 and Methods). To the best of our knowledge, this is the first study which extracted SWA and SWE from simulations of Process S and compared the predictions with the empirical data. The simulations show that in the restriction condition despite 24 per cent reduction in TST compared with baseline the theoretical increase in SWA/Process S was only around 6 per cent, and the theoretical decrease in SWE around 9 per cent. Likewise, in extension despite a 13 per cent increase in TST compared with baseline the predicted reduction in SWA/Process S was only around 3 per cent, and the predicted increase in SWE around 4 per cent. Substantial changes in TST in extension and restriction lead to only small changes in homeostatic markers, due to the properties of the exponential functions (Figure 2 and Supplementary Figure S2) underlying sleep homeostasis. Thus, it is important to realize the magnitude of the response of homeostatic variables that can be expected with a given challenge, before making conclusions about the effectiveness of a homeostatic model. Subjective overestimation of the expected response might lead to misinterpretations. Thus, looking at the induced deficits or surplus may thus help interpreting the results (see below).

Comparison of model predictions with empirical data provides a better understanding of sleep regulation. Applying these comparisons to chronic studies also allows for an assessment of adaptation, i.e. to evaluate whether the response to a challenge fades off over time. In case there are no or only minor differences between predictions and empirical data and deviations from the model predictions do not show increasing deviations over time, it would mean that sleep regulation can be accurately described by a homeostatic process. Furthermore, the homeostatic response to the experimental manipulation would decrease across nights in case of adaptation [44]. Based on the above-mentioned signs, there was only limited evidence of adaptation in our data. Thus, we conclude that sleep homeostasis remains operative during chronic sleep restriction (2 hr shorter sleep opportunity) and extension (sleep opportunity prolonged by 2 hr).

During sleep restriction, no differences between the data and predictions were observed. Similarly, the simulations of Brunner et al. [14, 15] of sleep restriction (2 or 4 days) predicted empirical SWA well. During sleep extension, the observed SWA was below the predicted values but only so during the last 3 days of sleep extension and only in central derivations.

The cumulative differences from baseline in SWE were calculated across the entire protocol and compared with simulations after the last condition nights (EN7 and RN7), and after recovery sleep. There was a good agreement between empirical and predicted levels of the cumulative difference from baseline, with an exception only in the extension condition (EN7) in frontal and central derivations, where the predicted surplus was not observed. Furthermore, the deficit in SWE increased in the course of sleep restriction (RN1-RN7, Figure 5), which is in line with sleep homeostasis. If a deviation from sleep homeostasis would occur, one would expect the deficit to level off, i.e. reaching a plateau in the course of the protocol. For sleep extension, the two-process model predicted a cumulative excess of SWE during extension nights. However, empirical data did not differ from baseline, except for the occipital derivation which showed the predicted surplus although not significantly different from baseline.

Overall, these findings indicate that homeostatic processes remain operative during both short-term (1 week) sleep restriction and extension and that in the applied experimental protocol, adaptive responses were not very prominent. However, we cannot rule out the possibility that restricting the sleep opportunity to 6 hr might not be a strong enough challenge to trigger deviations from a homeostatic response or whether it generalizes to longer periods (months to years).

Most discrepancies between empirical data and predictions were observed in the response to total sleep deprivation. After both sleep restriction and extension, the observed homeostatic responses to total sleep deprivation were larger than predicted in most derivations. We tested whether these underestimations by the model were related to sex or PER3 polymorphisms (Supplementary Figure S4). Discrepancies between predictions and empirical data were most pronounced for males.

However, the cumulative difference from baseline at the end of the protocol (after recovery sleep) was accurately predicted by simulations in both the extension and restriction conditions in all derivations. This implies that sleep homeostasis accurately keeps track of altered sleep opportunities over longer time periods.

Response to total sleep deprivation: affected by prior sleep history?

The total sleep deprivation (~40 hr of sustained wakefulness) following the 7 days of sleep restrictions or extension resulted in the expected homeostatic response. TST, SWA, SWE, and time spent in REM sleep (hr) were increased compared with baseline and did not differ between the two conditions.

Previous sleep history influenced recovery sleep following total sleep deprivation, whereby sleep latency was significantly shorter in recovery nights following sleep restriction than those following sleep extension. It had previously been reported that extended sleep prior to periods of sleep deprivation has a protective effect against performance and alertness decrements, also referred to as “sleep banking” [29]. Cognitive performance of our participants was poorer during total sleep deprivation (constant routine) when the prior sleep history was sleep restriction [6]. Despite rather small reductions in SWE compared with baseline during restriction, if these changes are accumulated over several nights, they lead to substantial deficits, i.e. after 7 nights of sleep restriction, the cumulative deficit in SWE was 0.6–0.8 baseline equivalents, whereas no difference to baseline was observed after 7 days of sleep extension. This large difference in cumulative deficit between sleep restriction and extension conditions in N7 may explain differences in cognitive performance during the subsequent ~40 hr of sustained wakefulness

[6]. Mathematical models have been developed to predict the build-up of neurobehavioral impairment across chronic sleep restriction, describing lapses in behavioral alertness as a function of cumulative additional wakefulness across the protocol [5]. In an extended version of the model, a bifurcation occurred and if wakefulness extended beyond a critical level (20.2 hr), performance impairments escalated [45].

Clasadonte et al. [22] reported an attenuated response to acute sleep deprivation in sleep restricted mice. In our study, however, participants showed an intact homeostatic response to total sleep deprivation (sustained wakefulness for 41 hr after sleep restriction).

Although homeostatic markers (SWA, SWA rise rate, and SWE) in recovery night after ~40 hr of total sleep deprivation did not differ between the two conditions, the cumulative difference in SWE from baseline across the entire protocol showed that levels of SWE after 12 hr recovery sleep were different in the two conditions in central and occipital derivations and did not lead to a full recovery (Figure 5).

SWS: a measure of sleep pressure?

Absolute time spent in SWS and time in SWS as a percentage of TST or of a common sleep duration are different measures. Although absolute time in SWS may remain rather constant during different sleep opportunities (Figure 4) and thus not reflecting sleep pressure, relative SWS might be considered as a homeostatic marker. Moreover, it has been postulated that absolute time in SWS cannot explain waking neurobehavioral impairments [5]. In our study, relative SWS was increased in restriction and decreased in extension, both expressed as %TST (Table 1), and as percentage of first ~2.8 hr of NREM sleep (Supplementary Table S2). Furthermore, SWS suffers from the artificial threshold of its definition. Thus, the decrease of SWS (Figure 4) in the extension condition may be related to a decrease in amplitude of slow waves, as reflected in the decreased SWA (Figure 5).

Controversies related to allostasis

Allostasis refers to an adaptive response to a change in an environment, which maintains stability through physiological or behavioral changes [21, 46]. There are, however, some controversies with the concept of allostasis in the context of sleep research: although allostasis was proposed to refer to changes in biological processes that promote adaptation so that homeostasis is preserved (e.g. Ref. 24), in some rodent studies allostasis was referred to as an additional process needed in order to explain the absence or attenuation of a homeostatic response under chronic sleep restriction conditions [20, 22, 23]. In our study, we investigated whether a deviation from a homeostatic response (adaptation) could be observed, similar to the allostasis concept of Kim et al. [23]. However, we basically did not observe deviations from sleep homeostasis. It is conceivable that mechanisms of allostasis acted to maintain homeostasis, and that these processes are not reflected at the level of the sleep EEG. McCauley et al. [47] proposed that prior sleep history affects adenosine receptor regulation, namely, adenosine receptor upregulation during chronic sleep restriction and downregulation across multiple recovery nights. Furthermore, adenosine receptor upregulation increases vulnerability to performance impairment during waking [47]. In rodents, sleep deprivation led to adenosine-dependent inhibition of synaptic activity, and this effect was attenuated during the 3 days of sleep restriction [22]. It is also conceivable that allostatic changes are different biological responses to chronic sleep restriction which act to adjust the set point of the homeostatic equilibrium to keep homeostasis functional [48].

Brain region–specific response

In the study of Leemburg and colleagues, the SWA response to sleep restriction in rodents was derivation dependent, i.e. a SWA rebound was present in frontal and central, but not in occipital derivations. This finding is in agreement with our results in so far as we also observed topographical differences in the response to sleep restriction and extension in the rise rate of SWA and SWE. It contrasts, however, with Plante et al. [17] who did not observe topographic differences in response to sleep restriction in SWE in a high-density EEG study. Cajochen et al. [49] and Finelli et al. [50] observed that the SWA response to acute sleep deprivation was most pronounced in anterior brain regions. Lazar et al. [51] investigated topographical aspects of homeostatic and circadian regulation of slow waves and demonstrated that the sleep-dependent modulation of slow-wave characteristics was most prominent in frontal brain areas. In our study, we observed smaller deficits in SWE in frontal and central derivations compared with the occipital ones during chronic sleep restriction. This suggests that sleep homeostasis is better preserved in frontal brain regions; thus, frontal regions are more protected from effects of sleep loss. This could explain why cognitive deficits are less apparent when solving more complex tasks (e.g. decision making). Furthermore, the dynamics of Process S has been shown to be brain region specific, both for the dynamics of the buildup and the dissipation of sleep pressure [52]. Thus, all together, it is important to take topographical aspects into account when investigating sleep regulation.

Sleep extension: sufficient or excess sleep?

During sleep extension, sleep latency was increasing, and sleep efficiency decreasing over the course of the protocol. This indicates that 10 hr TIB may be too long for this age group. During this condition, participants obtained, e.g., 8.5 hr of sleep in EN3, whereas they slept 7.5 hr during baseline. However, 8 hr of TIB may be interpreted as an insufficient sleep opportunity, since participants slept 1 hr longer when TIB was extended, and cognitive performance did not change over the course of the extension protocol [6].

Implications

The current data, and previous sleep restriction studies [5] and studies comparing short and long sleepers [53] imply that sleep restriction as experienced by many in society leads to a large REM sleep deficit and a smaller SWS deficit. Thus, in the search for the mechanisms underlying the negative health consequences of insufficient sleep, the implication of a REM sleep deficit should be considered. Furthermore, in the search of mechanisms underlying the negative consequences of long sleep duration, the consequences of reduced sleep continuity and SWS should be taken into account. We previously reported that sleep restriction

leads to a deterioration of waking performance in this protocol, whereas during sleep extension no changes from baseline were observed [6]. Although SWA and SWE were not much affected by changes in sleep opportunities, in the restriction condition, the accumulated loss of SWE across the protocol revealed substantial deficits. This implies that the observed deficits in waking performance after the chronic sleep restriction may be related to the accumulated deficits in SWE, but the contribution of deficits in TST or REM sleep should also be considered.

Conclusion

There was a good agreement between predictions from the two-process model of sleep regulation and empirical markers of sleep homeostasis derived from frontal, central, and occipital brain regions. Thus, sleep homeostasis was preserved under chronic sleep restriction (reduction by 2 hr) and extension (increase by 2 hr); there was only a limited indication for adaptation under these experimental conditions, but responses differed across brain regions.

Supplementary Material

Supplementary material is available at *SLEEP* online.

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Notes

Conflict of interest statement. None declared.

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