Homeostatic Sleep Regulation in Adolescents

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Study Objectives: To examine the effects of total sleep deprivation on adolescent sleep and the sleep electroencephalogram (EEG) and to study aspects of sleep homeostasis.

Design: Subjects were studied during baseline and recovery sleep after 36 hours of wakefulness.

Setting: Four-bed sleep research laboratory.

Participants: Seven prepubertal or early pubertal children (pubertal stage Tanner 1 or 2 = Tanner 1/2; mean age 11.9 years, SD ± 0.8, 2 boys) and 6 mature adolescents (Tanner 5; 14.2 years, ± 1.4, 2 boys).

Interventions: Thirty-six hours of sleep deprivation.

Measurements: All-night polysomnography was performed. EEG power spectra (C3/A2) were calculated using a Fast Fourier transform routine.

Results: In both groups, sleep latency was shorter, sleep efficiency was higher, non-rapid eye movement (NREM) sleep stage 4 was increased, and waking after sleep onset was reduced in recovery relative to baseline sleep. Spectral power of the NREM sleep EEG was enhanced after sleep deprivation in the low-frequency range (1.6-3.6 Hz in Tanner 1/2; 0.8-6.0 Hz in Tanner 5) and reduced in the sigma range (11-15 Hz). Sleep deprivation resulted in a stronger increase of slow-wave activity (EEG power 0.6-4.6 Hz, marker for sleep homeostatic pressure) in Tanner 5 (39% above baseline) than in Tanner 1/2 adolescents (18% above baseline). Sleep homeostasis was modeled according to the two-process model of sleep regulation. The build-up of homeostatic sleep pressure during wakefulness was slower in Tanner 5 adolescents (time constant of exponential saturating function 15.4 ± 2.5 hours) compared with Tanner 1/2 children (8.9 ± 1.2 hours). In contrast, the decline of the homeostatic process was similar in both groups.

Conclusion: Maturational changes of homeostatic sleep regulation are permissive of the sleep phase delay in the course of adolescence.

Keywords: Adolescence, puberty, sleep deprivation, slow-wave activity, sleep phase delay

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INTRODUCTION

ADOLESCENCE IS THE PERIOD OF MAJOR BIOLOGIC, COGNITIVE, EMOTIONAL, AND SOCIAL CHANGES THAT ENCOMPASSES THE YEARS BETWEEN EARLY SIGNS OF sexual maturation until full attainment of adult status in society. Typical key issues of adolescents are wishes for independence and increasing peer activities outside the family system. Other behavioral changes in the teen years include an altered sleep-wake timing: adolescents tend to go to bed later and get up later than prepubertal children.[1] Until recently, the changes of sleep patterns in the course of adolescence were viewed to originate primarily from shifts in peer culture, family configurations, academic demands, school culture, employment opportunities, and extracurricular activities.[2]

Data collected in numerous societies around the world have consistently described the sleep phase delay during the teen years despite substantial cross-cultural variations in adolescent lifestyles.[3-7] The low variability of adolescent sleep patterns across cultures has led some authors to conclude that biologic processes and not entirely changes of psychosocial milieu drive the sleep phase delay in teens.[8] Lately, this view has received support from scientific studies under strict control of psychosocial influences (reviewed in Carskadon et al[9]). Carskadon and colleagues have reported maturational changes in the biology of sleep-wake and circadian regulation during puberty that may provide impetus for a sleep phase delay.[9] They have proposed that the delay in evening bedtimes and sleep onset associated with pubertal changes of intrinsic sleep-wake regulatory processes may "open the gate" for increasing capacity to participate in opportunities in the evenings and at night.

The timing of sleep results from an interaction of 2 separate processes (conceptualized in the two-process model of sleep regulation[10-12]): the sleep-wake dependent homeostatic Process S and the sleep-wake independent, clock-like, circadian Process C. Process S is viewed to reflect the evolution of homeostatic sleep pressure or sleep need, which builds up during wakefulness and dissipates during sleep.[11-13] Slow-wave sleep (SWS, stages 3 and 4 of non-rapid eye movement [NREM] sleep) and its quantitative measure, electroencephalographic (EEG) slow-wave activity (SWA, power in the 0.75- to 4.5-Hz range), have been proposed as physiologic markers for Process S.[11-13] SWA is high in the early part of the sleep period, when the need for sleep is greatest, and exhibits an exponential decline across the night's successive NREM sleep episodes.[13-15] Sleep loss evokes an increase in SWA during subsequent sleep that is proportional to prior wake duration.[13,16,17]

The two-process model has also served as a conceptual framework for studying developmental changes of sleep-wake processes during ontogeny, particularly during infancy[18] and puberty.[9,19-21] Adolescent studies examining circadian processes have demonstrated that those children who rate themselves as more physically mature also rate themselves as more "evening" type in their circadian phase preference.[1] This finding was subsequently

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corroborated in a laboratory study in which Tanner stage was assessed by physicians and circadian phase was measured by the timing of salivary melatonin. Briefly, pubertal stage correlated with the circadian phase marker, such that more mature children showed a later phase of melatonin-secretion offset.[22] Another mechanism predicted by circadian processes is that a delay of the circadian phase may be related to a lengthening of the period of the circadian clock or to a heightened sensitivity to evening light or a decreased sensitivity to morning light across pubertal development.[9] Together, the adolescent sleep phase delay may originate from specific alterations of the circadian timing system during puberty.

Recently, we have begun to study homeostatic sleep regulation in adolescents.[20,21] The nocturnal dynamics of Process S were investigated by spectral analysis of the sleep EEG during baseline nights in early and late pubertal adolescents.[20,21] The decline of SWA across the sleep episode—essentially reflecting recovery processes during sleep—was similar in prepubertal and mature adolescents, confirming the findings of an earlier study by Gaudreau and coworkers.[23] Thus, we concluded that the nocturnal dynamics of S remain unchanged across puberty, which is in line with the clinical view that sleep per se is not altered during adolescence.[24] The present paper extends these recent studies by examining homeostatic sleep regulation using a sleep-deprivation paradigm with 36 hours of extended wakefulness.

The study aim was 2-fold: (1) to analyze the effects of total sleep deprivation on sleep and the sleep EEG in prepubertal or early pubertal children and mature adolescents and (2) to test the hypothesis that the build-up of homeostatic sleep pressure differs between these 2 groups. In line with the observed sleep delay of adolescents, we hypothesized that the increase of S during wakefulness is slower in mature adolescents compared with prepubertal or early pubertal children. Analyses presented here estimate the parameters of Process S on the basis of empirical SWA data and test whether the time course of SWA during baseline and recovery sleep after 36 hours of prolonged wakefulness can adequately be modeled.

METHODS

Participants

Participants were recruited through newspaper advertisements and flyers asking for volunteers for a study of sleep and circadian rhythms. Subjects underwent telephone and questionnaire screening to exclude personal or family history of psychopathologies (first-degree relative), sleep disorders, erratic sleep schedules (variation of more than 3 hours across week), more than 1 nap per week, a chronic major illness, a current illness, current use of psychoactive agents or other compounds known to affect sleep-wake patterns, history of head trauma, or evidence of a learning disability. Participants with sleep schedules that indicated chronic insufficient sleep accompanied by signs of excessive sleepiness were also excluded. No participant traveled across more than 1 time zone in the 3 months prior to the study.

The present analysis is based on data of 2 previous studies. One prepubertal participant took part in an investigation of the sensitivity of the circadian timing system to light during the summer months in 2002,[25] and 12 participated in a forced desynchrony study conducted from 1999 to 2002.[20] Data of 7 prepubertal or early pubertal children (pubertal stage Tanner 1 or 2 = Tanner 1/2; mean age 11.9 years, SD ± 0.8; range 10.3-12.8 years, 2 boys) and 6 mature adolescents (Tanner 5; mean age 14.2 years, ± 1.4; range 11.8-16.0 years, 2 boys) were analyzed. Baseline sleep EEG data of 5 prepubertal and all 6 mature participants were reported previ-

Table 1—Sleep variables derived from visual scoring and average duration of the first 4 NREM and REM sleep episodes

	Baseline		Recovery		F values		
	Tanner 1/2	Tanner 5	Tanner 1/2	Tanner 5	Group	Condition	Group × Condition
TST, min	513.8 (11.7)	511.8 (12.0)	544.6 (0.6)	541.0 (2.9)	NS	12.4	NS
Sleep efficiency, %*	91.7 (2.7)	91.4 (2.7)	98.2 (0.1)	97.5 (0.6)	NS	10.7	NS
Sleep stage duration, min							
1	37.1 (9.1)	44.1 (6.5)	16.0 (4.2)	14.7 (3.1)	NS	15.9	NS
2	182.1 (17.5)	218.0 (18.9)	183.6 (16.6)	215.2 (13.1)	(4.0)	NS	NS
3	34.5 (6.7)	38.9 (9.1)	49.0 (8.4)	42.4 (3.6)	NS	NS	NS
4	127.8 (11.2)	94.8 (9.5)	190.0 (14.1)	161.8 (15.5)	5.7	25.2	NS
REM sleep	132.2 (15.1)	116.1 (9.9)	106.0 (8.9)	107.0 (12.7)	NS	NS	NS
Movement time, min	12.3 (1.3)	16.2 (3.1)	9.3 (0.7)	12.2 (2.4)	NS	(3.1)	NS
WASO, min	28.4 (11.3)	26.5 (9.8)	0.6 (0.4)	1.3 (1.3)	NS	12.0	NS
Latency to sleep stage, min							
1	12.4 (3.0)	12.0 (6.6)	3.5 (1.2)	4.7 (1.1)	NS	5.3	NS
2	20.9 (2.2)	18.4 (6.7)	5.6 (1.2)	8.2 (2.0)	NS	13.3	NS
REM sleep	107.3 (10.8)	129.7 (14.3)	123.0 (23.2)	111.7 (15.1)	NS	NS	NS
Mean episode duration, min							
NREM sleep	80.4 (5.3)	81.4 (6.9)	81.3 (3.6)	90.8 (5.6)	NS	NS	NS
REM sleep	18.7 (2.6)	17.3 (2.7)	14.1 (2.3)	14.8 (2.6)	NS	NS	NS

Values represent means ± SEM (for NREM [non-rapid eye movement] sleep and rapid eye movement [REM] sleep episodes = mean duration of the first 4 episodes). The first 554.5 minutes after sleep onset (minimal common duration of all sleep episodes) were analyzed. WASO refers to waking after sleep onset (stage 2); stage 1, 2, 3, 4, NREM sleep stages; the last 3 columns represent significant ($P < .05$) F values of a 2-way analysis of variance with the factors "developmental group" (Tanner 1/2, Tanner 5) and "condition" (baseline, recovery). Values in parentheses indicate trends ($P < .1$). "Skipped" first REM sleep episodes as defined in our previous publication (see also methods in Jenni and Carskadon[20]): Tanner 1/2: baseline, n=4; recovery, n=2. Tanner 5: baseline, n=2; recovery, n=3.
*Total sleep time as a percentage of the first 554.5 minutes after sleep onset.

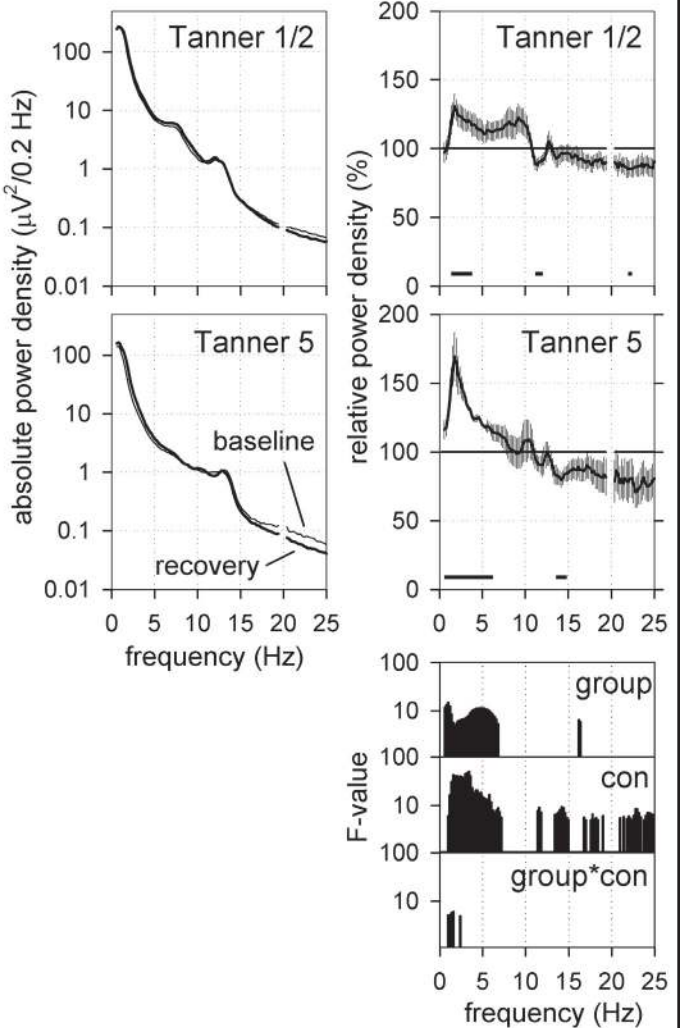

Figure 1—Average all-night spectra during non-rapid eye movement (NREM) sleep (stages 2-4) for baseline and recovery. Left panels: absolute spectra during baseline (thin line) and recovery sleep (thick line). Right: relative spectra (values of each 0.2-Hz bin in the recovery night expressed as a percentage of the corresponding value of the baseline night). Gray area represents ± 1 SEM. Black bars at the bottom of the right panels indicate frequency bins in which absolute power density of baseline and recovery night differed significantly ($P < .05$; paired *t* tests on log-transformed values, performed for frequency bins for which a 2-way analysis of variance within-subjects factor "condition" (con = baseline, recovery) or the interaction "group × condition" was significant; bottom panels at right; only significant F values ($P < .05$) are depicted). Average spectra were calculated for the first 554.5 minutes of sleep (minimal common duration of baseline sleep). The 3 frequency bins 19.8, 20.0, and 20.2 Hz were excluded from the analysis and the illustration because of a 20-Hz artifact in some recordings.

ously,[20] while sleep EEG data from the recovery nights were not published before. One female participant was studied longitudinally at both developmental stages (see Figure 3 in Jenni and Carskadon[20]). The 2 male subjects in the Tanner 5 group were brothers.

Pubertal status was determined at a brief physical examination using the standardized assessment scales developed by Tanner.[26] Tanner staging relies on rating genital development and pubic-hair growth in boys and breast development and pubic-hair growth in girls. Tanner staging was performed by 2 or 3 independent research physicians, and consensus ratings of pubic-hair growth were used to classify pubertal stage. Pubertal stage Tanner 1 represents absence of secondary sexual characteristics (prepubertal) and Tanner 5 indicates adult sexual maturity.

Experimental Protocol

Participants slept at home on a fixed 10-hour sleep schedule (lights off = 10:00 PM, lights on = 8:00 AM) for at least 10 nights. Sleep-time restrictions included no visitors, lights off, no television or radio on, sleeping alone in a room, and wearing eyeshades provided by the lab. Participants called the lab each morning and evening to report bed and rise times on an answering machine, completed daily sleep diaries, and wore actigraphs to ensure schedule compliance. Participants were also asked to abstain from caffeine and drugs throughout the study.

The in-lab protocol consisted of a baseline night (lights off = 10:00 PM, lights on = 8:00 AM, time in bed 10 hours) followed by a 36-hour sleep-deprivation period and a recovery night (lights off = 8:20 PM, lights on = 8:00 AM, time in bed = 11 hours 40 minutes). All participants had slept previously in our lab while taking part in other studies or during an adaptation night to ensure that they were aware of and adapted to the study conditions.

Extended wakefulness was achieved using a constant-routine protocol during which circadian markers and wake-dependent processes exhibited minimal influences from extraneous factors. Participants were kept in individual rooms sitting in bed in a semirecumbent posture (45°) in a dimly lit room (15-20 lux). Small meals were provided every 2 hours. Meal sizes were based on 24-hour caloric need determined by height, weight, age, and sex. The self-rated sleepiness state (Stanford Sleepiness Scale) was assessed every 2 hours (in 1 participant of the Tanner 1/2 group, these data were unavailable). A researcher stayed with each participant at all times, except during restroom activities.

On the day of study, the participants were in good physical and mental health, were on no medications, and had no current sleep complaints (as assessed by interview). The study protocols were approved by the Lifespan Institutional Review Board for the Protection of Human Subjects, and the studies were performed according to the Declaration of Helsinki. A description of the study procedures was given, and informed consent was obtained from the participants and their parents. Participants received monetary compensation.

Sleep Recording and Analysis

Overnight monitoring in individual darkened bedrooms included continuous recordings of EEG (international 10-20 system, electrodes placed on the mastoid and sensory motor areas C3/A2 or C4/A1, and occipital areas O1/A2 or O2/A1), electrooculogram (right and left outer canthus), electromyogram (mentalis, submentalis), and electrocardiogram. The central derivation was used for sleep-stage scoring and for power spectral analysis. Recordings were performed using the Albert Grass Heritage System (Astromed, Grass, West Warwick, RI). Signals were recorded on polygraph paper and were on-line digitized (12 bit AD converter, Butterworth filter, -12 dB/octave, low-pass filter, -6 dB at 35 Hz; time constant 1.0 seconds; storage resolution of 100 Hz for the EEG). A trained staff member monitored the quality of the recordings throughout the night. Electrode impedance was checked at the start of each recording.

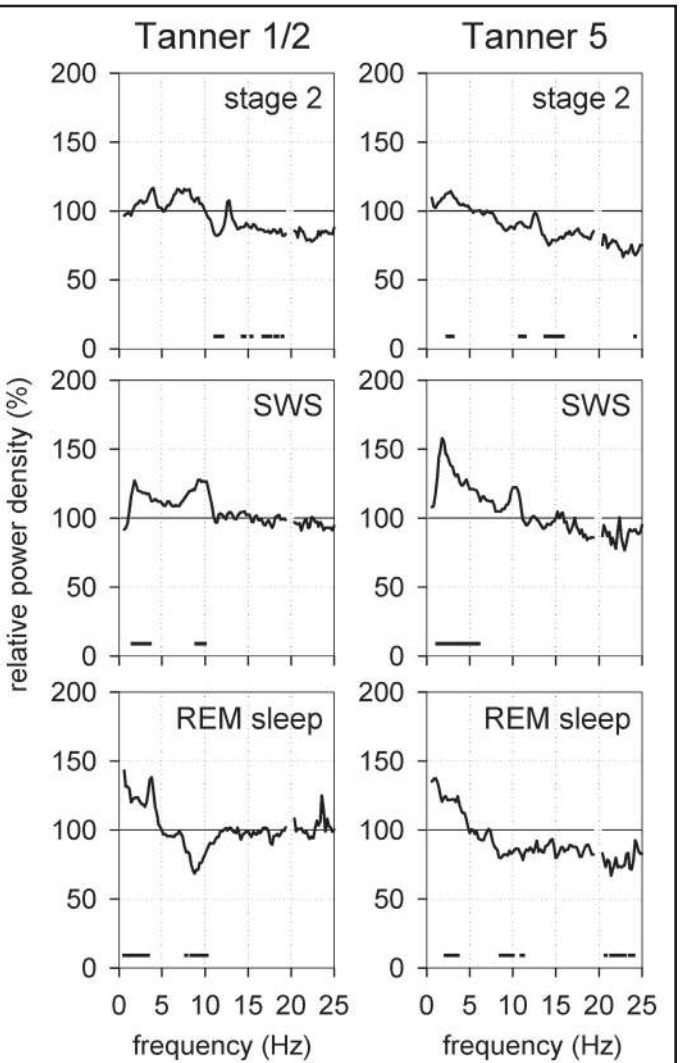

Figure 2—Effects of sleep deprivation on electroencephalogram (EEG) power spectra in stage 2, slow wave sleep (SWS), and rapid eye movement (REM) sleep. EEG power spectral values of each 0.2-Hz bin in the recovery night expressed as a percentage of each subject's corresponding value of the baseline night. Black bars at the bottom of each panel indicate significant differences between baseline and recovery nights ($P < .05$; paired t tests on log-transformed values).

The EEG was subjected to spectral analysis off line using a fast Fourier transform routine (Matlab, The MathWorks, Inc. Natick, Mass). Power spectra of consecutive 30-second epochs (Hanning window, averages of six 5-second epochs) were computed, resulting in a frequency resolution of 0.2 Hz. The lowest 2 frequency bins (0.2 and 0.4 Hz) were not used for further analysis due to their sensitivity to low-frequency EEG artifacts. Thirty-second epochs containing EEG artifacts (eg, eye blinks, movement artifacts, or signal noise) were excluded by careful visual inspection of the EEG (5%-14% of epochs scored as NREM sleep or rapid eye movement [REM] sleep were excluded). Spectral data were analyzed up to 25 Hz. The sleep stages were visually scored from the digital recordings for consecutive 30-second epochs according to the standard criteria of Rechtschaffen and Kales.[27] NREM sleep-REM sleep cycles were defined according to the criteria of Feinberg and Floyd.[28] NREM sleep episodes started with stage 2, ended with the beginning of REM sleep, and were required to last at least 15 minutes. The minimal duration of consecutive REM sleep episodes for completing a NREM sleep-REM sleep cycle

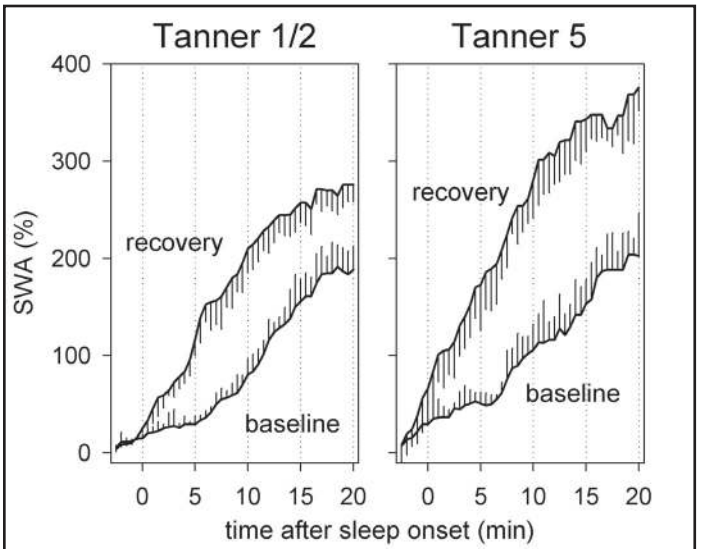

Figure 3—Build-up of slow-wave activity (SWA) in the first non-rapid eye movement (NREM) sleep episode. Time course of SWA plotted for 30-second epochs 3 minutes before sleep onset and during the first 20 minutes after sleep onset (0 = sleep onset). Data were expressed relative to mean all-night SWA (electroencephalogram power in the 0.6-4.6 Hz range) in NREM sleep during the baseline night. Mean values were smoothed with a 3-minute moving median. Vertical bars represent 1 SEM of unsmoothed data.

was 5 minutes (for the first REM sleep episode, no minimum criterion was applied). We divided the first NREM sleep episode into 2 separate episodes when SWS (stage 3 and 4 of NREM sleep) was interrupted by stages 1 or 2, wakefulness, or movement time for more than 12 minutes (skipped first REM sleep episode; for details see Appendix in Jenni and Carskadon[20]).

Parameter Estimation and Simulations

The homeostatic Process S was modeled by a saturating exponential function during wakefulness and an exponential decline during sleep[11,12]:

$$S(t) = (S_{SO} - LA) * e^{-t/\tau d} + LA \quad \text{during sleep}$$
$$S(t) = UA - (UA - S_{WU}) * e^{-t/\tau i} \quad \text{during waking}$$

with t = time, τ_d = time constant of the decreasing exponential function, τ_i = time constant of the saturating exponential function, UA = upper asymptote, LA = lower asymptote, S_{SO} = level of S at sleep onset, and S_{WU} = level of S at wake up. Empirical mean SWA (0.6-4.6 Hz) values per NREM sleep episode (normalized with respect to mean SWA during baseline) at episode midpoint served as the reference for the parameter estimation. To achieve a steady-state situation, the simulations were based on 2 baseline nights (sleep from 10:00 PM to 8:00 AM) followed by 36 hours of prolonged wakefulness and 3 recovery nights (first 8:20 PM to 8:00 AM; second and third 10:00 PM to 8:00 AM). Because data were available only for the baseline and the recovery night, data of the baseline night served as a second baseline and the third recovery night (Figure 4a, square symbols). The initial value of S was derived from the steady state. Parameters (UA, LA, τ_d, and τ_i) were estimated by minimizing the mean square error between data and simulations (Nelder-Mead simplex [direct search] method). According to the two-process model,[11,12] our approach implies that τ_d does not differ between baseline and recovery night,

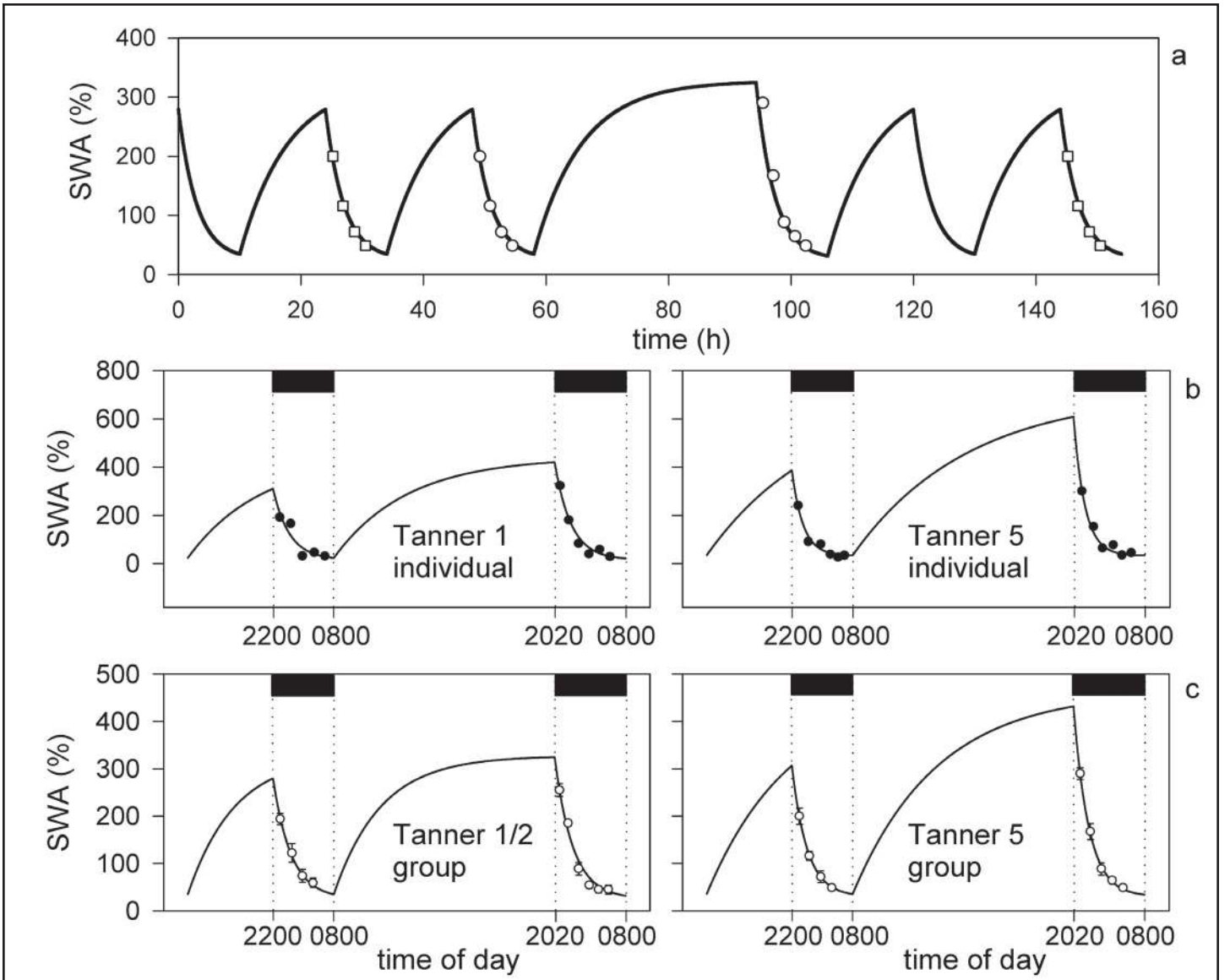

Figure 4—Empirical slow-wave activity (SWA) and simulated Process S in adolescents. a. Illustration of the parameter estimation of the homeostatic Process S. Empirical SWA plotted at non-rapid eye movement (NREM) sleep episode midpoints (open circles) served as a template to estimate the parameters of Process S. To achieve a stable steady-state situation, baseline data were repeated as prebaseline night and as a third recovery night (open squares; see Methods). Parameters were optimized by minimizing the mean square error between data and simulations. SWA and S are both expressed as a percentage of the mean all-night SWA during the baseline night. b. Individual data: Empirical data (filled circles, mean SWA per NREM sleep episode plotted at episode midpoint) and optimized Process S in 2 individuals (Tanner 1, girl, age 12 years, τ_i = 12.0 h, τ_d = 2.7 h, UA = 439.9%, LA = 15.6%; Tanner 5, boy, 16 years, τ_i = 18.9 h, τ_d = 1.8 h, UA = 705.5 %, LA = 32.4%). Black bars and dotted lines delimit the sleep episodes. c. Group data: Empirical data (open circles, mean SWA per NREM sleep episode, vertical bars ± SEM, plotted at episode midpoint) and optimized Process S for Tanner 1/2 (n=6) and Tanner 5 (n=6).

an assumption that was empirically tested for both developmental groups (for method see[20,21], data not shown). Parameter estimations were performed for individual data (Figure 4b, Table 2) and mean group data (Figure 4c, Table 2).

Statistics

The statistical package SAS® was used for statistical analyses (Version 8.02, SAS Institute, Inc., Cary, NC). One-, 2- or 3-way analyses of variance (ANOVA) included the between-subjects factor "developmental group" (Tanner 1/2, Tanner 5), and/or the within-subject factors "episode" (first 4 NREM sleep episodes), and/or "condition" (baseline, recovery), and/or "time bin" (30-second intervals 3 minutes before and within the first 20 minutes after sleep onset), and/or "2-hour interval" (interval during extended wakefulness) as appropriate. Probability values presented are based on Greenhouse-Geisser corrected degrees of freedom, but original F values are reported. The significance level was set at $P < .05$. Sleep variables and EEG power spectra were log transformed prior to statistical testing. Posthoc comparisons between and within the developmental groups were performed by unpaired or paired t tests, respectively.

RESULTS

Sleep Variables Derived From Visual Scoring

Table 1 summarizes sleep variables derived from visual scoring of the first 554.5 minutes after sleep onset (minimal common duration of all sleep episodes) of baseline and recovery nights. Sleep variables in the recovery night yielded the typical response to sleep

Table 2—Parameters of the Homeostatic Process S (Simulations)

	τ_i, h	τ_d, h	UA, %	LA, %	Difference,%
Tanner 1/2					
Individuals (SEM)	8.9(1.2)	3.1(0.4)	354.2(26.4)	21.0(8.5)	333.2(24.0)
Group data	8.9	2.8	346.4	33.2	313.2
Tanner 5					
Individuals (SEM)	15.4(2.5)	2.3(0.3)	503.5(44.4)	38.4(3.4)	465.2(44.8)
Group data	12.1	2.7	433.9	23.8	410.1
P value	.04	.17	.02	.09	.03

Values represent means ± SEM (n=6 in both groups) of the parameters estimated in individuals and mean group data. The fit in 1 Tanner 1/2 participant did not converge and thus was excluded. τ_i refers to time constant of increase, τ_d, time constant of decrease. UA, upper asymptote. LA, lower asymptote. Difference, difference between asymptotes. P values from unpaired 2-sided t tests on individual data (n=6).

deprivation (Table 1, main effect of "condition"). Thus, sleep latency was shorter in the recovery than in the baseline night, total sleep time per 554.5 minutes was longer, sleep efficiency was higher, the amount of stage 1 was decreased, the duration of stage 4 increased, and waking after sleep onset was reduced. A trend was observed toward a reduction of movement time during the recovery night compared with the baseline night. Group comparisons showed that NREM sleep stage 4 was lower in the Tanner 5 compared with the Tanner 1/2 group. The duration of NREM sleep and REM sleep episodes was similar in both groups. Episode duration was not affected by sleep deprivation and was similar in both groups. No significant "group × condition" interaction occurred in any sleep variable.

Sleep EEG Power Spectra

Average all-night EEG power spectra in NREM sleep during baseline and recovery are illustrated in Figure 1. The highest power values in both developmental groups and experimental conditions invariably occurred in the low-frequency range with an additional peak in the frequency range of sleep spindles. A 2-way ANOVA with the factors "developmental group" (Tanner 1/2, Tanner 5), and "condition" (baseline, recovery) yielded significant main effects of "group" in the frequency range up to 6.8 Hz. Main effects of "condition" were observed in the low-frequency range from 1.0 to 7.2 Hz, in the low (11.4-11.8 Hz) and high (13.4-15.0 Hz) sigma frequency ranges, and in the beta range (16.8-19.0 Hz and 21.8-24.8 Hz). The interaction "group × condition" for all-night average EEG spectra exhibited significant effects in the frequency range between 1.0 and 1.6 Hz, indicating that sleep deprivation affected the lowest frequency bins differently in the 2 developmental groups.

To better visualize the differences between baseline and recovery sleep, power density values of the recovery night were plotted as a percentage of the corresponding values in the baseline night (Figure 1, right panels). Power density in the Tanner 1/2 group was enhanced following sleep loss in the 1.6- to 3.6-Hz range, while in the Tanner 5 group, the enhancement encompassed a broader range (from 0.8-6.0 Hz). This increase was mainly restricted to SWS (Figure 2, middle panels). EEG power density in the sigma range (11-15 Hz)—corresponding to sleep spindle activity[29]—was significantly reduced during sleep after prolonged wakefulness in

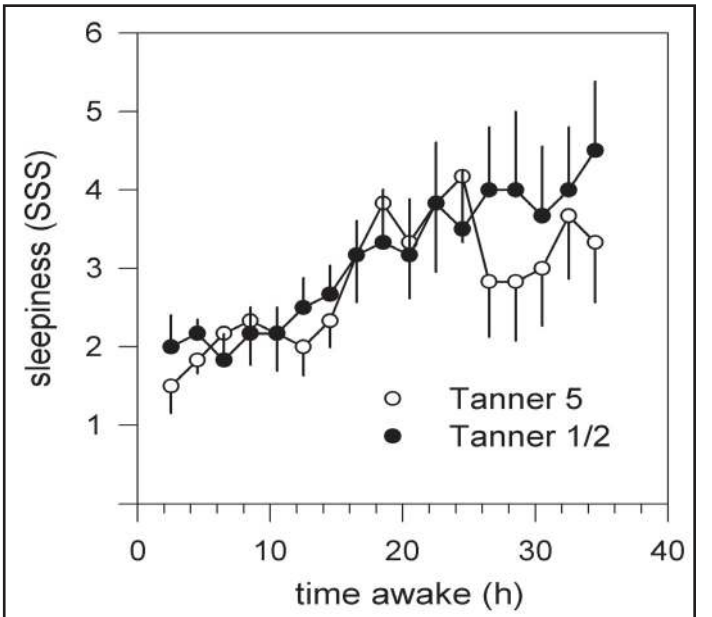

Figure 5—Time course of subjective sleepiness (Stanford Sleepiness Scale [SSS]) during 36 hours of extended wakefulness measured at 2-hour intervals. Values were averaged over subjects (n=6 in each group). Data of 1 participant of the Tanner 1/2 group was unavailable. Bars represent 1 SEM. Higher values of SSS indicate higher sleepiness. A 2-way analysis of variance with the factors "developmental group" (Tanner 1/2, Tanner 5) and "2-hour interval" (interval during extended wakefulness) yielded a significant main effect for "2-hour interval" ($F_{16,203} = 3.34$, $P < .0001$). The main effect "developmental group" and the interaction "developmental group × 2-hour interval" were not significant.

both developmental groups. The reduction included low and high sigma ranges (see also Figure 2, upper panels).

In the REM sleep EEG spectra (Figure 2, lower panels), an increase of power density for the recovery night was observed in the low-frequency range for both groups (0.6- to 3.4-Hz range in the Tanner 1/2 group and 2.2- to 3.6-Hz range in the Tanner 5 group). Conversely, a reduction of REM sleep EEG power during sleep following extended wakefulness was found in the alpha (8.4-10.2 Hz) and beta range (21.4-24 Hz) in both groups.

Sleep deprivation resulted in a stronger increase of SWA in Tanner 5 (39% above baseline) than in Tanner 1/2 adolescents (18% above baseline). In addition, sleep loss affected the increase of SWA in the first 20 minutes after sleep onset differently in the 2 developmental groups (first NREM sleep episode, Figure 3). A 3-way ANOVA on SWA expressed as a percentage of all-night mean SWA during baseline with the between-subjects factor "developmental group" (Tanner 1/2, Tanner 5), the within-subject factors "condition" (baseline, recovery), and "time bin" (30-second intervals; 3 minutes before and within the first 20 minutes after sleep onset) exhibited significant main effects of all factors (< .0001) and significant interactions "group × condition" (< .01) and "time bin × condition" (< .0001).

Simulation of Process S

Differences in sleep regulation between the developmental groups were investigated in the framework of the two-process model.[11,12] Parameters of the homeostatic Process S (time constants and asymptotes) were estimated by an optimization procedure (see Methods; Figure 4a). The parameters were determined on an indi-

vidual level (Figure 4b; Table 2, n=6 in both groups) and on mean group values (Figure 4c, Table 2, n=6 in both groups). A good correspondence between data and simulations was achieved (Figure 4). The parameters derived from group data closely resembled the average parameters of individuals (Table 2).

The decline of Process S (τ_d) was similar in both groups, whereas the increase (τ_i) was slower in Tanner 5 (average τ_i of individuals = 15.4 ± 2.5 hours, mean group τ_i = 12.1) compared with Tanner 1/2 adolescents (average τ_i of individuals = 8.9 ± 1.2 hours, mean group τ_i = 8.9). The upper asymptote was higher in the Tanner 5 than in the Tanner 1/2 group, and the difference between the asymptotes was larger in the more mature group (Figure 4c, Table 2).

Subjective Sleepiness

Subjective sleepiness (Stanford Sleepiness Scale) was measured at 2-hour intervals during prolonged wakefulness. Although sleepiness increased in the course of wakefulness in both groups (Figure 5), the groups did not differ in these subjective ratings.

DISCUSSION

This paper describes the effects of total sleep deprivation (ie, extended waking over a 36-hour period) on sleep and the sleep EEG in young humans between 10 and 16 years of age. The sleep-deprivation paradigm was performed with strict control of psychosocial confounders to allow specifying maturational changes of intrinsic sleep-wake regulation. We demonstrate here that the effects of total sleep loss on the sleep EEG in children and adolescents were similar to the effects in young adults,[13] although distinct differences were observed. Simulations in the framework of the two-process model of sleep regulation revealed that the build-up of homeostatic sleep pressure was slower in mature adolescents compared with prepubertal or early pubertal children, which may substantially contribute to the differences in sleep timing across this developmental stage (ie, the delay of the sleep phase in mature adolescents). Furthermore, we substantiate previous reports[20,21,23] that the nocturnal dissipation of sleep propensity—reflecting recovery processes during sleep—does not differ between prepubertal and postpubertal adolescents (Table 2). Such a difference on only one portion of the sleep homeostatic process is not unique. For example, mouse strains also differ with respect to the build-up and not to the decline of the homeostatic process.[30, 31]

The reliability of these data is enhanced by the care taken to control confounding effects before and during the study. For example, all participants slept on a fixed 10-hour sleep schedule for at least 10 nights before the in-lab sessions, and compliance was verified with sleep logs, activity monitors, and daily phone calls. A previous longitudinal study under well-controlled conditions revealed that (1) most adolescents need around 9 hours of sleep each night and (2) sleep need does not change across adolescence (from age 10 to 17 years).[24] The well-controlled prestudy sleep schedule (10:00 PM-8:00 AM) was, therefore, likely to provide adequate sleep quantity for participants in both developmental groups. Some might suggest that the differences in scheduled bedtime between baseline and recovery sleep and the variation of circadian phase markers between developmental groups (data not shown[22]) influenced the estimation of homeostatic parameters. We note, however, that sleep homeostasis is practically independent of the circadian timing system.[32]

Sleep Variables Derived From Visual Scoring

The reduction of stage 4 and the increase in stage 2 sleep in mature compared with prepubertal or early pubertal adolescents, accompanied by a reduction of low-frequency EEG activity (Table 1, Figure 1), corroborate other studies.[20,21,33-35] After sleep deprivation, both developmental groups showed the typical features of recovery sleep similar to those reported in young adults.[13,15] No interactions between developmental groups and condition were present for any sleep-stage variable, indicating no group-specific effects in the response to sleep loss (Table 1).

Effects of Sleep Deprivation on the Sleep EEG

Spectral analysis of the sleep EEG revealed that sleep deprivation affects the adolescent NREM sleep and REM sleep EEG similar to adults.[13,29,36,37] For example, an increase in the low-frequency portion of NREM sleep power spectra was observed in recovery relative to baseline sleep, while EEG activity in the frequency range of sleep spindles was reduced (Figure 1). The largest increase after sleep deprivation occurred between 1 and 2 Hz in both developmental groups. Distinct differences between the groups, however, were present. In particular, the EEG frequency range enhanced after sleep deprivation encompassed a broader range in the Tanner 5 than in the Tanner 1/2 group. Furthermore, the prolongation of waking affected SWA to a greater extent in mature (39% above baseline) compared with prepubertal or early pubertal adolescents (18% above baseline). The more prominent response of SWA to sleep deprivation in the Tanner 5 compared with the Tanner 1/2 group was also reflected in the acute growth of SWA within the first NREM sleep episode (Figure 3).

Another significant feature of the adolescent sleep EEG on the recovery night was the decrease of sigma activity (11-15 Hz) that occurred in the low and high sigma range (Figure 2). The trough and peak pattern in the sigma range of the relative spectra reflected differences in the peak frequencies of sigma activity. EEG power in the sigma range is thought to correspond to EEG activity of sleep spindles,[29] is reduced after sleep deprivation in adults,[13,29,38] and is under additional circadian control.[32] Because baseline and recovery sleep in the present study did not occur at the same clock time, interpretations about homeostatic and circadian effects on sleep spindles are not possible.

The deprivation procedure also affected REM sleep spectra during the recovery night (Figure 2, lower panels). The enhancement of REM sleep EEG power in the delta band (2-4 Hz) after sleep deprivation may reflect the intrusion of NREM sleep into REM sleep, while the attenuation of alpha activity (8-10 Hz) in REM sleep may result from increased REM sleep pressure after 36 hours of wakefulness.[39] In adults, the reduction of EEG power in the alpha band during REM sleep in the recovery period after sleep loss was proposed as a marker for REM sleep pressure.[39] Thus, some features of REM sleep regulation appear to be present already in children and adolescents.

Maturational Differences in Sleep Homeostasis

The age-related difference in the magnitude of the SWA response to sleep loss led to the idea that differences exist in the dynamics of the build-up of Process S between children and adolescents. We estimated the parameters of S to examine whether the time constants of

the increase of S would reflect such differences. Close fits between empirical data and simulations were obtained in individual recordings (Figure 4b) and from mean data in the 2 developmental groups (Figure 4c), indicating that the two-process model of sleep regulation can predict SWA on the basis of the temporal organization of sleep in children and adolescents. The statistical analysis revealed a faster increase of homeostatic sleep pressure during wakefulness in prepubertal or early pubertal children compared with mature adolescents, while the decrease of Process S was similar in both developmental groups. The upper asymptote after deprivation was lower and the difference between the asymptotes smaller in the Tanner 1/2 compared with the Tanner 5 group (Table 2). These findings may indicate that the brain reaches its capacity to generate slow waves with less waking in the young than in the mature brain. The more rapid saturation of the capacity for slow-wave generation may reduce the ability for young children to stay awake at the end of the day and may indicate that they live under higher sleep pressure (ie, closer to saturation). This rapid saturation manifests as a reduced relative increase of SWA during recovery from sleep deprivation in younger children compared with mature adolescents. Dijk and coworkers obtained preliminary estimates of the parameters of Process S for adults in a sleep-deprivation experiment with young (mean age 23.6 years) and old participants (67.8 years).[40] While the absolute levels of SWS and SWA were substantially lower in the old compared with the young people (as in mature adolescents compared with prepubertal children[20]), the relative increase of SWA during recovery after 40 hours of sleep loss was nearly identical (45% and 44% above the level during baseline for young and older people, respectively; in comparison to 18% in the Tanner 1/2 and 39% in the Tanner 5 group). These data indicate the greater correspondence of the SWA response in adults to that of mature adolescents than to prepubertal or early pubertal children, suggesting that the brain process underlying sleep homeostasis undergoes rapid changes early in development and minimal changes after adolescence.

Implications for Understanding Adolescent Sleep Behavior

The practical implications of the present study are that mature adolescents may experience a decrease in their sensitivity to extended wakefulness and live under lower sleep pressure at scheduled bedtime than prepubertal or early pubertal children. This interpretation is in agreement with a recent study demonstrating that mature adolescents manifest less sleep pressure than prepubertal children for approximately 4 hours following scheduled bedtime.[41] After 14.5, 16.5, and 18.5 hours awake, sleep tendency assessed by the latency to sleep onset was significantly lower in postpubertal than prepubertal adolescents, independent of circadian phase. We note that, in the present study, differences between developmental groups were not observed when examining subjective sleepiness using the Stanford Sleepiness Scale (Figure 5). Although the physiologic mechanisms underlying the suggested decrease in sensitivity to sleep loss in the course of puberty are not known, they are likely associated with rapid changes in brain development across the teen years.[42] We propose that the higher tolerance to prolonged waking may prepare children for adult lifestyles and for performing tasks under sleep deficits that are common in adults of modern societies.[8]

This report has examined aspects of the homeostatic Process S in adolescence. We submit, however, that circadian processes interact with the sleep homeostat to govern the timing of adolescent sleep (reviewed in[19]). Together, these processes may modulate not only sleep timing, but also neurobehavioral functions during waking, which can affect attention, memory, and learning.[43]

Roenneberg and coworkers have recently proposed that the adolescents sleep phase delay can be viewed as a normal developmental milestone.[44] The teenage years, however, may also represent a vulnerable period with respect to disorders of sleep-wake patterns.[45] This view is supported by epidemiologic data showing that delayed sleep phase syndrome, a specific clinical entity with inability to fall asleep and wake up at socially acceptable times, shows peak prevalence during adolescences (7%-16%[46-48]), while it is relatively rare in adults (0.13%-0.17%[49]). Studies in adolescent with delayed sleep-phase syndrome examining homeostatic and circadian aspects of sleep-wake regulation may be helpful for understanding the pathophysiology of this disorder.

We conclude that sleep homeostasis during puberty exhibits specific maturational changes. While the increase of sleep pressure during waking is slower in mature adolescents compared with prepubertal or early pubertal children, the nocturnal dissipation of the sleep drive is similar. Limitations of the study, however, should be considered when interpreting our results. The conclusion is based on indirect evidence (i.e., sleep deprivation) in a cross-sectional and relatively small sample. The dynamics of sleep homeostasis were derived from simulations of empirical SWA during nocturnal baseline (which also served as second baseline and third recovery night) and recovery sleep. Direct measures of sleep pressure during wakefulness in longitudinal samples are needed to confirm our conclusions. Quantification of the build-up rate of Process S in nap protocols (such as in Dijk et al[50]) or by examining theta activity in the waking EEG across extended waking[51,52] may be fruitful approaches.

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