Insufficient Non-REM Sleep Intensity in Narcolepsy-Cataplexy

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Study Objectives: To compare electroencephalogram (EEG) dynamics during nocturnal sleep in patients with narcolepsy-cataplexy and healthy controls. Fragmented nocturnal sleep is a prominent feature and contributes to excessive daytime sleepiness in narcolepsy-cataplexy. Only 3 studies have addressed changes in homeostatic sleep regulation as a possible mechanism underlying nocturnal sleep fragmentation in narcolepsy-cataplexy.

Design, Setting and Participants: Baseline sleep of 11 drug-naive patients with narcolepsy-cataplexy (19-37 years) and 11 matched controls (18-41 years) was polysomnographically recorded. The EEG was subjected to spectral analysis.

Interventions: None, baseline condition.

Measurements and Results: All patients with narcolepsy-cataplexy but no control subjects showed a sleep-onset rapid eye movement (REM) episode. Non-REM (NREM)-REM sleep cycles were longer in patients with narcolepsy-cataplexy than in controls (P = 0.04). Mean slow-wave activity declined in both groups across the first 3 NREM sleep episodes (P<0.001). The rate of decline, however, appeared to be steeper in patients with narcolepsy-cataplexy (time constant: narcolepsy-cataplexy 51.1 ± 23.8 minutes [mean ± SEM], 95% confidence interval [CI]: 33.4-108.8 minutes) than in controls (169.4 ± 81.5 minutes, 95% CI: 110.9-357.6 minutes) as concluded from nonoverlapping 95% confidence interval of the time constants. The steeper decline of SWA in narcolepsy-cataplexy compared to controls was related to an impaired build-up of slow-wave activity in the second cycle. Sleep in the second cycle was interrupted in patients with narcolepsy-cataplexy, when compared with controls, by an increased number (P = 0.01) and longer duration (P = 0.01) of short wake episodes.

Conclusions: Insufficient NREM sleep intensity is associated with nonconsolidated nocturnal sleep in narcolepsy-cataplexy. The inability to consolidate sleep manifests itself when NREM sleep intensity has decayed below a certain level and is reflected in an altered time course of slow-wave activity across NREM sleep episodes.

Keywords: Narcolepsy-cataplexy; homeostasis; slow-wave activity; slow-wave energy; hypocretin-deficiency

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NARCOLEPSY WITH CATAPLEXY IS CHARACTERIZED BY EXCESSIVE DAYTIME SLEEPINESS, CATAPLEXY (A SUDDEN BILATERAL LOSS OF VOLUNTARY MUSCLE tone provoked by emotions) and, facultatively, by other rapid eye movement (REM) sleep phenomena such as sleep paralysis and hallucinations (narcoleptic tetrad). Patients with narcolepsy with cataplexy have normal amounts of sleep over 24 hours, but their day-night sleep distribution shows greater amounts of daytime sleep and fragmented nocturnal sleep. Disturbed nocturnal sleep is often referred to as the fifth symptom of the narcoleptic tetrad and becomes particularly disabling with disease progression and may contribute to excessive daytime sleepiness in this disorder. Patients with narcolepsy-cataplexy may start nocturnal sleep with REM sleep (sleep onset REM period [SOREMP]). Once sleep is initiated, a high number of sleep-stage transitions, short bouts of wakefulness and/or sustained wake periods occur within the sleep period.

It has been hypothesized that a dysfunctional homeostatic NREM sleep-regulatory process contributes to sleep fragmentation in patients with narcolepsy-cataplexy. The process, referred to as sleep homeostasis, enables organisms to compensate for transient sleep loss from an average “reference level” by changes of sleep duration and sleep intensity. The 2-process model of sleep regulation assumes that the interaction of the sleep-wake dependent homeostatic process S and the circadian process C (which is independent of sleep and wakefulness) determines the timing, duration, and stability of sleep and wakefulness. Process S can be derived from the time course of electroencephalogram (EEG) slow wave activity (SWA; power within 0.75-4.5 Hz range) in NREM sleep. SWA dissipates roughly exponentially across successive NREM sleep episodes. The level of SWA at sleep onset is a function of the duration of prior wakefulness. SWA at sleep onset rises after prolonged wakefulness and declines after extended sleep. The temporal dynamics of SWA are characterized also by an opposite relationship to spindle-frequency activity (SFA; power within 12-14 Hz range). SFA exhibits an increasing trend over successive NREM sleep episodes. The intra-episodic time course of SFA resembles a U-shaped pattern that opposes the time course of SWA within a NREM sleep episode. Specifically, both activities, SWA and SFA, rise at the beginning and decline at the end of a NREM sleep episode. This positive correlation reverses in the middle of a NREM sleep episode, in which SWA peaks while SFA exhibits a trough.

Based on the dynamics of EEG SWA in 3 published studies, 3 hypotheses about abnormal sleep homeostasis in narcolepsy-cataplexy have been developed. (1) NREM sleep homeostasis is essentially intact in patients with narcolepsy-cataplexy, as shown by an exponential decline of SWA across the sleep period and enhanced SWA in patients with narcolepsy-cataplexy and in controls after sleep deprivation. Following 24 hours of...
wakefulness, the initial level of SWA is even more increased in patients with narcolepsy-cataplexy, and SWA declines faster, when compared with controls. Thus, NREM sleep homeostasis in patients with narcolepsy-cataplexy—although qualitatively intact—may be quantitatively different, as compared with controls. (2) NREM sleep homeostasis is impaired in patients with narcolepsy-cataplexy. A recent study failed to demonstrate a significant decay of SWA across subsequent NREM sleep episodes in patients with narcolepsy-cataplexy. (3) NREM sleep homeostasis is intact but controlled by a predominant ultradian rhythm. During a prolonged bed-rest condition of 32 hours with sleep ad libitum, peaks of SWA occurred every 4 hour. This temporal pattern of SWA distribution is thought to reflect a strong ultradian sleep drive that contributes to sleep-wake dysregulation in patients with narcolepsy-cataplexy.

Considering the conflicting results about homeostatic sleep regulation, we intended to further investigate sleep regulation in patients with narcolepsy-cataplexy. We performed analysis of the EEG in NREM sleep and REM sleep during baseline nights and studied the SWA and SFA dynamics across subsequent NREM sleep periods and their possible relationship to sleep fragmentation. We hypothesized that homeostatic regulation is generally intact in patients with narcolepsy-cataplexy. We were further interested in comparing the time course of SWA between patients with narcolepsy-cataplexy and controls. Because we had to expect a higher rate of nocturnal sleep fragmentation in patients with narcolepsy-cataplexy, we were specifically interested in learning how sleep fragmentation affects the time course of SWA and the intra-episodic SFA-SWA relationship in patients with narcolepsy-cataplexy.

METHODS

Subjects and study protocol

Baseline sleep recordings of 11 patients with narcolepsy and definite cataplexy (men: 5, women: 6; mean age, 28 years, range, 18-37 years) and 11 age- and sex-matched healthy controls (mean age 27 years, range, 18-41 years) who participated in previous (n=5) and ongoing studies (n=6) were analyzed. The diagnosis of narcolepsy-cataplexy was made according to standard criteria (American Sleep Disorders Association 2005) based on clinical symptoms and sleep studies. Cataplexy was considered to be definite according to proposed standard criteria. The patients’ Epworth Sleepiness score was 15.1 ± 3.0 (mean ± SD; range: 10-19), the Ullanlinna Narcolepsy Scale was 20.9 ± 5.7 (13-27), the Swiss narcolepsy scale was -42 ± 25.4 (-6 to -70) and the Stanford cataplexy scale showed a mean of 69.3% ± 24.6% (45.8%-91.7%). HLA typing was available in 9 of 11 patients and was positive for HLA-DQB1*0602 in all 9 patients tested. Since the study started before routine cerebrospinal fluid-hypocretin assessment, these measurements were obtained in only 2 patients and were not detectable in either patient. In all patients, pharmacologic treatments were discontinued for at least 5 elimination half-life times of the respective substances before entering the experiment. Such a procedure is feasible and ethically justifiable for clinical studies with patients with narcolepsy-cataplexy, but certain rebound or after effects of medication cannot be entirely excluded. Two of the patients had not previously taken any medication for narcolepsy.

Controls were recruited among the students of the Universities of Zürich and Berne and by advertisement in local newspapers. They were paid for participation. Controls reported having no sleep disturbances and no medical history of neurologic and psychiatric disease. All denied taking any medication or consuming illicit drugs. Interviews, questionnaires, and polysomnographic recording of a screening night in the sleep laboratory prior to the study excluded sleep disturbances. Participants with low sleep efficiency (< 80 %), sleep apnea (apnea-hypopnea index > 5 per hour), and nocturnal myoclonus (≥ 5 periodic limb movements per hour of sleep) were excluded from the study.

Controls had to abstain from caffeine and alcohol and had to maintain regular 8:16-hour sleep-wake cycles for 3 days before the experiment. Patients with narcolepsy-cataplexy were asked to restrict daytime napping to a minimum, but unavoidable short naps due to irresistible sleepiness were allowed. Compliance with the prestudy instructions was verified in a subsample of participants by determining the level of caffeine in saliva and breath ethanol concentration upon arrival in the sleep laboratory and by inspecting the records of activity monitors worn on the wrist of the nondominant arm.

All participants gave written consent to the study protocol, which was approved by the local ethics committee. Sleep recordings took place at the sleep laboratory of the Neurology Department (n=5), University Hospital Berne, Switzerland, and at the sleep laboratory of the Institute of Pharmacology and Toxicology (n=6), University of Zürich, Switzerland. The protocol included an adaptation night prior to the experimental baseline night. In both nights, sleep was scheduled from 11:00 p.m. to 7:00 a.m. (n=7) or from 12:00 p.m. to 8:00 a.m. (n=4). The data of only the baseline night were analyzed.

Polysomnographic recordings

Polysomnographic recordings included EEG (data from C3-A2 derivation are reported here), electrooculogram and submental electromyogram using polygraphic amplifiers (Berne lab: PSA 1; Zurich lab: PSA24, Braintronics Inc., Almere, The Netherlands). The analog signals were conditioned by a high-pass filter (-3 dB at 0.16 Hz), a low-pass filter (-3dB at 102 Hz and approximately -40 dB at 256 Hz), and a notch filter (50 Hz), digitized and transmitted via fiberoptic cables to a personal computer. Data were sampled with a frequency of 512 Hz, digitally filtered (EEG and electrooculogram: low-pass FIR filter, -3dB at 49 Hz; electromyogram: band-pass FIR filter, -3 dB at 15.6 and 54 Hz) and stored on a hard disk with a resolution of 128 Hz (see for further details of recording parameters in the Berne lab).

Sleep stages were visually scored for consecutive 20-second epochs (C3-A2 derivation) according to standard criteria. Artifacts were visually identified, and, in addition, a semi-automated algorithm with a sliding mean was applied to exclude epochs with high- (20-40 Hz) and low-frequency (0.75-4.5 Hz) artifacts. Power spectra of consecutive 20-second epochs were computed off-line by using a fast-Fourier transform (Hanning window, linear detrending, average of five 4-second epochs), resulting in a frequency resolution of 0.25 Hz. Values below 0.75 Hz and above 20 Hz were omitted. The frequency bins and bands will be indicated by the encompassing frequency range (i.e., the 1.0-Hz bin denotes 0.875-1.125 Hz).
The NREM sleep–REM sleep cycles were defined according to modified criteria of Feinberg and Floyd. NREM sleep episodes starting with stage 2 and containing at least 15 minutes of sleep stages 2 to 4 were succeeded by REM sleep episodes of at least 5 minutes in duration. For the completion of the first and the last cycle, no minimal criterion for the REM sleep duration was applied. Sleep-onset REM period (SOREMP) was defined as at least one 20-second epoch of REM sleep occurring in the first 15 minutes of sleep (NREM sleep stage 2, 3, 4 and REM sleep). In 1 narcoleptic patient and in 1 control, the first REM sleep episode was skipped, and an epoch of movement time was used as the criterion for the completion of the first cycle. The SOREMP did not contribute to sleep cycle length, i.e., when a SOREMP was present, the first cycle started after the SOREMP according to above-mentioned criteria (succession of a NREM sleep episode and a REM sleep episode). At least 3 NREM–REM sleep cycles were completed in all recordings.

Statistics and data analyses

Visually scored sleep variables, length of NREM and REM sleep episodes, and EEG power spectra in NREM sleep (stages 2, 3 and 4) and REM sleep were analyzed. To approximate a normal distribution, absolute power densities and ratios of power densities were log-transformed prior to statistical tests. Significant differences in sleep stages, cycle length, and power values in subsequent NREM sleep episodes were estimated by 2-way repeated measures analysis of variance (rANOVA) (general linear model), with the between-subject factor “group” and the within-subject factors “NREM sleep episode” (1-3). A Greenhouse-Geisser correction of degrees of freedom was applied when data sphericity was violated, but the original degrees of freedom are reported. For comparison between and within the 2 groups, unpaired or paired 2-tailed \( t \)-tests were performed. Differences in sleep latencies were tested with nonparametric tests. The comparison of the SFA-SWA relationship across subsequent NREM sleep episodes is described in the results.
section. The significance level was set at $\alpha < 0.05$. For statistical analyses, the SPSS Version 14.0 (SPSS, Inc, Chicago, IL) and SAS Version 8.02 (SAS Institute Inc., Cary, NC ) were used.

RESULTS

Sleep variables and cycle length

All patients with narcolepsy-cataplexy, but no control subjects, showed a SOREMP. Sleep latency and REM sleep latency were significantly shorter in patients with narcolepsy-cataplexy, compared with controls (Table 1). Time spent in wakefulness after sleep onset was longer in patients with narcolepsy-cataplexy, resulting in reduced sleep efficiency. No differences were observed in the time spent in slow-wave sleep and REM sleep. The durations of the NREM-REM sleep cycles differed between the 2 groups (main effect of “group”: $F_{1,20} = 4.95$, $P = 0.04$), with a longer second cycle in patients with narcolepsy-cataplexy than in controls, due to an increase in NREM sleep episode duration (see Figure 1; “NREMS-episode” × “group” interaction: $F_{2,40} = 4.71$, $P = 0.02$; NREM-REM sleep cycle 2: narcolepsy-cataplexy = 128 ± 40 minutes [mean ± SD]; controls = 96 ± 19 min; posthoc unpaired $t$-test $P = 0.03$; NREM sleep episode 2: narcolepsy-cataplexy = 97 ± 32 minutes; controls = 70 ± 14 minutes; posthoc unpaired $t$-test $P = 0.02$). Representative individual sleep profiles and slow-wave activity (SWA) of a patient with narcolepsy-cataplexy and a healthy control are shown in Figure 2.

All-night EEG power spectra and changes in EEG power over consecutive NREM sleep episodes

All-night absolute EEG power spectra (0.75-20 Hz) in NREM sleep (stages 2, 3, and 4) in both groups showed high power in the delta-frequency band (0.75-5 Hz) and a secondary peak in the sigma band (12-15 Hz). Power densities were lower in REM sleep. No differences between patients with narcolepsy-cataplexy and controls were found in either NREM sleep or REM sleep (data not shown).

**Figure 2**—Individual hypnogram and time course of slow-wave activity (SWA) in a patient with narcolepsy-cataplexy (upper panel) and a healthy control (lower panel). Sleep stages and electroencephalogram SWA (power within 0.75-4.5 Hz). The bold line with filled triangles (narcolepsy-cataplexy) or open circles (control) represents SWA over equal time intervals (7 parts in non-rapid eye movement (NREM) sleep episode and 3 parts in rapid eye movement (REM) sleep episode). W refers to wakefulness; M, movement time; R, REM sleep; 1, 2, 3, and 4, NREM sleep stages. Note different scales.

**Figure 3**—Relative electroencephalogram (EEG) power density spectra in non-rapid eye movement sleep (NREMS) in narcolepsy-cataplexy (NC, upper panel; n=11) and controls (C, lower panel; n=11). Relative EEG power densities (0.75-20 Hz) in the second (filled triangles) and third (open circles) NREMS episodes were expressed as a percentage of the corresponding value of the first NREMS episode (dashed line 100%). Bottom panels show F values of 2-way repeated analysis of variance for log-transformed absolute values: factors “group” (narcolepsy-cataplexy, controls), “episode” (1-3). Significant F values ($P < 0.05$) in black and nonsignificant ($P > 0.05$) in white bars.
The temporal evolution of EEG power spectra over the first 3 NREM sleep episodes are shown in Figure 3. Each frequency bin in the second and third NREM sleep episode was expressed relative to the corresponding value of the first NREM sleep episode. Power density changed over a large frequency range across subsequent NREM sleep episodes (see significant F-values in “episode” panel at the bottom of Figure 3). In the delta (0.75-3.75 Hz) and beta (above 14.75 Hz) range, these changes evolved differently in the 2 groups (“episode” × “group” interaction: minimum $F_{2, 40} = 3.31, P \leq 0.05$). In controls, power density of the 0.75- to 3.75-Hz band progressively decreased over consecutive NREM sleep episodes. These changes were not observed in patients with narcolepsy-cataplexy. In patients with narcolepsy-cataplexy, a marked decrease of power density in the 0.75- to 7.0-Hz frequency band already occurred in the second episode, but no further decrease evolved in the third episode. Patients with narcolepsy-cataplexy also differed from controls in most frequency bins above 14.75 Hz (minimum $F_{2, 40} = 3.55, P \leq 0.05$). In REM sleep, power densities remained stable over consecutive episodes (data not shown).

Dynamics of SWA

The time course of SWA over consecutive NREM-REM sleep episodes is shown in Figure 4 (upper panels). Each NREM sleep and each REM sleep episode was subdivided into equal time intervals (7 parts for NREM sleep episodes and 3 parts for REM sleep episodes) and plotted against the mean timing of NREM and REM sleep. The evolution of SWA after sleep onset is delayed in the narcolepsy-cataplexy group, as compared with the control group, due to the occurrence of SOREMP. In both groups, SWA was highest in the first NREM sleep episode and declined across consecutive NREM-REM sleep episodes, yet the temporal evolution of SWA declined differently in the groups. SWA was lower in the second NREM sleep episode in patients with narcolepsy-cataplexy than in controls. The different dynamics of SWA were confirmed by a 2-way rANOVA (1 value per episode) with the between-factor “group” (narcolepsy-cataplexy, controls) and the within-factor “NREM sleep episode”; 1-3 (main effect for “NREM sleep episode”: $F_{2, 40} = 32.21, P = 0.001$; “group” × “NREM sleep episode” interaction: $F_{2, 40} = 4.18, P<0.03$; posthoc $t$-test for SWA in the second NREM sleep episode, $P<0.02$). To further compare the dynamics of the SWA decline, an exponential function was fitted to all available individual SWA data (i.e., not restricted to the first 3 NREM sleep episodes (for details refer to legend to Figure 5). The time constants differed between patients with narcolepsy-cataplexy (51.1 ± 23.8 minutes, 95% CI: 33.4 -108.8 minutes]) and controls (169.4 ± 81.5 minutes, 95% CI: 110.9 - 357.6 minutes), as demonstrated by the nonoverlapping confidence intervals. The lower SWA value of patients with narcolepsy-cataplexy in the second NREM sleep episode was accompanied by a prolongation of the episode duration (Figure 1).
and Figure 4), suggesting that the amount of SWA integrated over episode time was similar in both groups. This assumption was confirmed by a 2-way rANOVA of slow-wave energy (SWE, i.e., EEG power of 0.75-4.5 Hz integrated over time of NREM sleep episode) with the factors “group” and “NREM sleep episode.” SWE declined across consecutive NREM sleep episodes (F<sub>2,40</sub> = 27.51, P<0.001), yet the decline was similar in both groups (“group” × “NREM sleep episode” interaction: F<sub>2,40</sub> = 1.71, P = 0.2). Relative SWE expressed as a percentage of the all-night SWE was 48.8% ± 7.5% (mean ± SD; narcolepsy-cataplexy) vs 40.4% ± 16.1% (controls) in the first NREM sleep episode, 20.9% ± 12% versus 28.6% ± 7.1% in the second NREM sleep episode, and 16.9% ± 9.7% versus 16.5% ± 6.3% in the third NREM sleep episode. To examine whether the build-up of SWA within the first 30 minutes of each NREM sleep episode differed between the 2 groups, the rise rate of SWA was calculated from the median slopes of adjacent 2-minute epochs. The mean values of the median slopes were subjected to unpaired t-tests. The build-up of SWA was similar in both groups in the first and the third episode but shallower in patients with narcolepsy-cataplexy in the second episode (P = 0.04) (Figure 6). An analysis of sleep-wake transitions that occurred within the NREM sleep episodes demonstrated that the shallow build-up of SWA was related to both the number and duration of brief intervening awakenings (defined as at least one 20-second epoch of wakefulness after sleep onset); see Table 2 and Figure 4. The mean number of awakenings and mean duration of wakefulness was higher in patients with narcolepsy-cataplexy in NREM-REM sleep cycles (factor “group”: F<sub>1,20</sub> = 8.82, P = 0.01 for duration of wakefulness; F<sub>1,20</sub> = 5.42, P = 0.03 for duration of wakefulness; F<sub>1,20</sub> = 5.01, P = 0.04 for number of awakenings). A significant “group” × “cycle” interaction for mean duration of wakefulness (F<sub>2,40</sub> = 4.68, P = 0.02) and posthoc t-test revealed that duration of wakefulness was highest in second cycle in patients with narcolepsy-cataplexy compared with controls (narcolepsy-cataplexy = 7.9 ± 2.3 minutes, controls = 1.1 ± 0.3 minutes; P = 0.03).

Dynamics of spindle frequency activity

The time course of spindle frequency activity (SFA) and its relation to the time course of SWA is illustrated in Figure 4. The evolution of SFA across consecutive NREM sleep episodes (expressed as percentage of the mean nocturnal value and plotted at midpoints of NREM sleep episodes) was similar in both groups (data not shown). The time course of intra-episodic SFA, however, was disturbed in narcolepsy-cataplexy with the beginning of the second NREM sleep episode. A typical U-shaped pattern of SFA was present only in the first NREM sleep episode but not in subsequent NREM sleep episodes. By contrast, controls exhibited a U-shaped pattern across all 3 NREM sleep episodes. To quantify the SFA-SWA relationship, correlation coefficients were computed over 7 time intervals in each NREM sleep episode. Repeated measures ANOVA on Fischer-Z transformed SFA-SWA correlation coefficients per NREM sleep episode confirmed the evolution of SFA-SWA differed between narcolepsy-cataplexy and controls.
The most important findings of the present study are the changes in the dynamics of SWA across subsequent NREM sleep episodes in patients with narcolepsy-cataplexy. Similar to controls, patients with narcolepsy-cataplexy showed a typical declining trend of SWA during nocturnal sleep, yet the time course of SWA dissipation per NREM sleep episode differed between the 2 groups. Most importantly, the build-up of SWA in the second WA cycle was attenuated in narcolepsy-cataplexy and resulted in a steeper decline in patients with narcolepsy-cataplexy, compared with controls. Spectral analysis of the sleep EEG per sleep cycle corroborated sleep-cycle–related changes of NREM sleep in narcolepsy-cataplexy. Lower power densities in the delta band (0.75-3.75 Hz) were present in the second NREM sleep episode of patients with narcolepsy-cataplexy. The changes in NREM sleep dynamics were accompanied by a prolongation of the second NREM sleep episode. Also, the physiologic U-shaped time course of SFA and the inverse SFA-SWA relationship was preserved only in the first, but lost in subsequent, NREM sleep episodes. These abnormalities in the dynamics of NREM sleep in narcolepsy-cataplexy are contrasted (apart from the occurrence of SOREMP at sleep onset) by the lack of changes in REM sleep episode duration.

The differences between patients with narcolepsy-cataplexy and controls in SWA evolution cannot be explained by different levels of sleep pressure in the 2 groups for several reasons. Firstly, absolute values of all-night SWA and SWE per NREM-REM sleep cycle (i.e., SWA integrated over sleep-cycle time of each NREM sleep episode) were similar in both groups. In particular, SWE of the second NREM sleep episode did not differ between patients with narcolepsy-cataplexy and controls. This means that patients with narcolepsy-cataplexy and controls dissipated the same amount of SWA in the second NREM sleep episode, but patients with narcolepsy-cataplexy needed more time (evident by the prolonged duration of the second NREM sleep episode; see Figure 1(A) and Figure 4(A)). Secondly, SWA attenuation of the second cycle in patients with narcolepsy-cataplexy cannot be attributed to a different SWA evolution in the first NREM sleep episode because the absolute level of SWA and duration of the first NREM sleep episode were comparable in the 2 groups. Also, NREM sleep pressure did not differ between the 2 groups, as demonstrated by a similar build up of SWA within the first 30 minutes of the first NREM sleep episode (see Figure 6(A)).

An attenuated SWA evolution in the second NREM sleep episode has been previously and consistently described in narcolepsy.\textsuperscript{3-6,21} Thus, changes in the second cycle appear to be a key feature in nocturnal sleep of narcolepsy-cataplexy and provide a window into the mechanisms underlying sleep dysregulation in narcolepsy-cataplexy. Others have explained these changes in SWA time course with a different dynamics of process S\textsuperscript{5} or have postulated an ultradian rhythm that predominates intact NREM sleep homeostasis.\textsuperscript{3} Considering both previous hypotheses, we instead propose a threshold-dependent insufficient NREM sleep intensity as a basic mechanism underlying fragmented nocturnal sleep in narcolepsy-cataplexy.

### Threshold-dependent Insufficient NREM Sleep Intensity

A possible explanation for both the shallow evolution of SWA and the increased duration of the second sleep cycle is our finding of frequent wake intrusions most prominent in the second NREM sleep episode. The frequency of short wake bouts was low in the first NREM sleep episode but markedly increased across subsequent NREM sleep episodes, with a peak in the second NREM sleep episode. This means that nocturnal sleep was most fragmented in the second NREM sleep episode of narcolepsy-cataplexy. The impaired build-up of SWA within a NREM sleep episode was related to the frequency of sleep-wake transitions and the cumulative duration of wakefulness (refer also to Figure 4(A) and for individual recordings to Figure 2). We therefore assume that the time course of SWA in narcolepsy-cataplexy is an expression of a threshold-dependent sleep fragmentation. In other words, the inability to consolidate sleep manifests itself when NREM sleep intensity decays below a certain level. In the present study, such a threshold level was rapidly achieved after the first NREM sleep episode. We conclude that such a mechanism is a possible cause of nocturnal sleep fragmentation resulting in reduced SWA, although we cannot exclude that, alternatively, insufficient NREM

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### Table 2: Duration of wakefulness and numbers of awakenings in NREM and REM sleep episodes and NREM-REM sleep cycles

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<td>7.9 1.7</td>
<td>2.1 0.7</td>
</tr>
<tr>
<td>3</td>
<td>8.2 1.6</td>
<td>2.3 0.7</td>
</tr>
</tbody>
</table>

WASO refers to the amount of wakefulness in minutes (wake within non-rapid eye movement [NREM] sleep and rapid eye movement [REM] sleep episodes is defined as at least one 20-second epoch of wakefulness after sleep onset [WASO]).

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The most important findings of the present study are the changes in the dynamics of SWA across subsequent NREM sleep episodes in patients with narcolepsy-cataplexy. Similar to controls, patients with narcolepsy-cataplexy showed a typical declining trend of SWA during nocturnal sleep, yet the time course of SWA dissipation per NREM sleep episode differed between the 2 groups. Most importantly, the build-up of SWA in the second WA cycle was attenuated in narcolepsy-cataplexy and resulted in a steeper decline in patients with narcolepsy-cataplexy, compared with controls. Spectral analysis of the sleep EEG per sleep cycle corroborated sleep-cycle–related changes of NREM sleep in narcolepsy-cataplexy. Lower power densities in the delta band (0.75-3.75 Hz) were present in the second NREM sleep episode of patients with narcolepsy-cataplexy. The changes in NREM sleep dynamics were accompanied by a prolongation of the second NREM sleep episode. Also, the physiologic U-shaped time course of SFA and

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sleep intensity leads to increased sleep fragmentation. High sleep fragmentation may reflect a state instability in narcolepsy-cataplexy. State instability is a core feature of narcolepsy-cataplexy, which was originally suggested as "state boundary dyscontrol" by Broughton. State instability refers to facilitated multiple transitions between all behavioral states. Other components of state instability include impaired consolidation of wakefulness and dissociative states such as cataplexy or hallucinations. Although we cannot exclude that abnormalities in REM sleep also contribute to sleep instability we found (apart from SOREMP) no profound qualitative and quantitative differences of REM sleep across nocturnal sleep, including data obtained from spectral analysis.

Changes in Homeostatic Sleep Regulation?

An exponential decline of SWA across NREM episodes with a strong reduction of SWA from the first to the second cycle has been consistently observed in previous studies. Following the assumption that SWA is an EEG marker of sleep propensity and that its exponential decline reflects the homeostatic process S of sleep regulation, it has been proposed that NREM sleep homeostasis is qualitatively intact but exaggerated in narcolepsy-cataplexy. The higher decay rate of SWA would then reflect faster dynamics of process S starting from of a higher level of the process. This assumption would indicate that sleep pressure (with a higher sleep propensity at the beginning of the night) is increased in patients with narcolepsy-cataplexy. However, we argue that under pathologic conditions, SWA does not necessarily reflect the level of process S. A time course of SWA that is altered by wake intrusions is of limited value to estimate the level of process S. Similar theoretic assumptions have been made previously for disorders with disturbed sleep continuity, e.g., depression and are supported by experimental and modeling studies on disturbed SWS. These studies have shown that changes of process S are proportional to the amount of SWA. Dijk et al compared the time course of SWA of an undisturbed night with the time course of SWA power density following an experimental suppression of SWS by acoustic clicks for the first 3 hours of the night (without awakening the subjects). Both time courses (undisturbed all-night sleep and undisturbed sleep following suppression of SWS by acoustic stimulation) appropriately predicted process S, whereas the time course of SWA in the first 3 hours in the experimental night did not. Because the level of process S was the same at the beginning of both nights, the level of process S was reflected by SWA in the undisturbed condition only. Accordingly, in the present study, the dynamics of SWA may reflect only the changes of process S within sleep time but not the level of process S.

Predominant Ultradian Rhythm?

The reduced SWA in the second NREM sleep episode and the lengthening of sleep cycles in narcolepsy have been alternatively explained by the impact of a strong ultradian rhythm un-

Figure 6—Build-up of slow-wave activity (SWA) in the first 30 minutes of non-rapid eye movement sleep (NREMS) episodes. Mean values (± 1 SEM) are plotted for consecutive 2-minute epochs. P= significance level of unpaired t-test (calculated with the means of median slopes of consecutive 2-minute epochs)

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derlying homeostatic NREM sleep regulation in narcolepsy-cataplexy.3,12,13,21 Evidence has come from studies with 16-hour diurnal sleep deprivation followed by a prolonged3,17 bed-rest condition with sleep ad libitum. Patients with narcolepsy-cataplexy showed an intact homeostatic regulation in the first night, as indicated by increased SWA, and an exponential decline of SWA during sleep after 16 hours of sleep deprivation. During bed rest, SWA occurred at 4-hour intervals due to recurring daytime sleep. SWA continued to evolve in a 4-hour periodicity during sleep in the second night, with a normal evolution in the first, attenuated in the second and resurrected SWA in the third NREM sleep episode.3,5,6 This periodicity appeared to be supportive for an ultradian SWA cyclicity in patients with narcolepsy-cataplexy. Although homeostatic regulation was evident under high sleep pressure, circadian measures were less obvious under decreased homeostatic influences during the second night. These findings suggest that a different interaction of process S and process C may unmask the presence of an ultradian rhythm in SWA in patients with narcolepsy-cataplexy, when compared with controls. According to this idea, narcolepsy-cataplexy may represent a dysintegration of biologic rhythms.31 Our hypothesis of insufficient NREM sleep intensity provides alternative or additional mechanisms to explain essential features of abnormal nocturnal sleep in narcolepsy-cataplexy, specifically the SWA distribution and prolongation of NREM-REM sleep cycles. Our hypothesis is also consistent with the increased frequency of waking and the disturbed SFA-SWA relationship with the beginning of the second NREM sleep episode. These changes cannot be sufficiently explained by a predominant ultradian rhythm. Because we did not manipulate sleep pressure, we cannot estimate changes of homeostatic and ultradian influences under different conditions. Although both mechanisms may coexist, our data do not permit us to discriminate their relative contribution to nonconsolidated sleep in narcolepsy-cataplexy.

Limitations of the study

All of our patients with narcolepsy-cataplexy started nocturnal sleep with a SOREMP. This frequency is high when compared to 25%-40% of SOREMPs in narcolepsy-cataplexy as described in the literature.3,32 The high frequency of SOREMPs may reflect a selection bias because only well-characterized patients with narcolepsy with clear cut cataplexy (see standard score and HLA-typing) were included. In addition, it is possible that prior pharmacologic treatments may have contributed to the high frequency of SOREMPs. Although anticitaplectic and stimulant medications were stopped at least 5 half-lives before a patient entered the study, it cannot be ruled out that polysomnographic signs of REM sleep may be influenced by some rebound or after effects of medication. Finally, it is possible that short daytime naps due to irresistible sleepiness in patients with narcolepsy-cataplexy affected SWA at night. Previous studies have shown that daytime naps can affect various aspects of postnap sleep, including changes in sleep latency, the build-up of SWA in the first NREM sleep episode, and the nocturnal declining trend of SWA.3,32,33 A primary aim of our study was to investigate “natural sleep” in narcolepsy. Therefore, it was our conscious decision not to interfere with short daytime naps that would possibly occur in patients with narcolepsy-cataplexy. It has been shown in a previous study that avoiding naps during daytime (i.e., keeping patients awake for 16 hours) already induces sleep deprivation in narcolepsy-cataplexy and affects the level of SWA.3 In contrast, prolonged daytime napping in narcolepsy-cataplexy decreases “delta power,” when compared with “baseline” (when defined as relative delta power (0.5-4 Hz) per cycle) or abolishes the exponential decay of SWA in a forced bed-rest protocol.3 Thus, our finding of an exponential decline of SWA in narcolepsy-cataplexy cannot be readily explained by the presence of some daytime sleep.

CONCLUSIONS

We propose a new hypothesis of insufficient NREM sleep intensity to explain nonconsolidated sleep in narcolepsy-cataplexy. Our hypothesis helps to explain all key findings of nocturnal sleep fragmentation in narcolepsy-cataplexy—(1) the distribution pattern of SWA, (2) the prolongation of sleep cycles, and (3) the disturbed SFA-SWA relationship and the high number of intervening wake episodes. We cannot exclude from our data that additional mechanisms contribute to the lack of consolidation of nocturnal sleep in narcolepsy-cataplexy. Homeostatic sleep regulation appears to be intact, but—as shown above—it may not be appropriate to estimate process S from the time course of SWA under baseline conditions. Further evidence is needed to support our hypothesis of threshold-dependent, insufficient NREM sleep intensity. Manipulations of sleep continuity and sleep intensity (either disturbing sleep continuity and attenuating the time course of SWA by acoustic stimulation or enhancing sleep intensity by sleep deprivation) may be powerful approaches to define the hypothesized threshold for wakefulness and to develop an advanced mechanistic hypothesis. In addition, it is possible that a deficient waking system (probably mediated by the absence of hypocretins orexins) may affect the arousal threshold and result in a lower level of process S in narcolepsy-cataplexy. At that moment, the net effect of altered sleep regulation in interaction with a deficient wake-promoting system is difficult to quantify. Total sleep deprivation will increase sleep pressure and should reduce nocturnal sleep fragmentation, hence promote sleep consolidation. Consolidated sleep will then provide the opportunity to estimate process S from the time course of (undisturbed) SWA power density and help to answer the question whether the homeostatic process of sleep regulation is fully functional in narcolepsy-cataplexy.

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