Short Note

Sleep Fragmentation in Normals: A Model for Sleepiness Associated With Upper Airway Resistance Syndrome

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Summary: Eight young adults underwent 1 night of auditory sleep fragmentation followed by four naps of the multiple sleep latency test and performance testing the next day. A Latin-square design was used to compare results with baseline. Efforts were made to eliminate effects of learning on repeated performance tests. A mean of 303 arousals, lasting a mean of 11 seconds, disrupted nocturnal sleep. This sleep fragmentation was induced to mimic as closely as possible the nocturnal sleep disruption seen in subjects with upper airway resistance syndrome. There was a significant disruption of nocturnal sleep architecture with a significant overall decrease in slow-wave sleep (SWS) and a significant but more moderate decrease in rapid eye movement (REM) sleep during the fragmented night. The most interesting finding related to analysis by thirds of the night, which indicated an important increase over time in arousal threshold during SWS followed by REM sleep. This threshold increase was associated with a parallel increase in dB(A) levels needed to induce an arousal. Stages 1 and 2 nonrapid eye movement (NREM) sleep were less affected by the stimulation, but the amount of stage 1 NREM sleep decreased from the beginning to the end of the night, again indicating an increase in pressure to sleep. Following 1 night of sleep fragmentation, subjects had significantly shorter sleep latencies on the multiple sleep latency test for naps 2, 3 and 4. There was a significant relationship between percent nocturnal SWS and mean sleep latencies. The selected performance tests were not affected by 1 night of sleep fragmentation, despite the obvious sleepiness. Key Words: Sleep fragmentation—Upper airway resistance syndrome—Sleepiness—Performance testing.

Upper airway resistance syndrome (UARS) has been described recently (1,2). It is seen in both genders and is associated with a complaint of daytime sleepiness and/or daytime fatigue, and an abnormal number of short electroencephalogram (EEG) arousals lasting between 2 and 14 seconds [usually not scored according to the guidelines of Rechtschaffen and Kales (3)]. An abnormal increase in respiratory effort with mild to moderate decrease in tidal volume for one to four breaths, not translated into a drop in oxygen saturation (SaO2) measured by pulse oximetry, is also noted. Periodic leg movement syndrome, which also leads to transient EEG arousals, has been similarly reported to induce complaints of daytime sleepiness in some subjects (4). The role of transient sleep EEG arousals in the appearance of sleepiness (5–7) has been questioned, as hypoxemia has been considered an important feature in the sleepiness observed in sleep-disordered breathing (8). Considering the shortness of arousals associated with UARS, we questioned how much daytime sleepiness would be observed following 1 night of sleep fragmentation in a group of normal subjects with a mean age based on the last 15 patients seen and diagnosed with this syndrome in our sleep center.

PROTOCOL

Population

Young highly motivated volunteers including men and women were recruited for the study. Volunteers were screened for past or familial history of psychiatric disorders, drug abuse, presence of chronic illness, hearing loss, abnormal sleep/wake schedule, sleep disorder, daytime napping, excessive intake of alcohol or caf-
feinated beverages and current medication intake other than birth control pills. After signing informed consent forms approved by the internal review board, subjects were requested to follow a very regular sleep/wake schedule, based on information obtained at prior interviews, and to eliminate alcohol or caffienated beverages (with the exception of a morning cup of coffee) for 1 week prior to the experimental manipulations. All subjects underwent determination of unilateral lowest sound recognition threshold. Several training sessions (a minimum of five) to learn how to perform a battery of tests we planned to administer during the experimental protocol were performed. The practice procedures helped the motivation of subjects during the testing procedures.

Study design

The study was planned with a latin-square design with an equal number of men and women in each segment. Women had to be in the follicular (or pseudofollicular if taking birth control pills) phase of their menstrual cycle. All subjects were monitored off protocol (screening and habituation) before beginning the experiment. Eight days elapsed between experimental night 1 and experimental night 2, independent of the order of the sleep fragmentation and baseline nights.

Paradigms selected for the study

Test battery

Several tests were scheduled due to their monotonous quality and their potential to induce drowsiness and "lapses". The battery consisted of finger-tapping tests (five successive 10-second periods on right and left hands); digit symbol substitution tests (10 minutes long, scored by number of digits handled and number of errors) (9); Benton tests (percent figures presented for 10 seconds each, evaluation of number of errors at reproduction) (10); the Wilkinson Addition Test (30 minutes long, scored on number of problems performed and number of errors made) (11,12); and a verbal memory test (list of 14 words, subject asked to repeat all words after each of five presentations and again a sixth time after no presentation, scores based on number of repetitions or omissions of words).

The last training sessions were scheduled the day prior to the experimental protocols and confirmed that no further improvement was noted in the selected volunteers and that a ceiling effect had been reached.

Nocturnal polysomnography

Each subject had their usual dinner at 1830 hours and prepared for monitoring at 1930 hours. Electrodes were applied between 2000 and 2100 hours. Based on information given by subjects on their usual bedtime, lights-out time had been fixed for at least 1 week at a specific time between 2200 and 2300 hours. The same lights-out time was used on the polygraphic night. A total time in bed of 8 hours and 15 minutes was planned, and if subjects awakened earlier, they were asked to stay in bed for that scheduled time. The following variables were monitored on a Grass polygraph and a Nicolet Ultrasom sleep system simultaneously: EEG (C3/A2, C4/A1 and O1/A2), electrooculogram, chin and leg electromyograms (EMG), electrocardiogram (modified V2 lead), oro-nasal airflow and thoraco-abdominal movements (breathing sound and oxygen saturation were monitored only on the habituation night).

Auditory stimulation

To avoid any potential harm to the subject, a maximum of 115 dB for auditory stimuli was preselected. This level had been previously used in humans during sleep fragmentation studies. The following stimulation protocol was used: A Sony earphone was placed in the subject's dominant ear before sleep onset. It was connected to an audiometer with the capacity to apply a continuous 1,000-Hz tone varying from 65 to 115 dB(A). Tones could be applied in a series. The first tone was applied for 5 seconds at 65 dB(A), and the experimenter had to make an immediate judgement on arousal response. The judgement was based only on EEG using central and occipital leads. Other channels, particularly EMG responses, could be used for help, but decision-making was based particularly on the EEG. It had been preestablished that 3 seconds was necessary to recognize alpha EEG arousals in these normal subjects. Within a total of 5 seconds, the decision was made by the experimenter. If no EEG arousal was noted, a second tone was sent at 65 dB(A), but this time the tone lasted 10 seconds. If no response was observed, tone duration was kept constant (10 seconds) and sound intensity was augmented in 10-dB(A) increments.

All tones were administered only after establishment of stages 2 and 3-4 nonrapid eye movement (NREM) or rapid eye movement (REM) sleep for a full 30-second epoch. Each tone series was terminated by the experimenter upon indication of EEG arousals. A tone series was initiated only if 30 seconds of well-established sleep (stages 2, 3 and 4 NREM or REM sleep) had elapsed following a long awakening. No new stimulation could be initiated if 1 minute of sleep had not

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performed the prior stimulation. To avoid discrepancy in arousal recognition, the same experimenter evaluated the transient alpha-EEG arousals in all monitored subjects. A second experimenter continuously tabulated the time spent awake during the night. This “wake time” was based upon the Rechtschaffen and Kales’ (3) definition of “arousals”; it had to last more than 15 seconds. These ≥15-second arousals could be distributed on two adjacent recording epochs. Subjects had to be left asleep longer than the scheduled total sleep time on the sleep fragmentation night; this increase in time in bed was equal to the amount of time spent with >15-second arousals and awakenings associated with the stimulations.

Multiple sleep latency test (MSLT) (13) and performance schedule

The MSLT was administered following the American Sleep Disorders Association guidelines (13) in a darkened bedroom. It consisted of four naps scheduled at 1100, 1300, 1500 and 1700 hours, each lasting a minimum of 20 minutes if subjects did not fall asleep.

Sleep latency was defined as time to the first nonwake 30-second epoch. The nap was interrupted after 90 seconds of stage 1 NREM sleep or one epoch of any other sleep stage or state. The performance tests were scheduled in the intervals between sleep latency tests (SLT). The test battery had to be terminated at least 30 minutes before the following SLT. Performance tests were administered three times during the day at 0930, 1330 and 1530 hours.

DATA ANALYSES

Each test (polygraphic recording and performance) was coded so that scorers were unaware of night and presence or absence of stimulation. Records were scored following Rechtschaffen and Kales’ manual (3) and our published definition of transient alpha arousals (1), which is closely related to the recently published ASDA transient arousal scoring criteria. The number of stimuli necessary to induce an arousal and the dB(A) threshold reached were determined independently from the polygraphic scoring. Subjects who underwent the fragmentation night before the baseline night were analyzed separately from subjects whose fragmentation night followed the baseline night. Data of the two subgroups were compared and analysis of data from the total population was performed only if subgroup comparison did not reach significance level. Analysis on total population was performed on data for total nocturnal sleep and by third of the night. Nonparametric Mann–Whitney 4 test, ANOVA and MANOVA were performed to analyze the data.

RESULTS

The eight volunteers were highly motivated young adults with prior experience with research protocols and a good understanding of the need to follow study requirements. They had stable sleep/wake patterns and overall did not differ widely from each other in their nocturnal sleep patterns outside of the study period. Mean age was 24 ± 3.5 years (range 20–35 years) and body mass index was 25.4 ± 2.8 kg/m². Comparisons of sleep parameters [total sleep time (TST), total NREM sleep, REM sleep and stages 1, 2, 3 and 4] indicated no significant difference between the two subgroups independently of the experimental night. Data were thus analyzed for the total group.

Baseline versus stimulation night

Baseline mean TST was 392.2 ± 36.7 minutes, and sleep fragmentation mean TST was 387.8 ± 38 minutes (ns). A mean of 303 ± 38 stimulations was performed during the fragmentation night. The mean duration of an EEG arousal was 11 seconds. Sleep architecture was significantly modified after sleep fragmentation. There was a significant increase in stage 1 NREM sleep from a mean of 10.4 ± 8% to 23 ± 6%. There was a significant decrease in slow-wave sleep (SWS), from a mean of 15.3% to a mean of 7.5%. REM sleep also decreased from a mean of 22% to a mean of 15.5%. Table 1 presents the data obtained on the fragmentation night broken into thirds of the night. Total sleep time was extended by amount of wake time to avoid sleep deprivation. All sleep architecture changes were highly significant (p < 0.0001).

Stimulation night

Investigation of the arousal response to a stimulation indicated that the stimulation threshold [number of repeat dB(A) reached] had to be increased a mean of 1.96 times to induce an arousal during stages 1 and 2 NREM sleep. During SWS it had to be increased a mean of 4.04 times, and 3.03 times during REM sleep from the first to the third part of the night. The number of repeat stimulations necessary to induce an arousal during SWS increased from a mean of 2.4 during the 1st hour of sleep to a mean of 11 after the 4th hour of sleep, and from a mean of 1.1 during the first REM period (2nd hour of sleep) to a mean of 3.08 during the last REM period (6th and 7th hours of sleep). The number of trials necessary to induce an arousal during stages 1 and 2 NREM sleep increased much less from the 1st to the 4th hour of sleep, from a mean of 1.54 to a mean of 2.84. If we consider dB(A) there is a...
TABLE 1.  Sleep variables obtained on fragmentation night (presented by third of the night)

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>SE</th>
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<tr>
<td>2nd</td>
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Abbreviations used: TST = total sleep time, TWT = total wake time, ST = stage 1 NREM sleep, ST2 = stage 2 NREM sleep, SWS = slow-wave sleep, TREM = total REM sleep time, TMT = total movement time, 1st = first third of night, 2nd = second third of night and 3rd = third third of night.

similar finding: at the beginning of the night (1st hour), transient arousals were obtained with stimulations between 65 and 75 dB(A) [mean = 70 dB(A)], independent of sleep state or stage. In the last hour of the night, the mean dB(A) for arousal was 105 dB(A) in SWS, 95 dB(A) during REM sleep and 85 dB(A) in stage 2 NREM sleep.

The results obtained indicate that despite prolongation of sleep to avoid sleep deprivation and a protocol set up to obtain sleep fragmentation with transient arousals only, the sleep architecture was significantly altered compared to the baseline night. The most interesting findings are those noted over time on the sleep fragmentation night. As can be seen in Table 1, the amount of stage 1 NREM sleep does not increase by thirds of the night, and the total amount of wake time [defined following the criteria of Rechtschaffen and Kales (3)] in fact decreases from the first third to the last third of the night, with a significant difference between the first and last third of the night (p < 0.01). This is associated with a significant increase in the number of trials needed to lead to transient arousals. This increase, however, is sleep-stage dependent, with a statistically significant difference between stage 2 and stages 3–4 NREM sleep (p < 0.001), and showed greater difficulty in inducing an arousal during SWS compared to stage 2 NREM sleep. SWS was significantly curtailed during the last third of the night compared to the first and second thirds. The increase in dB(A) associated with arousals was significant when comparing the first and third parts of the night for stage 2 NREM and REM sleep. The reduction in SWS during the last third of the night limits statistical analysis.

MSLT investigation

Baseline mean MSLT was 15.4 ± 4 minutes compared to 8.8 ± 5 minutes after sleep fragmentation (one-factor ANOVA, p = 0.009). Analysis of the different SLTs indicated that the sleep latencies became more and more significantly different from nap 2 to nap 4 (from p = 0.014 to p = 0.009), indicating a progressive shortening of sleep latencies from nap 2 to nap 4 (from a mean of 8.7 minutes to a mean of 6.4 minutes, see Fig. 1).

This investigation thus indicates a progressive increase in daytime sleepiness from morning to evening after 1 night of sleep fragmentation. Linear regression analyses of percent of SWS and percent of REM sleep on the following day mean sleep latencies during baseline and sleep fragmentation nights were performed. The REM sleep analysis did not indicate a significant relationship (r² = 0.28). However, the percent of SWS
(stages 3–4 NREM sleep) compared to the following day mean sleep latencies showed a significant relationship \( r^2 = 0.762 \), that is the lower the percent of nocturnal stages 3–4 NREM sleep (SWS) in these subjects, the shorter the sleep latency (i.e. the degree of sleepiness, see Fig. 2).

The results of the different performance tests were all unaffected by sleep fragmentation. Analyses considered tests independently and also with regard to time of day, that is they took into account the progressively shorter sleep latencies with the progression of the day. No trend could be seen in any of the selected tests.

**DISCUSSION**

The effects of sleep deprivation and sleep fragmentation have been of interest to sleep researchers for some time. Carskadon and Dement (14) considered the cumulative effects of sleep restriction on daytime sleepiness. Stepanski et al. (7) found that in four subject groups (sleep apneics, periodic leg movement patients, insomniacs and normal volunteers), the total number of arousals (including complete awakenings) correlated significantly with sleepiness index. But these authors indicated that the type and duration of an arousal had an impact on the sleepiness index. Bonnet (15) also used auditory stimulations to disrupt the sleep of normal young volunteers; however, his protocol differed from ours in that subjects verbally acknowledged wakefulness. Badia et al. (5) also had a different goal and protocol with their sleep fragmentation study, but found also a disruption of sleep structure with more stage 1 and less SWS. In their study, the deleterious effects of sleep disruption on daytime functioning were noticeable. Our protocol was aimed at understanding the problems seen in subjects presenting with the recently reported UARS (1,2) rather than with severe obstructive sleep apnea. We tried to have a shorter arousal duration (mean arousal duration 11 seconds) than other protocols have used. We also did not induce experimental hypoxemia, as in the study of Colt et al. (8). Finally, we tried to avoid inducing sleep deprivation. TST on the two different nights was kept as close to equal as possible. When sleep fragmentation was induced on the 1st monitored night, we aimed for a total sleep time extrapolated from the subject’s sleep logs. Results indicated that TSTs on the 2 nights were very close (mean 398 vs. 387 minutes = ns). Of course, sleep structure was very different on the fragmentation night, with great abatement of SWS and, to a lesser degree, REM sleep.

The most interesting finding was that arousal thresholds are found with different sleep stages. A very significant increase in arousal threshold was found for SWS and REM sleep compared to stage 2 NREM sleep during the last third of the night compared with the first. There was a need to increase the stimulation level, and this increase in stimulation was associated with an increase in the dB(A) level required to reach arousal threshold. Changes were much less when considering stage 2 NREM sleep. This is of interest because an unpublished ongoing study by Guilleminault et al. has found that there is an important difference in arousal threshold in patients with UARS: End inspiratory negative esophageal pressure is always much more marked in SWS than in any other stage, and arousal occurs at a much more negative esophageal pressure than in stages 1 and 2 NREM sleep. The changes from the first to the third segment of the night, seen independent of sleep stage or state, indicate that even transient arousals as short as those induced here have an important impact on a significant defense mechanism, the arousal threshold, which is worsened with the repetition of the fragmentation, from the beginning to the end of the night.

With these findings in mind, our results are also of interest in that they demonstrate that 1 night of sleep fragmentation was sufficient to significantly impair MSLT results but not performance test results. These findings are in line with those of Stepanski et al. (6), who used longer arousal criteria.

Tests such as the finger-tapping tests were unaffected

**FIG. 2.** Linear regression analysis of percentage of nocturnal SWS (stage 3–4 NREM) on following day mean sleep latencies (MSL, expressed in minutes). Data from both the baseline and sleep fragmentation nights of each subject are presented. As indicated in the text and as shown by the above curve, there was a significant relationship between the percentage of SWS that occurred during nocturnal sleep and the mean sleep latency scores of each subject the following day.
by 1 night of sleep fragmentation. Efforts were made to eliminate any possible learning effect, and there was no indication of any improvement of performance with repeated testing on baseline and the experimental day. Young motivated adults have the ability to overcome sleepiness and to perform adequately on performance tests after 1 night of sleep fragmentation and sleep stage disruption. If fragmentation had been repeated for several days, results may have been different. It is interesting to note that the progressive shortening of sleep latencies over the day supports the homeostatic theories of sleep and that the important relationship between shortening of mean sleep latencies (i.e. daytime sleepiness) and a decrease in nocturnal SWS would be predicted by Borbely's model in our young subjects.

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REFERENCES