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The alteration of human sleep and circadian rhythms during spaceflight

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SUMMARY Numerous anecdotes in the past suggest the concept that sleep disturbances in astronauts occur more frequently during spaceflight than on ground. Such disturbances may be caused in part by exogenous factors, but also an altered physiological state under microgravity may add to reducing sleep quality in a spacecraft. The present investigation aims at a better understanding of possible sleep disturbances under microgravity. For the first time, experiments were conducted in which sleep and circadian regulation could be simultaneously assessed in space. Four astronauts took part in this study aboard the Russian MIR station. Sleep was recorded polygraphically on tape together with body temperature. For a comparison, the same parameters were measured during baseline periods preceding the flights. The circadian phase of body temperature was found to be delayed by about 2 h in space compared with baseline data. A free-run was not observed during the first 30 d in space. Sleep was shorter and more disturbed than on earth. In addition, the structure of sleep was significantly altered. In space, the latency to the first REM episode was shorter, and slow-wave sleep was redistributed from the first to the second sleep cycle. Several mechanisms may be responsible for these alterations in sleep regulation and circadian phase. Most likely, altered circadian zeitgebers on MIR and a deficiency in the process S of Borbély's sleep model cause the observed findings. The change in process S may be related to changes in physical activity as a result of weightlessness.

KEYWORDS circadian rhythms, sleep regulation, spaceflight

INTRODUCTION

A survey of sleep complaints on the Space Shuttle has shown that the incidence of sleep disturbances was remarkably high (Santy *et al.* 1988). This observation is supported by personal communications with cosmonauts that have worked on the MIR station. In spite of the occurrence of sleep disturbances and a shorter sleep, consistent alterations in sleep parameters have not been reported yet (Adey *et al.* 1967; Frost *et al.* 1975; Litsov and Bulyko 1983; Quadens and Green 1984; Litsov and Shevchenko 1985; Stoilova *et al.* 1990; Polyakov *et al.* 1994). Sleep disturbances in space may occur for a variety of reasons. In individual astronauts they may be caused by exogenous factors such as space motion sickness, perception of light flashes when high energy protons hit the retina, emotional stress, high work load, an abnormal work schedule, thermal discomfort, noise, muscle pain, or an unsuitable sleeping bag. But also changes in the physiological basis for the regulation of sleep and the circadian clock may result in sleep disturbances.

The human circadian system has not been assessed in space until recently, when in a single astronaut a phase delay of 2–3 h was found (Gundel *et al.* 1993). Since this astronaut stayed in space for only 8 d, it was not clear whether the delay was a constant phase shift or the beginning of a circadian free-run. A free-run might occur because a 24-h light/dark cycle is lacking in an orbiting spacecraft.

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Sleep recordings of this single astronaut were evaluated by methods that were based on a model for sleep regulation (Borbély 1982; Daan *et al.* 1984). An analysis of amplitudes of delta waves during non-REM sleep resulted in new findings regarding sleep regulation in space. The latency to the first REM episode was shorter and the second non-REM sleep phase showed higher amplitudes of delta waves than on the ground.

The new findings in a single astronaut (Gundel *et al.* 1993) lead to the hypotheses that could then be reformulated and tested for a total of four subjects. The sample size of four seems reasonable regarding cost and effort for experiments in space. The main questions were:

(1) Is the circadian phase delayed and if so, is the delay a sign of a constant phase shift under space conditions or does it mark the beginning of a circadian free-run of rhythms?
(2) Is the non-REM/REM regulation changed and if so, does the change reflect a transient adaptation process or is it a general response to space conditions?

METHODS

The astronauts who participated in the experiments gave their informed consent, and this study complies with the recommendations of the Declaration of Helsinki. At the time of their mission subjects were 39, 47, 52, and 53 y of age (subjects no. 1, no. 2, no. 3 and no. 4).

Subjects spent the first 2 days and nights of their spaceflight in the launch vehicle SOYUZ before they entered the orbital complex MIR. The slow approach of SOYUZ to the MIR station is common to all missions. The experiment could only begin after the astronauts arrived on MIR. Sleep recordings were obtained for subject no. 1 during nights 3–7 of the mission. The recorded nights for the other subjects were nights 17, 18, 25, 26, 94, 103 for no. 2, nights 3, 4, 16, 17, 23, 29, 30 for no. 3, and for subject no. 4 nights 4, 5, 11, 12, 17, 23. Body temperature was measured continuously during a recorded night and the following day. For astronauts no. 2, no. 3, and no. 4, 48-h experimental measurement blocks that were a week apart were planned and requested to test the free-run hypotheses. The recordings that were actually obtained reflect the operational constraints for the experiments on board MIR.

For a comparison of data that were obtained during the mission, baseline measurements were taken for up to 6 d including a night for adaptation to the recording procedures. At least 4 weeks before the launch baseline experiments were conducted. Immediately before the launch astronauts were occupied by operational work and their availability for scientific experiments was limited.

The spaceflights were operated under the local time of the ground control and astronaut training centre, i.e. working and sleeping were scheduled accordingly. When subjects spent the days prior to mission close to the launch site which is two time zones eastward of the training site, they were forced to keep their sleeping times and their meals according to the local time of mission control. Thus there was no shift in time between baseline, pre-mission period and the mission. The training programme for the astronauts continued during baseline measurements. They lived in their apartments and left during the day to attend classes and for other activities. Astronauts did not exercise during baseline measurements in order to avoid the influence on body temperature. Subjects sometimes exercised during mission measurement blocks. As on the orbital complex where operational constraints also determined sleeping times to some extent, subjects were free to choose their sleeping times during baseline. They were encouraged to stick to their habitual sleeping times.

As a control for possible masking effects imposed by the rest/activity cycle bedtimes during baseline and mission measurements were compared. Astronauts went to bed on average 1.01 h later during the mission than during baseline days (00.19 and 1.20 h, respectively). This difference was not statistically significant (repeated measure ANOVA $F_{1,3} = 1.05$, $P = 0.38$). The difference would reach statistical significance with a sample size of 15 subjects. The mean get-up time was delayed by 50 min in space.

The environmental temperature could not be controlled during any period of the experiments. Information about actual exposure to light during the mission could not be obtained. In general, astronauts were only exposed to artificial light in the MIR station. However, when they looked out of a window they may have received sunlight depending on the position of the MIR station.

The main hardware item used was an Oxford Medilog eight-channel recorder (Oxford Instruments, Oxford, UK) that allows the continuous recording of body temperature for 24 h in addition to sleep polygraphies. Equipment had to be suitable to be handled only by the astronauts themselves without assistance from others. To meet these constraints, an elastic head-band with integrated Ag/AgCl-electrodes was used for polygraphic recordings. EEG electrodes were placed according to the international 10–20 system. The electrode positions of this band were C3, C4, Cz (ground electrode), and O2. Two EOG signals were derived from the forehead. The band provided also had clip-on connectors for four disposable electrodes that served as mastoid references (A1, A2) and as EMG derivations from the neck. Thus, the seven polygraphic channels were C4-A1, C3-A2, O2-A1, EOG1-A2, EOG2-A1, EMG1-A2 and EMG2-A1. This setting provided some useful redundancy. Body temperature was measured by a rectal thermistor probe.

In addition to the recordings, a general sleep questionnaire was filled out by the astronauts after each sleep recording. However, it turned out that cultural differences between astronauts resulted in different attitudes towards the sleep questionnaire. Therefore, these questionnaires were used only as a means to help analysing the tape recordings. Group results from the sleep questionnaire will not be presented.

Recording tapes were brought back to earth and sent to our laboratory in Cologne for evaluation. First of all data were A/D converted. The computer allowed a visual scoring of sleep stages in 30-s epochs according to Rechtschaffen

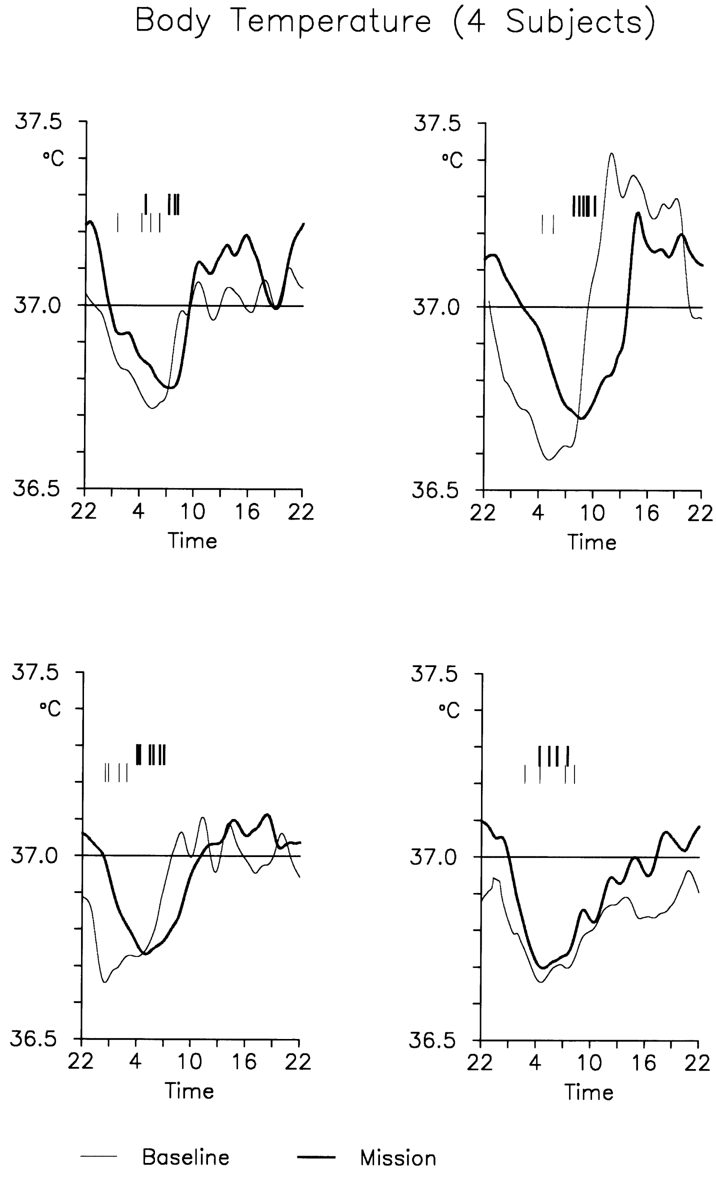

Figure 1. Average profiles of body temperature for four astronauts. Temperature curves from days on ground (baseline) and in space (mission) were averaged for each of the four astronauts separately. Circadian phase estimates for individual days are indicated by short vertical lines. Data are arranged by age of astronauts with age increasing from right to left and top to bottom.

and Kales (1968). At the same time signal quality was screened and rated for artifacts and completeness. The artifact rating served as input for subsequent automatic analysis. This included evaluation of the time course of body temperature and EEG power density. EEG power density during sleep is dominated by slow-wave activity. To assess amplitudes of delta waves broadband power was determined in the frequency range from 0.5–5.0 Hz. Power density was calculated for the channels C3 and C4 and then averaged. Epochs with artifacts were excluded from the power analysis resulting in missing values. These missing values were linearly interpolated. The amount of missing values was small and could not influence results substantially. Circadian phase was determined from the minimum body temperature after nonparametric regression (Gasser *et al.* 1985) of values that were obtained every 30 s. Non-parametric regression analysis resulted in a smoothing of temperature curves. A second phase estimate was obtained by a Fourier transformation using a basic period of 24 h and three higher harmonics. Statistical evaluation of data was conducted by a repeated measure ANOVA using SAS software.

RESULTS

Circadian phases were estimated from body temperature curves of individual days. The estimation procedures that were applied, i.e. non-parametric local smoothing (Gasser *et al.* 1985) and Fourier transformation, yielded similar times for the absolute daily minimum in body temperature. First, phase estimates were screened to see whether they would reveal a circadian free-run. None of the four astronauts showed a systematic shift or trend in the phase estimates for the duration of the mission. In addition, the spread of phases was not different for baseline days and for days in space as can be seen in Fig. 1 where

Table 1 ANOVA of circadian phase of core body temperature as estimated by Fourier analysis and non-parametric regression

	Fourier analysis	*Non-parametric regression*
Main effect 'mission'		
$F_{1,3}=$	15.30	7.82
$P=$	0.03	0.07
Mean values		
Baseline	04:38 h	04:23 h
Mission	06:39 h	06:46 h

individual phase estimates are displayed by vertical lines above the temperature curves.

Since the spread of circadian phases was similar for measurements on ground and in space, further analysis was conducted by using averages of daily temperature curves and of phase estimates for each astronaut. The number of days for which means were determined ranged from 2 to 6. The average daily body temperature curves are shown in Fig. 1. They reveal an obvious phase delay for three of the four astronauts in space. The circadian troughs showed a small phase advance with age. The phase estimates of individual days coincided with the troughs in the average curves. The phase estimates showed that the phase shift already appeared on the first day of the stay on MIR.

Individual averages of the phase estimates were statistically analysed by a repeated measure ANOVA with repetitions (mission and baseline) on a factor that was called 'mission' (Table 1). These averages result in a mean phase delay of 2.01 h (Fourier analysis) or 2.23 h (local smoothing). The delay was significant for the estimate obtained by a Fourier analysis and showed a trend ($P<0.1$) for the other estimate.

As a check for possible masking effects by the rest/activity cycle that might have caused the phase delay, the correlation between circadian phase and bedtime was determined. For this analysis individual means for each astronaut were subtracted from circadian phase and bedtime. The result was that 0.5% and 1.8% of the variance could be explained by these correlations regarding baseline and mission, respectively.

The average body temperature during sleep was higher in space (36.83°C) than on ground (36.73°C). This difference was statistically significant ($F_{1,3}=23.92$, $P=0.016$). The differences for the individual astronauts were 0.11, 0.16, 0.06 and 0.09°C. Body temperatures during the day fluctuated as a result of activities including occasional exercise.

The Rechtschaffen and Kales analysis of sleep is presented in Table 2. It did not show significant differences for any of the parameters. However, the data indicated a reduced sleep duration and quality in space, e.g. reflected by the reduction in sleep efficiency from 0.956–0.891 in space. This difference was not significant since it is mainly because of a single subject (no. 4) who showed a reduction in sleep efficiency from 0.982–0.783 and in increase in sleep onset latency from 6.0–47.5 min.

Figure 2 displays sleep architecture up to the third non-REM period. Sleep was terminated during the third REM sleep period in 13 out of 42 nights. Therefore, the third REM phase and later sleep were excluded from the statistical analysis of sleep structure. Non-REM phases also included stage 1 sleep. As with the circadian phase trends in sleep parameters over time were not observed and consequently data were pooled over nights. According to Fig. 2, the amount of delta waves is reduced for the older astronauts. Comparing mission and baseline data it can be seen that the latency to the first REM sleep period is shorter in space for the first three subjects. The second non-REM period showed more delta sleep in space than on ground. The short sleep cycle length of the fourth astronaut was 70.8 min on ground and 88.2 min in space in comparison to averages for the other three astronauts of 102.6 and 106.0 min. Data were analysed by a repeated measure ANOVA with the factors 'mission' and 'sleep cycle'. *F*-values and error probabilities are given in Table 3. Analysis of the duration of the first three non-REM periods resulted in a significant interaction of 'mission' and 'sleep cycle'. Contrasts to the average of the other two sleep cycles revealed that the significant interaction was caused by the first non-REM period, i.e. the shorter REM latency in space (56.2 min vs. 71.3 min on ground). The third non-REM period showed a trend to being longer in space (80.4 min vs. 67.9 min on ground). The analysis of the duration of REM periods did not lead to any significant effect ($F<1$ for all effects) and was not included in the table.

The amount of slow-wave sleep during a non-REM phase was quantified as the product of the average delta power and the duration of that particular non-REM period. ANOVAs were conducted with logarithmically transformed values. The ANOVA for the amount of slow-wave sleep showed a trend ($P=0.07$) for the interaction of the factors 'mission' and 'sleep cycle'. The contrasts showed that the higher amount of slow-wave sleep in the second non-REM period on board MIR is responsible for this statistical effect. Both main effects were not significant.

DISCUSSION

Circadian phase as assessed by the trough in core body temperature is delayed in astronauts during spaceflight. The

Table 2 Means and results of an ANOVA of different sleep parameters obtained from manual scoring according to Rechtschaffen and Kales

	Baseline	*Mission*	$F_{1,3}$	*P*
TIB (h)	6.66	6.85	<1	
TST (h)	6.37	6.11	<1	
Efficiency (TST/TIB)	0.956	0.891	1.97	0.25
Latency to first stage 2 (min)	6.5	19.2	<1	
Stage 1 (% TST)	1.9	3.5	5.97	0.09
Stage 2 (% TST)	63.0	59.6	<1	
Stage 3+4 (% TST)	12.9	16.9	2.30	0.22
REM (% TST)	22.1	20.1	<1	
Movement time (% TIB)	0.3	0.4	<1	
Awake (% TIB)	4.3	10.6	1.76	0.28
Number of awakenings	7.68	12.22	1.52	0.31

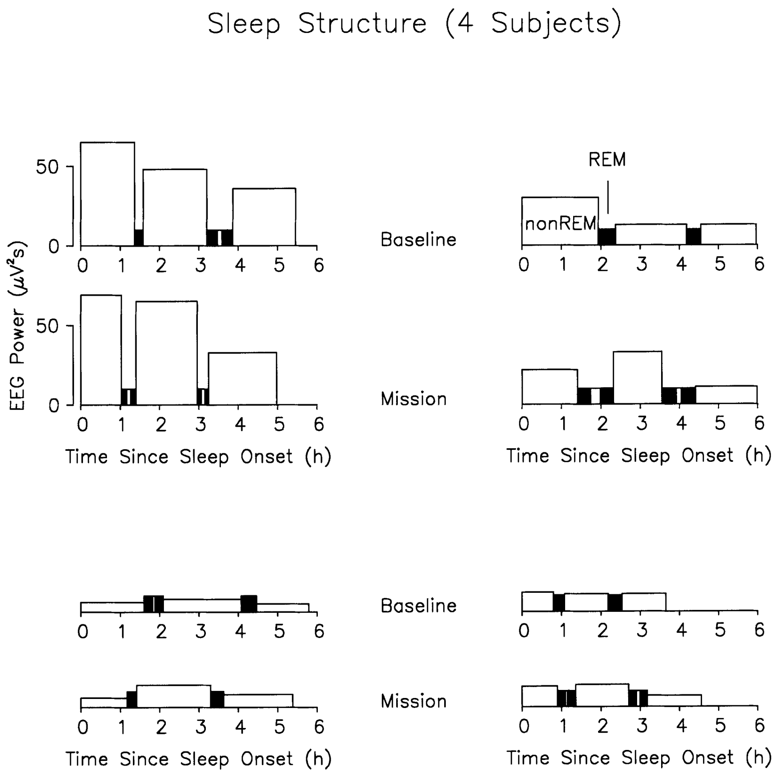

Figure 2. Average sleep structure for four astronauts. Results from nights on ground (baseline) and in space (mission) were averaged for each of the four astronauts separately. The height (y-axis) of an open non-REM area corresponds to the average power of slow waves in that particular non-REM period. The height of hatched REM areas has been arbitrarily chosen for display. Data are arranged by age of astronauts, with age increasing from right to left and top to bottom.

delay relative to ground-based measurements amounts to more than 2 h. The phase delay already appeared on the first day when measurements were possible, i.e. after leaving the launch vehicle and entering the MIR station about 2 d after launch. A circadian free-run was not observed in the course of the mission. A free-run should occur if bright light would have been the only effective circadian zeitgeber (Wever *et al.* 1983; Czeisler *et al.* 1989) since there is no natural 24-h light/dark cycle in an orbiting spacecraft. However, recent studies showed that light of lower intensity can synchronize the circadian system to a 24-h day (Boivin *et al.* 1996). Also non-photic or social time cues or the combination of photic and non-photic zeitgebers may possibly synchronize the body clock and 24-h day (Wever 1979).

The phase delay in space can be explained by alterations of the circadian zeitgebers. For two reasons, it is very unlikely that the observed phase shift is because of masking of body temperature by the rest/activity cycle (Minors and Waterhouse 1989). First, the phases during individual days were not correlated with the bedtimes. Second, two different phase estimates one of which was not influenced by activity during daytime showed the same phase delay. However, it is possible that the delayed bedtimes may have contributed to the circadian phase delay.

A weaker zeitgeber results in a delayed phase as was shown by mathematical simulations of a circadian oscillator (Wever 1979; Gundel and Spencer 1992). This is as a result of the fact that the intrinsic period of the circadian pacemaker is longer

Table 3 ANOVA for sleep structure. Adjustments of the degrees of freedom for non-sphericity of the sample variance-covariance matrix according to Huynh and Feldt are indicated by H-F

	Duration of non-REM periods	*Slow-wave sleep*
Main effects		
'mission'	$F_{1,3} < 1$	$F_{1,3} = 1.42$ $P = 0.320$
'sleep cycle'	$F_{2,6} = 2.51$ $P = 0.161$ (H-F)	$F_{2,6} = 3.38$ $P = 0.142$ (H-F)
Interaction		
'mission by sleep cycle'	$F_{2,6} = 8.16$ $P = 0.020$ (H-F)	$F_{2,6} = 4.56$ $P = 0.071$ (H-F)
Contrasts for interaction		
'mission by sleep cycle 1'	$F_{1,3} = 15.09$ $P = 0.030$	$F_{1,3} = 4.82$ $P = 0.116$
'mission by sleep cycle 2'	$F_{1,3} < 1$	$F_{1,3} = 28.87$ $P = 0.013$
'mission by sleep cycle 3'	$F_{1,3} = 9.12$ $P = 0.057$	$F_{1,3} < 1$

than 24 h. Also the time structure of the zeitgeber can lead to a phase delay (Wever 1979). Both these effects would explain the phase delay from a normal training day of an astronaut to a day on MIR where the light/dark modulation is reduced.

A phase delay in the circadian rhythm of body temperature has been found in rhesus macaques that were in space for up to 14 days (Fuller *et al.* 1996). The coincidence of these results with the findings in astronauts is striking. As in humans, the primates' body temperature rhythms were delayed by about 2 h and the delay already occurred at the beginning of the mission. The phase shift did not change during the stay in space.

Results from space show a similarity to findings for the Antarctic region. A phase delay from the Antarctic summer to winter was found (Broadway *et al.* 1987). In addition, subjects showed generally later phases than subjects living in regions at moderate latitudes. This is supported by another study in which subjects could be observed in New Zealand and later during the Antarctic summer (Gander *et al.* 1991). In a group of isolated overwintering personnel a circadian free-run could be observed (Gander *et al.* 1991). A bedrest study simulating weightlessness (Samel *et al.* 1993) did not show a circadian phase delay.

Though a circadian free-run was not observed it cannot be excluded that an individual astronaut will free-run under the conditions of a spaceflight taking into account the weakened zeitgebers. The exact light exposure of astronauts on MIR is not yet known and remains to be determined. The circadian system would be sensitive in particular to early morning and late night exposure.

Body temperature during night was higher in space. This may be an indication of reduced circadian amplitudes. A weaker zeitgeber would result in such reduced amplitudes (Wever 1979). It is unlikely that sleep disturbances have caused this increase since it does not show a relation to sleep quality of individual astronauts. But a thermoregulatory response to the particular environment of a space station cannot not be ruled out.

Human circadian dynamics was measured in astronauts for the first time. There were no indications that gravity directly influenced circadian rhythms in these astronauts. However, for other species an effect of gravity on the circadian system is discussed (Ferraro *et al.* 1995). For astronauts it cannot be excluded that weightlessness indirectly influences the circadian system since it causes changes in physical activity which is a possible non-photic zeitgeber.

An analysis of sleep structure going beyond a Rechtschaffen and Kales analysis by quantifying the amount of slow-wave sleep reveals significant differences in sleep architecture in space compared with sleep on ground. The latency to REM sleep was shorter and the amount of slow-wave sleep was higher in the second sleep cycle. The occurrence of early REM episodes has been discussed in the context of findings in depressed patients (Schulz and Lund 1985). Three different hypotheses for the shortening of REM latency in these patients were considered, two of them are related to circadian alterations. Findings in depressed patients were compared with free-running subjects in whom REM propensity was largest around the trough in body temperature (Zulley 1980). Obviously, a phase delay of circadian rhythms relative to sleep onset as observed in space cannot explain a shorter REM-latency. Another connection is seen in lower circadian amplitudes observed in depressed patients. This could be an explanation for the present findings if one would accept that the higher temperatures during sleep indicate that amplitudes are lower. Unfortunately, this hypothesis could not be tested by daytime temperatures since they may be partly increased because of exercise of astronauts in space.

Besides the attempt to explain changes in sleep structure by alterations in the circadian clock, the homeostatic sleep regulation was considered. The process S in the model of Borbély (Borbély 1982; Daan *et al.* 1984) influences REM latency and slow-wave sleep as well. A deficiency in process S favours REM sleep. Mathematical simulations showed that the findings in space are equivalent to alterations observed in a night sleep following an afternoon nap (Achermann and Borbély 1990). The afternoon nap reduces S at sleep onset and consequently shortens the latency to the first REM sleep and shifts some slow-wave sleep to the second non-REM phase. In space process S may be reduced at sleep onset as a result of metabolic alterations or changes in physical activity. The observed changes in sleep regulation do not present a transient phenomenon but persisted throughout the experiments.

The less detailed Rechtschaffen and Kales analysis gave different findings for the amount of slow-wave sleep in space. This may be also the reason why earlier studies did not report comparable changes (Adey *et al.* 1967; Frost *et al.* 1975; Litsov and Bulyko 1983; Quadens and Green 1984; Litsov and Shevchenko 1985; Stoilova *et al.* 1990; Polyakov *et al.* 1994). Psychological stress can be excluded as a source for the findings in sleep structure, in particular REM latency is not influenced by stress (Lauer *et al.* 1987). Another environmental stressor that is known to affect sleep, high ambient noise levels, would rather result in a general depression of slow-wave sleep (Dijk *et al.* 1989) which was not observed in space.

Significant sleep disturbances were found in one out of four astronauts. They seem not to be related to the circadian phase delay nor to changes in sleep structure which were not exhibited by this particular astronaut. If one considers the circadian phase delay and the shortening of the latency to REM being a physiological adaptation to the space environment then it may be concluded that this astronaut did not adapt to the environment. In addition, he showed the shortest sleep cycle duration of all four astronauts. The sleep disturbances were characterized by a reduced sleep efficiency and a long sleep onset latency. He seems to be one of those astronauts who develop ‘space insomnia’ during mission. It is an interesting hypothesis to raise the question whether the difference in adaptation to the space environment is related to these sleep disturbances.

In conclusion, the circadian system does not free-run but shows a phase delay in astronauts. This phase delay is likely to be the result of changes in zeitgeber strength and zeitgeber structure aboard MIR. A shortened REM latency and more slow-wave sleep in the second non-REM period characterize the change in sleep structure that is a consequence of microgravity. Both phenomena, the circadian phase delay and the alteration of sleep structure present a persistent adaptation to the space environment. Sleep disturbances occur in individual astronauts. The observed sleep disturbances do not seem to result from the circadian phase delay nor from the alteration of sleep structure.

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