J. Sleep Res. (1999) **8**, 189–195

Circadian variation of EEG power spectra in NREM and REM sleep in humans: Dissociation from body temperature

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Accepted in revised form 22 April 1999; received 21 December 1998

SUMMARY In humans, EEG power spectra in REM and NREM sleep, as well as characteristics of sleep spindles such as their duration, amplitude, frequency and incidence, vary with circadian phase. Recently it has been hypothesized that circadian variations in EEG spectra in humans are caused by variations in brain or body temperature and may not represent phenomena relevant to sleep regulatory processes. To test this directly, a further analysis of EEG power spectra – collected in a forced desynchrony protocol in which sleep episodes were scheduled to a 28-h period while the rhythms of body temperature and plasma melatonin were oscillating at their near 24-h period – was carried out.

EEG power spectra were computed for NREM and REM sleep occurring between 90–120 and 270–300 degrees of the circadian melatonin rhythm, i.e. just after the clearance of melatonin from plasma in the 'morning' and just after the 'evening' increase in melatonin secretion. Average body temperatures during scheduled sleep at these two circadian phases were identical (36.72°C). Despite identical body temperatures, the power spectra in NREM sleep were very different at these two circadian phases. EEG activity in the low frequency spindle range was significantly and markedly enhanced after the evening increase in plasma melatonin as compared to the morning phase. For REM sleep, significant differences in power spectra during these two circadian phases, in particular in the alpha range, were also observed.

The results confirm that EEG power spectra in NREM and REM sleep vary with circadian phase, suggesting that the direct contribution of temperature to the circadian variation in EEG power spectra is absent or only minor, and are at variance with the hypothesis that circadian variations in EEG power spectra are caused by variations in temperature.

KEYWORDS alpha, electroencephalogram, forced desynchrony, melatonin, sleep, spindle

INTRODUCTION

Forced desynchrony of the sleep/wake cycle and endogenous circadian rhythms has revealed that NREM EEG power density in the frequency range of sleep spindles varies with circadian phase, as derived from either the core body temperature rhythm (Dijk and Czeisler 1995) or the plasma melatonin rhythm (Dijk *et al*. 1997b). Low frequency sleep spindle activity (12.25–13.0 Hz) in particular exhibits a prominent circadian modulation, such that during circadian phase of melatonin secretion low frequency spindle activity is abundant. During this phase EEG power density in the frequency range of 12.75–13.0 Hz is at 157.5% relative to the EEG power values collected outside the phase of melatonin secretion. NREM EEG power density in the frequency range of sleep spindles also varies with time of day during entrainment (Aeschbach *et al*. 1997a).

Analyses of the EEG with spindle detection algorithms have demonstrated that characteristics of sleep spindles, such as

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their average frequency, amplitude, duration, and incidence, all vary with circadian phase (Wei *et al.* 1999). These data have been interpreted as evidence for either a circadian modulation of the frequency of sleep spindles or a circadian modulation of two types of sleep spindles (Dijk *et al.* 1997b).

Circadian modulation of EEG power density is neither limited to the frequency range of sleep spindles nor to NREM sleep. For instance, alpha activity in NREM sleep as well as in REM sleep varies with circadian phase (Dijk *et al.* 1997b), and there is growing evidence that the spectral power of the EEG recorded during wakefulness is also modulated by circadian phase (Gundel and Witthöft 1983; Aeschbach *et al.* 1997b; Cajochen *et al.* 1998; Dumont *et al.* 1999).

Recently, it has been hypothesized that the differences between the EEG power spectra during sleep occurring inside and outside the circadian phase during which melatonin is present in plasma, may not represent phenomena relevant to sleep regulatory processes, and are caused by differences in body temperature at these two phases (Deboer and Tobler 1998a, 1998b; Deboer 1998). This interesting hypothesis was based on computer simulations in which EEG power was assigned to frequency bins different from the original power spectrum. The frequency shift was determined under the assumption that EEG power density in humans is temperature dependent with a Q10 of 2.5. Remarkable similarities between the data and simulations were reported for assumed temperature differences of 0.7°C (Deboer and Tobler 1998b), or 0.6°C and 0.8°C (Deboer 1998).

The hypothesis that circadian variation in EEG power spectra is caused by temperature differences was tested in this instance by a comparison of EEG power spectra collected during sleep occurring at two different phases of the circadian melatonin rhythm, while average body temperature during those phases was nearly identical. The hypothesis that circadian variation in the EEG is caused by differences in temperature predicts that EEG power spectra would be identical at these two phases of the circadian rhythm of plasma melatonin. If body temperature is not the sole cause of this circadian variation of EEG power spectra but a major determinant, we expect only minor differences in EEG power spectra at these two circadian phases at which body temperature is identical.

METHODS

The results contained in this manuscript represent a further analysis of previously published data (Dijk *et al.* 1997a; Dijk *et al.* 1997b). Details of the methods and subject recruitment, and screening methods can be found elsewhere (Dijk and Czeisler 1995; Dijk *et al.* 1997b).

Seven healthy men participated in an approximately one month long experiment while living in rooms in which they had no access to information about time-of-day. After three baseline days and a constant routine, subjects were scheduled to a 28-h sleep/wake cycle. Rectal temperature was collected continuously throughout each study using a rectal thermistor (YSI, Yellow Springs, OH) and stored with a one-minute resolution. Blood samples were drawn at hourly intervals during selected sections of the protocol (starting prior to the forced desynchrony segment of the protocol and typically at weekly intervals). Blood samples were drawn through an indwelling intravenous catheter with side port holes (Deseret Medical Inc., Sandy, UT) placed in a forearm vein. Samples were centrifuged immediately, and the plasma was frozen at −20°C and later assayed for melatonin at Diagnos Tech (Osceola, WI), applying a radioimmunoassay. In the present analyses a total of 1623 samples are included. Illuminance during the scheduled wake episodes was < 20 lux. Under these conditions the circadian rhythms of plasma melatonin and core body temperature oscillate with near identical periods averaging 24.2 h across subjects (Czeisler *et al.* 1995).

In the present analyses, circadian phase was derived from the plasma melatonin data collected during the protocol as described elsewhere (Dijk *et al.* 1997b). After the circadian melatonin period and phase were assessed, all body temperature data were assigned a circadian melatonin phase. In addition, for every minute of body temperature, the time within the 28-h sleep/wake schedule was determined. Thereby it could be determined whether a particular body temperature value was collected during the scheduled sleep episode or the scheduled wake episode. Similarly, every melatonin value was assigned a circadian phase and time within the sleep/wake schedule. Because melatonin was used as a circadian phase marker, and to account for interindividual differences in melatonin concentrations, all values were z-transformed.

All sleep episodes, which occurred at many different circadian phases, were recorded polysomnographically and subjected to spectral analysis based on the fast Fourier transform. The original spectral resolution was 0.25 Hz, but the spectral data were stored with a resolution of 0.5 Hz. All polysomnographic recordings were scored according to standard criteria, and epochs contaminated by artifacts were excluded from the analysis. All epochs were assigned a circadian phase.

The values presented here were computed first by subject and then across subjects. Standard errors represent the between subject standard error (SE).

RESULTS

Body temperature during wakefulness and body temperature during scheduled sleep episodes varied with circadian phase of the plasma melatonin rhythm such that lowest values occurred shortly after the crest of the fitted melatonin rhythm (Fig. 1A, B). Although the two body temperature curves appear to run largely in parallel, the difference between the two curves varied with circadian phase (ANOVA for repeated measures: $F_{23,138} = 4.22$; $P < 0.0001$) such that the 'masking' effect was largest when scheduled sleep episodes coincided with the phase of melatonin secretion.

The circadian waveform of plasma melatonin values collected during scheduled wake and scheduled sleep episodes were similar. However, melatonin values were higher during scheduled sleep episodes than during scheduled wake episodes,

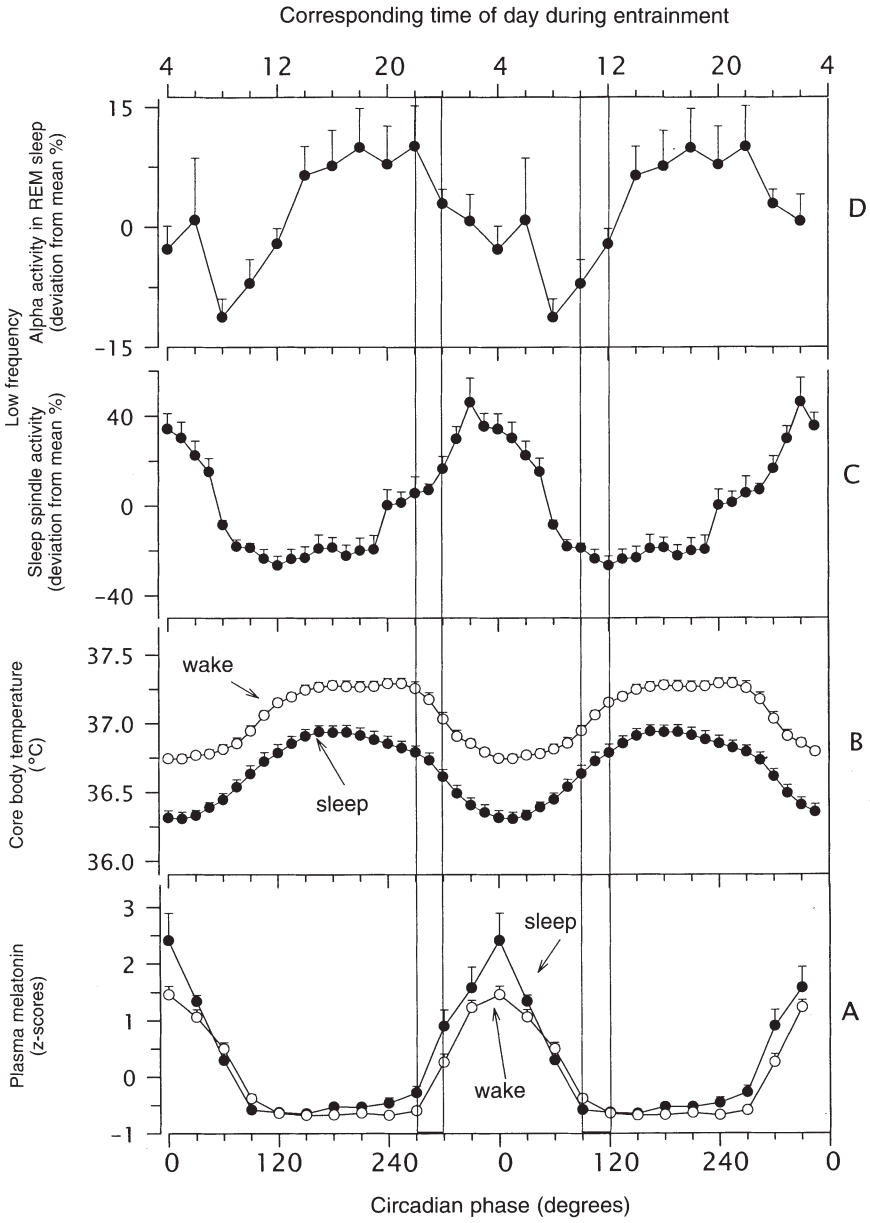

Figure 1. Circadian variation of plasma melatonin (A), core body temperature (B), low frequency (12.25–13.0 Hz) sleep spindle activity in NREM sleep (C) and low frequency (8.25–10.5 Hz) alpha activity in REM sleep (D). For core body temperature and plasma melatonin, the circadian wave-forms were educed separately for data collected during scheduled sleep (filled circles) and scheduled wakefulness (open circles). All data are plotted at the midpoints of the 15 or 30 degree bins and are double-plotted. Circadian phase was derived from plasma melatonin. The two vertical boxes delineate the two circadian phase intervals (270–300 degrees and 90–120 degrees) that were used for the analyses presented in Figure 2. $N=7$ for all variables with the following exceptions: plasma melatonin during sleep, phase bins 0 and 30 degrees ($n=4$), 60 degrees ($n=6$), 240 degrees ($n=5$).
Panels A, C and D, re-analyzed or modified from data published in Dijk *et al.* 1997b; Panel B, re-analysis of data published in Dijk *et al.* 1997a.

in particular on the rising limb of the melatonin rhythm (Fig. 1A). ANOVA revealed a significant effect of circadian phase ($F_{11,135}=79.05$; $P<0.0001$), a significant effect of state [i.e. scheduled sleep vs. scheduled wakefulness ($F_{1,135}=14.30$; $P<0.0002$)] and a significant interaction between phase and state ($F_{11,135}=2.47$; $P=0.0077$).

Low frequency (12.25–13.0 Hz) sleep spindle activity varied with circadian melatonin phase such that high values occurred when melatonin was present in plasma (Fig. 1C). The 'evening' rise in low frequency sleep spindle activity occurred at 240 degrees, in close proximity to the increase in plasma melatonin levels. Alpha activity in REM sleep exhibited circadian variation such that highest values occurred at and shortly after the crest of the circadian body temperature rhythm (Fig. 1D).

Next, body temperature and the EEG in the interval of 270–300 degrees of the melatonin rhythm was compared to the

interval of 90–120 degrees. The first interval occurred just after the 'evening' increase in plasma melatonin – an increase that was especially evident when sleep was scheduled at this phase – which will be referred to it as the 'evening' phase. The second interval occurred just after the 'morning' clearance of melatonin, i.e. when plasma levels have returned to very low levels, and will be referred to it as the 'morning' phase. Body temperatures during scheduled sleep at these two circadian phase intervals were 36.72°C (SE 0.05) and 36.72°C (SE 0.07) for the evening and morning phase, respectively. The average difference in body temperature between the morning and evening phase was 0.002°C (SE 0.05).

Despite these virtually identical body temperatures, low frequency sleep spindle activity was very different at these two phases (see values within vertical boxes of panels A, B and C of Fig. 1). During the evening phase, high values of low frequency sleep spindle activity were observed whereas in the morning phase values were close to the minimum of the circadian rhythm of low frequency sleep spindle activity. Similarly, alpha activity in REM sleep was different at these two circadian phases (Fig. 1D).

To further investigate the effects of circadian phase on the sleep EEG, the power spectra for NREM sleep occurring during the evening phase and the morning phase were computed (Fig. 2). All seven subjects contributed to both the morning and evening phase, and the average number of minutes of NREM sleep included in the analyses was 631.0 (SE: 46.7) and 486.6 (SE: 29.3) minutes per subject, respectively. The absolute spectra in NREM sleep exhibited the typical frequency-dependent decline in power, with a local increase in the frequency range of sleep spindles. Details of the power spectra in the frequency range of sleep spindles are presented in Fig. 2B. Average local peak power was observed in the 13.25–13.5 Hz bin during both morning and evening NREM sleep. During the evening sleep, statistically significant elevations of EEG power density were observed between 11.25 and 13.0 Hz ($P < 0.05$, two tailed t-test in all cases). Although high frequency spindle activity was somewhat lower during evening phase sleep, this effect was not statistically significant. Total spindle activity, i.e. EEG power in the frequency range of 12.25–15.0 Hz, was significantly higher during evening phase sleep than during morning phase sleep ($P < 0.01$).

To further illustrate the effect of circadian phase, EEG power spectra during evening phase sleep were expressed relative to EEG power spectra in NREM sleep during the morning phase (Fig. 2C).

NREM EEG power density during evening phase sleep was moderately but significantly increased compared to morning phase sleep in the 7.25–8.0 Hz range as well as in the 11.25–13.0 Hz range ($P < 0.05$ in all cases, two-tailed paired t-test on absolute power density values). This representation of the data shows that low frequency sleep spindle activity increased during evening phase sleep to levels as high as 153.2% (SE 7.8%) compared to morning phase sleep despite the identical body temperatures.

REM EEG power density during evening phase sleep was moderately but statistically significantly elevated between 7.5–9.5 Hz ($P < 0.05$), 15.75–17.5 Hz ($P < 0.05$) and 20.5–21.0 Hz ($P < 0.05$). No other statistically significant differences were observed (data not shown).

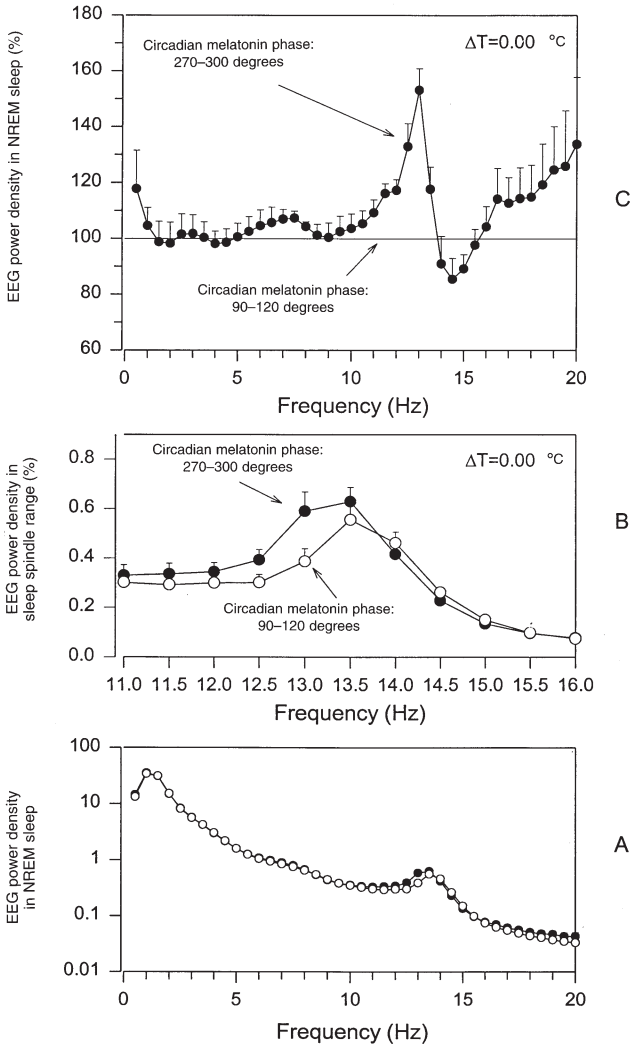

Figure 2. EEG power spectra in NREM sleep occurring during circadian interval 270–300 degrees (filled symbols) and 90–120 degrees (open symbols) of the plasma melatonin rhythm. Panel A: power spectra during these two phases. For all subjects power density values during both circadian intervals are normalized to the average power spectrum for that subject. The average power spectrum was based on all recorded sleep (stage 1,2,3,4 and REM) during the entire forced desynchrony section of the protocol ($N = 7$). Panel B: power spectra in the frequency range of sleep spindles. Panel C: EEG power spectra during NREM sleep occurring between 270–300 degrees expressed relative to power spectra during NREM sleep occurring between 90–120 degrees ($N = 7$). All data are plotted at the upper limit of the frequency bins.

DISCUSSION

The analyses presented here demonstrate that EEG power spectra during sleep occurring at two different phases of the circadian melatonin rhythm are very different despite identical

body temperatures at these two circadian phases. This is in direct contrast to the hypothesis that the temperature difference between the phase of melatonin secretion and the phase in which it is absent causes the effects in the relative power density spectrum (Deboer 1998).

It may be argued that the current analysis cannot demonstrate that the circadian variation in EEG power density in the frequency range of sleep spindles is not caused by changes in temperature, because brain temperature and not body temperature is the relevant variable. In the context of the present analysis this would imply that while body temperature was identical at these two circadian phases, brain temperature was different by as much as 0.6 or 0.8°C. The available data suggest that the time course of core body temperature and brain temperature during sleep are quite similar. (See Fig. 1 in Dijk and Czeisler 1993 and Fig. 3 in Landolt *et al*. 1995.) Even if a difference between body and brain temperature were to exist, the hypothesis presented by Dr Deboer requires that the brain–body temperature *difference* varies with circadian phase. Such an interaction between circadian phase and a variable measured at two locations or during two different states (sleep or wakefulness) is not unprecedented. The difference between body temperature during scheduled sleep and scheduled wakefulness varied with circadian phase in the present data set. This variation was not greater than 0.17°C in the present data [see also Fig. 1 in (Dijk *et al*. 1997a) and (Wever 1985)]. However, the hypothesis and computer simulations (Deboer 1998) require that the difference between body and brain temperature varies with circadian phase by as much as 0.6 or 0.8°C. This exceeds the range of circadian modulation of temperature and is therefore unlikely to be observed.

The present analysis confirms the previously reported close temporal association between plasma melatonin and the EEG in the frequency range of sleep spindles. In the current analyses we present melatonin variations separately for scheduled sleep and scheduled wakefulness. These current analyses confirm that the sleep/wake cycle and associated changes such as posture, modulate the circadian rhythm of plasma melatonin in accordance with previous reports (Deacon and Arendt 1994; Shanahan and Czeisler 1995). This modulation is such that the rise of plasma melatonin levels occurs earlier in the circadian cycle (i.e. as early as 240 degrees) when scheduled sleep coincides with this phase. Interestingly, the increase in low frequency sleep spindle activity nearly coincides with the increase in plasma melatonin at this phase. The evening rise of melatonin heralds, and is associated with, a variety of changes related to sleep regulatory mechanisms. For instance, the circadian drive for wakefulness subsides abruptly at, or shortly after, this phase, and changes in thermoregulatory processes also occur. The evidence that melatonin rhythm is driven by the suprachiasmatic nucleus and may contribute to these changes is accumulating (Cagnacci *et al*. 1997; Dijk and Cajochen 1997; Kräuchi *et al*. 1997; Sack *et al*. 1997; Shochat *et al*. 1997; Zhdanova *et al*. 1997). Furthermore, daytime administration of 5 mg of melatonin has been shown to affect the EEG during sleep (Dijk *et al*. 1995) and wakefulness (Cajochen *et al*. 1996). In view of the present and previously published data it seems reasonable to suggest that in view of these changes and the changes in sleep, EEG may reflect circadian components of sleep-regulatory mechanisms.

In our previous analyses (Dijk *et al*. 1997b) we compared EEG power spectra in NREM sleep collected during the intervals 270–90 circadian degrees (i.e. the night phase) to the 90–270 circadian degrees interval (i.e. the day phase) of the plasma melatonin rhythm. We reported an increase of EEG power density in the 12.75–13.0 Hz bin during night phase sleep to 157% compared to 'day' sleep. It has been stated that these differences in the EEG power spectra are remarkably similar to computer simulations when the temperature difference between these two circadian phases is assumed to be 0.6°C, 0.8°C (Deboer 1998) or 0.7°C (Deboer and Tobler 1998b). In the publications in which this was stated, a difference of 0.5°C (see Fig. 5D in Deboer1998; and Deboer and Tobler 1998b) was erroneously attributed to two of our publications (Dijk and Cajochen 1997; Dijk *et al*. 1997b). The computed average body temperatures during scheduled sleep are 36.47°C (SE 0.05) for the night phase and 36.85°C (SE 0.05) for the day phase, with an average difference of –0.39°C (SE 0.03). Thus the underlying assumption that the observed differences in EEG power spectra were due to differences in body temperature was based on an incorrect estimation of the actual difference.

Even with an assumed temperature difference of –0.8°C the computer simulations (Deboer 1998) yielded an increase in low frequency sleep spindle activity (< 140%) smaller than our observed value (157%). With an assumed temperature difference of –0.4°C (close to our actual observed temperature difference of –0.39°C) the computer simulations yielded an increase of low frequency sleep spindle activity value of approximately 120%. This is not particularly similar to our observed value of 157%. While making this comparison between our actual data and the simulations, it should be kept in mind that the simulated power spectra in the frequency range of sleep spindles are presented with a resolution of only 1.0 Hz in contrast to the 0.5 Hz resolution of our published data. In the simulations 0.5 Hz and 1 Hz frequency bins were divided into 0.1 Hz bins with every 0.1 Hz bin being allocated the power density value of the corresponding 0.5 Hz or 1.0 Hz bin. Such an approach to describe original power spectra that were computed with a resolution of 0.25 Hz is not without potential caveats. Power density, and especially so in the frequency range of sleep spindles in the human EEG, changes rapidly with frequency, and the assumption that an accurate estimate of power density can be obtained by either applying a step function (with steps of 1.0 Hz) or even by linear interpolation is unrealistic (See Fig. 2B of this manuscript and Werth *et al*. 1997). This more technical aspect of the simulations is another reason why the conclusion that the large similarity between data and simulation suggests that the circadian variation in EEG power spectra is caused by variation in body temperature is not warranted (Deboer and Tobler 1998b; Deboer 1998).

EEG power spectra, sleep spindles: amplitude, frequency, duration, and incidence

The power spectrum represents the combined and, in this representation, inextricable contribution of amplitude and frequency of the EEG. A reduction of frequency will result in an increase in power in frequency bins lower than the frequency bin that contains peak power and a reduction in power in the higher frequencies within the spindle band, in accordance with the data. Therefore, in interpreting our spectral data we listed a change in the frequency of sleep spindles as one of two possible mechanisms underlying the observed changes in the relative spectra (Dijk *et al*. 1997b). To better quantify the characteristic of EEG oscillations that underlie these changes in the relative power spectra, we have applied methods of sleep spindle analyses that are aimed at quantification of amplitude, frequency, duration and incidence of sleep spindles (Dijk *et al*. 1993; Wei *et al*. 1999). These analyses have shown that the sleep dependent, the sleep deprivation induced, and the circadian variation of sleep spindles indeed include, but are not limited to, changes in frequency. For instance, spindle amplitude and spindle incidence reach a maximum and spindle frequency reaches a minimum when sleep coincides with habitual sleep times, i.e. when melatonin is present in plasma and body temperature is low (Wei *et al*. 1999). We have interpreted these data to suggest that sleep spindles are actively promoted by the circadian pacemaker at this circadian phase and that this may represent a mechanism by which the circadian pacemaker modulates arousability and sleep consolidation at night (Dijk *et al*. 1997b).

The other frequencies: is there evidence for an effect of temperature on EEG power spectra?

Because body temperature is identical at the two circadian phases that we have presented here, difference in body temperature cannot be the sole cause of the circadian variation in alpha activity in REM sleep. In our previous comparison of day vs. night sleep, alpha EEG power in NREM sleep was slightly lower during the night phase. In our current comparison alpha activity in NREM sleep was slightly higher in the evening phase. Therefore, we cannot exclude a contribution of temperature within a range of 0.2–0.4 degrees to EEG spectra. However, no direct evidence for such a contribution is currently available.

In the current analyses we observed a difference in power density in the frequency range of sleep spindles at two circadian phases at which body temperature was identical. The relative value of power density in this frequency range during the evening phase was 153% compared to EEG power density during the morning phase. In our original analyses we compared EEG power spectra at two circadian phases (night and day) with very different body temperatures. In that comparison the relative value of power density in the frequency range of sleep spindles during the night phase was 157% compared to EEG power density during the day phase. Thus whereas in one comparison body temperatures were near identical and in the other comparison body temperatures were very different, the differences in power spectra were near identical. Our current observations therefore do not only indicate that temperature cannot be the cause of the circadian variation in spectra but the data are also at variance with the notion that moderate temperature changes contribute significantly to the EEG spectrum.

Dissociations between changes in EEG power spectra and body temperature have been reported in humans. Evening bright light exposure prior to sleep induced elevations of body temperature of approximately 0.3°C during the first three NREM/REM cycles of nocturnal sleep (Cajochen *et al*. 1992). These changes in body temperature were not associated with changes in EEG power spectra except for a reduction of power density in the 0.75–1.00 Hz band in NREM episode 1 and a reduction in the 15.25–17.00 Hz band in NREM episode 3. Both of these changes contradict those predicted by the hypothesis that temperature affects the EEG during sleep (Deboer 1998). Dissociations between changes in temperature and EEG spectra have also been reported in the animal literature. Tobler *et al*. (1994) observed that in the rat melatonin administration affected NREM EEG power spectra in the 1–8 Hz range, but did not affect brain temperature. In another paper from the same laboratory it was reported that in the Djungarian hamster melatonin significantly raised cortical temperature (see Fig. 3 in Huber *et al*. 1998), but no significant changes in EEG spectra during either NREM sleep, REM sleep or wakefulness were observed. Finally, Franken *et al*. (1998) concluded that differences in EEG activity, including differences in peak frequencies in selected frequency bands, between inbred strains of mice were unlikely to have been caused by differences in temperature.

CONCLUSION

The circadian rhythm of body temperature is closely associated with the circadian variation in sleep propensity, sleep structure and the sleep EEG (see Dijk and Czeisler 1995 and Kräuchi *et al*. 1997 for references, and Gilbert *et al*. 1999). It is possible that variations in body and brain temperature directly affect sleep propensity, sleep structure and the EEG by effects on the multitude of ionic currents, receptors, neuromodulators and neurotransmitters involved in the genesis of electro-encephalographic oscillations as well as by effects on the multitude of efferent signals emerging from the suprachiasmatic nuclei involved in the circadian regulation of sleep (McCormick and Bal 1997; Moore and Silver 1998). However, the mechanisms by which such effects of temperature – and in particular its variation within the range occurring during the circadian cycle – could affect sleep regulatory mechanism and the EEG remain unidentified. The present analysis suggests that the direct contribution of temperature to the circadian variation in EEG power spectra is absent or only minor and demonstrates that circadian variation in relative power spectra,

especially in the frequency range of sleep spindles, cannot be explained solely by variations in body temperature.

ACKNOWLEDGEMENTS

I thank Drs Charles A. Czeisler, Jeanne F. Duffy and Christian Cajochen for comments on the manuscript. The data collection and/or analyses were supported by NIA-P01-AG09975 (C. A. Czeisler), and NASA Cooperative Agreement NCC 9–58 with the National Space Biomedical Research Institute (D.-J. Dijk). The studies were performed in a General Clinical Research Center supported by a grant from the National Center for Research Resources (NIH-RR2635).

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